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Safety and Efficacy of Using Nuts to Improve Bowel Health in Hemodialysis Patients

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Safety and Efficacy of Using Nuts to Improve Bowel Health in Hemodialysis Patients

Abstract

Objective: Constipation is common in patients with end-stage kidney disease. Nondrug strategies to manage constipation are challenging because of dietary potassium, phosphate, and fluid restrictions. Nuts are a high-fiber food but are excluded from the diet because of the high potassium and phosphate content. The aim of this study was to examine the safety and efficacy of using nuts to improve constipation in adults undertaking hemodialysis (HD). Design and Methods: Adult patients undertaking HD were recruited to this nonrandomized, 10-week repeated measures, within-subject, pragmatic clinical trial, conducted in two HD units. The intervention consisted of consumption of 40g of raw almonds daily for four weeks, followed by a two-week washout and four-week control period. The primary safety outcome measures were change in predialysis serum potassium and phosphate levels. The primary efficacy outcome was reduction in constipation, measured using the Bristol Stool Form Scale and Palliative Care Outcome Scale (POS-S) renal symptom score. Secondary outcomes included quality of life, selected uremic toxins, cognition, gut microbiota profile, and symptom burden. Results: Twenty patients completed the trial (median age: 67 [interquartile range: 57.5-77.8] years, 51% male). After controlling for dialysis adequacy, anuria, dietary intake, bicarbonate, and parathyroid hormone, there were no statistically significant changes in serum potassium (P = 0.21) or phosphate (P = 0.16) associated with daily consumption of almonds. However, statistically significant improvements in constipation were seen at weeks 2, 3, 4, and 10. There were statistically significant improvements in quality of life (P = 0.030), overall symptom burden (P = 0.002), vomiting (P = 0.020), itching (P = 0.006), and skin changes (P = 0.002). Conclusion: Daily consumption of almonds for four weeks was safe, effective, and well tolerated. Improvements in quality of life and symptom burden warrant further research to elucidate potential mechanisms. The findings support the potential reinclusion of foods such as nuts into the diet of patients who underwent HD.

Publication Details

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Title: **S**afety and efficacy of using nuts to improve bowel health in hemodialysis patients

Abstract:

Objective:

Constipation is common in patients with end stage kidney disease (ESKD). Non-drug strategies to manage constipation are challenging due to dietary potassium, phosphate and fluid restrictions. Nuts are a high fiber food but are excluded from the diet due to the high potassium and phosphate content. The aim of this study was to examine the safety and efficacy of using nuts to improve constipation in adults undertaking hemodialysis (HD).

Design and methods:

Adult patients undertaking HD were recruited to this non-randomised, 10-week repeated measures, within subject, pragmatic clinical trial, conducted in two HD units. The intervention period consisted of consumption of 40g raw almonds daily for four weeks, followed by a two-week washout and four-week control period. The primary safety outcome measures were change in predialysis serum potassium and phosphate levels, and the primary efficacy outcome was reduction in constipation, measured using the Bristol Stool Form Scale and Palliative Care Outcome Scale (POS-S) renal symptom score. Secondary outcomes included quality of life, selected uremic toxins, cognition, gut microbiota profile, and symptom burden.

Results:

Twenty patients completed the trial (median age 67 (IQR: 57.5-77.8) years, 51% male). After controlling for dialysis adequacy, anuria, dietary intake, bicarbonate, and parathyroid hormone there were no statistically significant changes in serum potassium (p=0.21) or phosphate (p=0.16) associated with the daily consumption of almonds. However, statistically significant improvements in constipation were seen at weeks 2, 3, 4 and 10. There were statistically significant improvements in quality of life (p=0.030), overall symptom burden (p=0.002), vomiting (p=0.020), itching (p=0.006) and skin changes (p=0.002).

Conclusion:

Daily consumption of almonds for four weeks was found to be safe, effective and well tolerated. Improvements in quality of life and symptom burden warrant further research to elucidate potential mechanisms. The findings support the potential re-inclusion of foods such as nuts into the diet of haemodialysis patients.

Keywords: hemodialysis, nuts, clinical trial, treatment outcome, constipation

Introduction

Abnormal bowel health is common in patients with end stage kidney disease (ESKD), and is characterised by impaired motility [1], and symptoms such as abdominal pain, indigestion, reflux and constipation [2]. Constipation is estimated to affect more than three quarters of hemodialysis patients [3]. In addition to reduced quality of life (QOL) [4], constipation also contributes to hyperkalaemia [5], and abdominal discomfort [3]. In patients undertaking peritoneal dialysis, constipation can also cause catheter dislodgment [6,7]. Constipation has also been identified as an outcome of concern by patients and carers [8].

Poorly designed renal diet prescriptions for patients with ESKD can worsen constipation [9,10] due to overzealous restriction of fruits, vegetables, legumes, nuts and whole grain cereal products. Typical strategies suggested to manage constipation in healthy populations such as increasing physical activity, fiber and fluid intake [11] are particularly challenging for those with ESKD. This is due partly to the dietary phosphate, fluid and potassium restrictions that are required.

In recent years several studies have challenged the paradigm that some nutrient dense foods that are typically restricted in the renal diet may not need to be. For example, the bioavailability of phosphorus from plant-based food sources appears to be significantly lower than the phosphorus in animal derived food sources and phosphate additives [12]. Similarly, the bioavailability of potassium in diets rich in fruit, vegetables and legumes has been shown to be less than was previously predicted [13,14]. Studies such as these, in addition to the recent evidence of reduced mortality in patients following healthy diet patterns in Chronic Kidney

Disease (CKD) [15,16], have led to suggestions that liberalisation of the renal dietary restrictions for patients with ESKD may be warranted [17].

Given the extent of bowel health problems such as constipation, and poor medication compliance in patients undertaking dialysis [18-20], alternative non-drug strategies to improve constipation in hemodialysis patients are needed. Nuts may be one potential option to improve the management of constipation. Nuts are high in protein, fiber, micronutrients and polyunsaturated fatty acids [21]. However, they are also high in potassium and phosphate and as result, are typically not recommended for inclusion in the diet of a patient who is undertaking hemodialysis. However, large epidemiological studies have demonstrated that regular nut consumption is associated with improved laxation in healthy populations [22], as well as improved gut microbiota profile [23], increased vascular health improved cognition function [24] and reduced mortality [25]. A recent meta-analysis reported that a dietary pattern high in fruits, vegetables, legumes and nuts was associated with a reduced risk of death [15].

Despite the benefits of nut consumption in the general population [21], whether regular nut consumption is safe and effective at improving bowel habits in patients undertaking hemodialysis has not been explored. Given these knowledge gaps, the overall aim of this study was to determine the safety and efficacy of using a non-drug treatment in the form of almonds to improve bowel health in adult haemodialysis patients. The hypotheses of this trial were that consumption of 40g of almonds daily for four weeks is safe and would result in an improvement in bowel health and specifically a reduction in the prevalence of constipation. As a secondary outcome, we hypothesised that the intervention would result in improvements in symptom burden, QOL, uremic toxins, cognition and gut microbiota profile.

Methods

Study design and study population

A non-randomised 10-week repeated measures, within subject, pragmatic clinical trial was conducted and is reported in accordance with the guidelines for transparent reporting of studies with non-randomized designs [26], and the checklist for intervention description and replication [27]. The clinical trial was registered with the Australian New Zealand Clinical Trials Registry (Registration number ACTRN 617000600347p). The joint University of Wollongong Illawarra Shoalhaven Human Research Ethics Committee approved the study (HE2017/332) and all study procedures were followed in accordance with the Declaration of Helsinki.

The trial setting was two satellite haemodialysis units in a regional health district of New South Wales, Australia. The trial population consisted of haemodialysis patients attending the units for therapy. Exclusion criteria were individuals who were pregnant; allergic to almonds; suffered from dysphagia; or had dental problems that would prohibit consumption of nuts. Those with a current diagnosis of acute diverticulitis or faecal impaction and those deemed by nursing or medical staff as unable to follow instructions adequately due to language or cognitive impairment were also excluded from the trial.

Recruitment

All hemodialysis patients were approached while undertaking hemodialysis by a member of the research team. No treating health professionals on the research team assisted with

recruitment. Interested patients provided written informed consent prior to commencing the trial.

Study procedures

All assessments were conducted with participants during the second hour of their first thrice weekly hemodialysis therapy sessions. Following two weeks of pre-intervention assessments, participants were required to consume the intervention food for a four-week period, followed by a two-week wash-out period; followed by a subsequent four-week control period.

Intervention

The intervention consisted of the consumption of 40g raw unsalted almonds with skin daily for four weeks. This equates to approximately 27 almonds per day. A schematic of the study is shown in the Supplemental material, Figure 1. Almonds were chosen due to the small volume required to supply 8g of protein and at least 3 g of fiber. This volume of almonds also supplied 210mg of phosphate and 318 mg of potassium [28]. According to renal diet specifications this quantity of almonds was considered to be a high phosphate and high potassium food source [29]. Other nuts such as walnuts or macadamias were not considered for the study as they required daily consumption in excess of 60g which was considered to be a deterrent to optimal intake. A one-week supply of almonds was provided to all participants at the start of each trial week. All other components of their usual renal dietary restrictions were maintained (i.e. the diet continued to be fluid, potassium, phosphate, and sodium restricted). Participants were instructed to consume the intervention ad libitum but not exceed the 40g almonds within a 24-hour period. A 40g scoop was provided to all participants to ensure an accurate and consistent dose was consumed daily. To ensure intervention fidelity, participants

were instructed to return any remaining amounts of almonds each week prior to provision of the following week's supply. Residual almond quantities were weighed to ascertain average consumption of the intervention each week and adherence with the study protocol. During the wash out and control weeks, participants were instructed to avoid all nut and nut products as per usual renal diet recommendations and to maintain their usual renal dietary prescription.

Primary outcome measures

The primary *safety* outcome measure of the trial was change in predialysis serum potassium and phosphate levels. All pathology measures were taken on the first dialysis session of each week following the long dialysis break. Hyperkalaemia was defined as serum potassium ≥ 6 mmol/L. Hyperphosphatemia was defined as serum phosphate ≥ 5.74 mg/dL (or ≥1.85 mmol/L.)

The primary *efficacy* measure was change in bowel habits. Three measures of bowel health were utilised, based on previous research that demonstrated self-report of bowel habit to be highly variable using different tools [9]. Participants rated their bowel habits at baseline, weeks 1-4, 7 and 10 using the Bristol Stool Form Scale with a score of 1 or 2 indicative of constipation [30]. Participants rated their bowel health using a bowel management algorithm [9] which includes questions from the Rome III criteria for the diagnosis of constipation. Participants also self-rated their bowels using the Patient Outcome Scale- Renal [31]. This tool lists 18 symptoms including weakness, nausea, vomiting, and constipation, and patients rate the severity and presence of the symptoms.

Secondary outcome measures

The secondary outcomes of the trial included QOL, serum total and free concentrations of the uremic toxins p-Cresyl Sulfate (PCS) and Indoxyl Sulfate (IS), stool microbiota, cognition and symptom burden. The methods used to measure and collect these outcomes are described in the Supplemental material.

Other measures

Nutrition assessment was completed by a trained dietitian using a validated nutrition assessment tool for use with hemodialysis patients (the Patient Generated Subjective Global Assessment [32]). This assessment was completed at baseline, week 4, 7, 10 of the trial. Dietary intake during the study was recorded using a three-day food record completed by the patient (or carer) including one weekend day, dialysis day and non-dialysis day. This was completed at baseline, weeks 1- 4, 7, 10 of the trial. A diet history interview [33] was also obtained from the particpants by the same trained dietitian . This information was obtained at baseline, weeks 4, 7 and 10. Quantitative analysis of dietary intake was undertaken using FoodWorks (version 9, Xyris Pty Ltd, Highgate Hill, Queensland, Australia), using the AUSNUT 2011-13 food composition database [28]. All nutrient data was presented as mean (SD). All prescribed and over the counter medications, supplements or herbal preparations taken by the participants to assist with bowel health were recorded at the commencement of each week of the trial. This was confirmed by having patients bring in pill bottles and/or prescription lists to the research team for verification.

Adverse events

An adverse event was defined as any fatal or life-threatening event, or an event posing a significant hazard, or causing a side effect, and any experiences requiring hospitalisation. Events were monitored and those occurring during the trial were discussed, documented and actioned by the clinical team.

Statistical analyses

Normality of variables was assessed using the Shapiro Wilk test. Data is reported as median and interquartile range or mean and standard deviation where appropriate. All analyses were conducted using SPSS (version 25, IMB Corporation, Chicago, IL, USA). General linear models for repeated measures were tested using a heterogeneous compound symmetry structure as the variance at each time point were assumed not to be constant. These models were used to determine the change in serum potassium and phosphate after controlling for dialysis adequacy, dietary intake of potassium or phosphate, urine output, serum bicarbonate and serum PTH level. Analysis of the change in uremic toxins after controlling for anuria and dialysis adequacy was also conducted. The McNemar test was used to determine changes in the proportion with hyperkalaemia, hyperphosphatemia, adequate bowel habit and laxative use. The Friedman test on one way ANOVA for repeated measures was used to assess the change in QOL, uremic toxins, and cognition. Per protocol analyses are reported and a pvalue of 0.05 was considered statistically significant.

Results

Thirty two patients were recruited to the study, and 20 participants completed the study (Figure 2). More than half of the participants were male, with a median age of 67.5 (IQR: 57.5-77.75) years (Table 1). The majority of participants were well nourished according to

the PG-SGA; almost half (45%) were anuric (defined as less than 100mL urine per day), and almost half (45%) were deemed to be cognitively impaired at baseline on formal assessment. Multi-morbidity was evident with diabetes, coronary artery and peripheral vascular disease common. Laxative use was common, with 65% taking laxatives or aperients at baseline. When compared to evidence based guidelines for the management of hemodialysis patients, baseline dietary intake was considered to be inadequate for energy, protein, phosphate and fiber [34]. Only 15% of participants reported consuming an adequate intake of dietary fiber (>25g/day).

Assessment of safety

Consumption of 40g almonds daily for 4 weeks was not associated with increases in serum potassium (Table 2, $p = 0.21$) or serum phosphate (Table 2, $p = 0.16$) after controlling for confounders. The proportion of participants who were considered hyperkalemic or hyperphosphatemic also did not change. There was one adverse event during the trial related to the intervention which consisted of a patient experiencing a choking episode. No further medical assistance was required.

Assessment of efficacy

As shown in Table 2, compared to baseline, there was a significant reduction in the proportion of participants who reported constipation at weeks 2, 3 and 10 ($p = 0.04$, $p = 0.006$ and $p = 0.03$, respectively). The mean POS renal score for constipation also reduced significantly during the study ($p = 0.02$). Laxative use declined significantly between baseline and week 4 of the intervention from 65% to 20 % ($p = 0.02$). The mean individual

consumption of almonds during the intervention weeks indicated that adherence to the intervention was high (Table 2, mean: 89%).

Secondary outcomes

There was a significant improvement in QOL over the 10 weeks (Table 3). The EQ-5D-5L index score increased by 0.15 quality-adjusted life-years (QALY) from baseline by week 10 ($p = 0.03$). There was no change in mean EQ-5D-5L Visual Analogue Scale score, uremic toxins, or cognition. However, total symptom burden decreased significantly from a mean score at baseline of 16.7 ± 6.7 to 10.2 ± 6.0 by week 4 and 11.3 ± 9.0 by week 10 ($p = 0.002$). Other significant changes in symptom scores occurred for vomiting ($p = 0.02$), constipation ($p = 0.02$), itching ($p = 0.006$) and skin changes ($p = 0.002$).

No differences were observed in faecal microbiota diversity (alpha- or beta-diversity), either before or following the intervention. The consumption of 40 g daily of almonds over 4 weeks did not have a measurable effect on faecal microbiota composition (the relative abundance of specific bacterial taxa) in individuals undertaking hemodialysis.

Discussion

In this safety and efficacy trial, consumption of 40g almond daily for four weeks was not associated with harmful elevations of serum potassium or phosphate, or other major adverse events. The intervention was associated with significant improvements in constipation when measured using two separate patient reported outcome tools. This trial also saw significant improvements in QOL and symptoms such as vomiting, itch and dry skin during the

intervention period. This non-drug intervention was also well tolerated by participants, with excellent adherence to guidelines for consumption of the almonds provided.

Given the high prevalence of constipation among dialysis patients, safe and effective management methods are required. This trial suggests that regular nut consumption may be a potentially effective and safe non-drug alternative or adjunct to traditional methods used to manage constipation. The effect size of the reduction in constipation between baseline and week 4 was equivalent to a moderately large effect (Cohen's *d* 0.58) and has obvious practical importance [35]. Physiological mechanisms for how nuts may assist with laxation appear to be more than just the provision of the additional fiber. For example, some authors suggest the effect on laxation may be related to the presence of large amounts of fermentable carbohydrates including xylose and galactose in the almond cell wall. These carbohydrates are known to exert a prebiotic effect [36], providing the substrate for bacterial metabolism that may confer a benefit for the human host [37]. Others suggest that nut digestion induces remodelling of the gut microbiota [38] via improved butyrate synthesis from the metabolism of the fiber and polyphenol content.

In addition to constipation, patients undergoing dialysis commonly report dermatological symptoms. Mechanisms for the improved skin and reduction in itch (pruritus) reported by participants in our trial are unknown. Pruritus and xerosis (dry skin) in dialysis patients are understudied [39], despite pruritus being experienced by almost half of dialysis patients. These complaints are also associated with reduction in the QOL of dialysis patients [40]. Traditionally, it is thought that xerosis is due to a reduction in the eccrine sweat glands and atrophy of sebaceous glands [41]. It is unclear what role diet may have in these conditions. However, one

may speculate that the improvements in skin and pruritus may be due to the high monounsaturated fat and vitamin E composition of the almonds. Vitamin E intake has been associated with skin quality [42], and dietary intake of vitamin E is reduced in individuals with end stage kidney disease due to a reduction in consumption of rich food sources (nuts, spinach and wholegrain cereals). Metabolism of vitamin E is also impaired in dialysis patients [43]. Future research to examine the relationship between skin and dietary quality is warranted.

This trial adds to the evidence base regarding the high symptom burden and poor QOL amongst dialysis patients [44], especially those with constipation [4]. In this trial, the participants experienced a range of symptoms in addition to constipation, and the QOL was far below reported Australian norms (mean index score 0.91 and mean VAS score 78.55) even at baseline [45]. The reasons for the gain of 0.15 of a QALY during the trial period are unknown. Qualitative research to ascertain why this occurred would have been beneficial and could be an area for future research.

There are several strengths to this study. This includes the comprehensive collection of data regarding potential confounders to the results including in depth dietary data. However, there are also several obvious limitations. These include the small sample size and short follow up period. Unlike drug studies, it is difficult to blind participants to whole food interventions, thus, it is also possible that participants may have been subject to reporting bias. We used standard tools to assess efficacy outcomes, however, it should be noted that these tools rely on self-reported changes in bowel habits, which may have also introduced bias. Given the free-living nature of the participants, this challenge is likely to persist in future studies. We

attempted to minimise inter-individual variation by using a study design where participants acted as their own controls and undertook the intervention first. This was due to concerns regarding compliance and potential contamination of the intervention. It was also not considered appropriate to randomise participants in each site to start on either the intervention or control period and practical challenges coordinating between sites prevented randomisation by shift. As a result, we cannot conclude that bias may have influenced the study findings. It should be noted that many of the improvements seen during the intervention period (for example frequency of bowel movements, use of laxatives) were mitigated during the control period, although they remained more favourable than baseline levels. These results suggest that the intervention was partly responsible, although there may have been some continued carry-over effects observed during the control period.

To conclude, this trial offers insights into the utility of including nuts in the diet of haemodialysis patients to improve bowel health. In addition to being a safe, effective and well tolerated treatment, this trial also found there were improvements in QOL, and symptoms such as vomiting, itching and skin changes. Future research into the use of foods such as nuts to assist with constipation are needed, especially studies with a more robust study design. Despite no known mechanism, studies exploring the relationship between dietary changes and skin quality and pruritus will be beneficial for developing potential treatments. Additional research to elucidate potential mechanisms for these findings is warranted. Further exploration of dietary patterns in those undertaking dialysis, especially in those with suboptimal bowel health may also be useful.

Practical Application

The findings of this study support the potential re-inclusion of foods such as nuts into the diet of haemodialysis patients.

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Supplemental material

Methods

Secondary outcomes:

Overall symptom burden was evaluated using the Patient Outcome Scale- Renal [31] at baseline, weeks 1- 4, 7, 10 of the study. Reporting of scores is as per the reporting guidelines of the authors[46], with a total score for overall symptom burden ranging from 0 to 68 (indicative of a high symptom burden) . Quality of life was assessed using the EuroQol 5 level Quality of Life Assessment tool (EQ-5D-5L) [47]. This tool was completed at baseline, week 4,7 and 10. Assistance to complete these tools due to poor vision was provided by members of the research team when required. Analysis of crude scores was undertaken using the EuroQOL Crosswalk Value Calculator available from https://euroqol.org/eq-5d-instruments/eq-5d-5l-about/valuation-standard-value-sets/crosswalk-index-value-calculator/ utilising the United Kingdom cross walk scores.

Serum total and free concentrations of the uremic toxins, p-Cresyl Sulfate and Indoxyl Sulfate were analysed by ultra-performance liquid chromatography (UPLC) using a fluorescence detection method developed by the research team [48]. Serum samples were stored at -80°C and then analysed in a single batch. The free fraction of each toxin was defined as a percentage of total concentration (free serum concentration divided by the total concentration multiplied by 100). These samples were collected at weeks 1,4, and week 10.

Serum total and free concentrations of the uremic toxins, p-Cresyl Sulfate (pCS) and Indoxyl Sulfate (IS) were analysed by ultra-performance liquid chromatography (UPLC) using a fluorescence detection method developed by the research team [48]. Serum samples were stored at -80°C and then analysed in a single batch. Chromatography was performed with a Waters

Acquity UPLC I class system comprising of a Binary solvent manager, flow through needle autosampler, fluorescence detector and column manager (Milford MA, USA) and an Acquity HSS T3 1.8µm (2.1 x 50 mm) column with an Acquity BEH C18 1.7µm VanGuard pre-column (2.1 x 5 mm). Mobile phase A was 50 mmol/L ammonium formate (pH 5.0) and mobile phase B was 100% acetonitrile. Mobile phase B increased with a linear gradient from 5 to 25 % over 2.1 min, was then maintained isocratically at 70 % for 0.4 min, followed by 0.5 min at 99%. The column was re-equilibrated with initial conditions for 0.5 min. The load-ahead facility within the system was enabled to minimize the run time. Injection volume was 2 µL for total IS (tIS) and total *p*CS (t*p*CS) and 5 µL for fIS and f*p*CS samples. Column temperature was maintained at 45ºC. We quantified IS, *p*CS and the internal standard (50 µmol/L 4-ethylphenol) with timed programmed fluorescence detection monitoring at specific excitation / emission wavelengths (IS: 300/390 nm; pCS: 260/283 nm; 4-ethylphenol: 285/310 nm).

f*pCS* and fIS were measured directly, without addition of an internal standard, on ultrafiltrates prepared at room temperature from 200 µl of serum centrifuged for 10 min at 13000 rpm with a 30000 MWCO filter (Merck, Kilsyth, Australia). tIS and t*p*CS were measured after deproteinization of 100 µL serum with 300 µl of ethanol that contained internal standard (50µmol/L 4-ethylphenol). The mixture was vortexed for 1 min, centrifuged for 5 min at 13000 rpm and poured into a 2.0 mL tube that contained 200µL H_2O and 1mL dichloromethane. After vortexing for 1 min and centrifuging for 5 min at 13000 rpm, 150 µL of the aqueous supernatant was transferred to an injection vial. The free fraction of each toxin was defined as a percentage of total concentration (free serum concentration divided by the

total concentration multiplied by 100). These samples were collected at weeks 1,4, and week 10.

The Montreal Cognitive Assessment (MoCA) Tool [49] was used to screen for cognitive impairment and changes in cognition during the study. This tool is more sensitive at detecting mild to moderate impairment than other tools such as the Mini Mental State Examination [50]. The MoCA also comes in a range of more than thirty language versions and a version for blind participants which we have utilised in our unit previously [51]. The MoCA was completed at week 1, week 4, and week 10 using a different version of the tool each time to limit learning effects. Assistance to complete these tools due to poor vision was provided by members of the research team when required. A score of ≤24/30 was used to indicate cognitive impairment was present [52].

Faecal samples for gut microbiome analysis were collected from participants using DNA/RNA shield - Faecal collection tubes (Zymo Research). These samples were collected at baseline, and the commencement of week 4, week 7 and week 10. Samples were frozen at -80C and then analysed in one batch. Briefly, DNA was extracted using a DNeasy PowerSoil HTP 96 DNA Isolation kit (Qiagen) _and the 16S rRNA V4 region was used to study the bacterial community. Amplicon sequencing of the V4 hypervariable region of the bacterial 16S rRNA gene was performed using an Illumina MiSeq platform. The forward and reverse primers for the V4 region were GTGCCAGCMGCCGCGGTAA (5′ end 515F) and GGACTACHVGGGTWTCTAAT (3′ end 806R), respectively.

Sequence data was analysed using QIIME2 2018.2 (https ://qiime 2.org). Raw sequence data were first demultiplexed and quality filtered using the q2-demux plugin. This was followed

by denoising with DADA2 [53] for quality filtering and identification of sequence variants. Sequence variants were aligned and used to construct a phylogeny with FastTree programme (using the q2-phylogeny plugin). Core diversity metrics including alpha-diversity (observed OTUs, Faith's Phylogenetic Diversity), beta-diversity (weighted and unweighted UniFrac) and principal coordinate analysis (PCoA) was calculated at a depth of 5508 sequences per sample. Sequence variants were taxonomically classified against the Silva 132 99% OTUs reference sequences.

Confounders

Demographic and clinical information was collected from the electronic medical record and dialysis flow sheets. Information included age, gender, urine output, laxative use, antibiotic use, phosphate binder type and dose, potassium binder (Resonium) use, dialysis prescription including dialyser size and bath strength, and interdialytic weight gain. A weekly pooled Kt/V was also conducted on each patient. Additional pathology measures were taken on a weekly basis including urea, creatinine; bicarbonate; calcium; corrected calcium; magnesium; albumin; C Reactive Protein, liver function tests; and Parathyroid hormone (PTH).

Table 1. Baseline characteristics of study participants (n = 20)

Characteristic	Number
Gender (male)	11 (51)
Age, years median	67.5 (IQR: 57.5-77.75)
Age category, years	
18-54	3 (15%)
55-64	6 (30%)
65-74	7 (35%)
75-84	2 (10%)
>85	2 (10%)
Dry weight (kg)	78 (67.1-99.9)
Nutritional status	
Well nourished	18 (90%)
Moderately malnourished	2 (10%)
Severely malnourished	0 (0)
Anuric	9 (45%)
Comorbidities	
Diabetes	8 (40%)
Cerebrovascular Disease	3 (15%)
Peripheral Vascular Disease	7 (35%)
Coronary Artery Disease	8 (40%)
Chronic Lung Disease	5 (25%)
Cognitive impairment present	9 (45%)
MoCA score	
>24/30 (cognitively normal)	11 (55%)
Between 20-24 (mild-moderate impairment)	8 (40%)
Less than 20/30 (severely impaired)	1 (5%)
Laxative use according to type	
Nil	7 (35%)
Movicol	5 (25%)
Coloxyl	7 (35%)
Other	1 (5%)
Dietary intake	
Protein (g/kg) (Ideal: 1.1g/kg)	1.05
Protein (g/day)	82.3 (21.7)
Energy (kJ/kg) (Ideal: 125-146 kJ/kg)	81.5
Energy (kJ/day)	6354 (1922)
Sodium (mmol/day) (Ideal: <100 mmol/day)	79.4 (28.7)
Sodium (mg/day)	1826 (661)
Potassium mmol/kg (Ideal: 1 mmol/kg)	0.76
Potassium (mg/day)	2301 (671)
Phosphate (mg/day)	1221 (423)
Fibre (g/day) (Ideal: >25g/day)	19.1 (7.8)
Proportion with adequate fibre intake, n (%)	3 (15)
Dialysis adequacy (Kt/V) (mean, sd)	1.5 (0.3)

Legend: Data are mean (SD), median (interquartile range) or n (%). MoCA: Montreal Cognitive Assessment (MoCA) Tool. Cognitive Impairment suggested when score <24/30.

Table 2. Analysis of primary outcomes : safety and efficacy

	Baseline	Week 1	Week 2	Week 3	Week 4	Week 7	Week 10	P value
Safety outcomes								
Predialysis potassium (mmol/L)	5.43 ± 0.66	5.4 ± 0.6	5.37 ± 0.63	5.34± 0.69	5.45 ± 0.69	5.15 ± 0.96	5.25 ± 0.66	0.21
Hyperkalemic n (%)	6 (30)	3 (15)	4 (21.1)	4 (20)	4 (20)	4 (20)	4 (20)	0.96
Predialysis phosphate (mg/dL) (mmol/L)	4.77± 1.64 1.54 ± 0.53	4.90 ±1.58 1.58 ± 0.51	5.33±1.64 1.72 ± 0.53	5.39±2.02 1.74 ± 0.65	5.27±1.89 1.70 ± 0.61	4.37±1.61 1.41 ± 0.52	4.90±1.64 1.58 ± 0.53	0.16
Hyperphosphatemic n (%)	5 (25)	3 (15)	6 (31.5)	6 (30)	9 (45)	3 (15)	5 (25)	0.37
Efficacy outcomes								
Constipation rated using Bristol Stool Form Scale, n (%)	10 (50.0)	5 (25)	3 (16.6)*	1 (5.3)*	4 (20)	4 (22.2)	2 (13.3)*	a
Constipation according to POS-Renal	1.0 ± 1.0	0.8 ± 1.1	0.5 ± 0.8	0.5 ± 0.8	0.5 ± 0.7	0.6 ± 0.8	0.4 ± 0.7	0.02
Frequency of bowel movement n (%) Daily Second daily <3 times per week	 15 (75) 4 (20) 1 (5)	 12 (63.2) 5 (26.3) 2 (10.5)	 15 (78.9) * 4 (21.1) 0	 15 (78.9) * 3 (15.8) 1 (5.3)	 15 (78.9)* 2 (11.1) 2 (11.1)	 10 (52.6) 9 (47.3) 0	 12 (75.0) 3 (18.75) 1 (6.25)	b
Frequency of straining n (%) Never/ rarely Sometimes Often Always	 9 (45) 10 (50) 1 (5) 0	 13 (68.4) 4 (21.1) 2 (10.5) 0	 13 (68.4) 1 (5.3) 3 (15.8) 2 (10.5)	 15 (78.9) 3 (15.8) 1 (5.3) 0	 11 (57.9) 6 (31.5) 1 (5.2) 1 (5.2)	 9 (47.3) 7 (36.8) 1 (5.2) 3 (15.6)	 12 (75.0) 3 (18.75) 1 (6.25) 0	-
Frequency of hard/lumpy stool n (%) Never/ rarely Sometimes	 10 (50) 7 (35)	 10 (52.6) 7 (36.8)	 12 (63.2) 5 (26.3)	 14 (73.6) 4 (21.1)	 11 (57.9) 6 (31.6)	 9 (47.3) 9 (47.3)	 10 (62.5) 3 (18.75)	-

Often Always	3 (15) 0	2 (10.5) 0	1 (5.3) 1 (5.3)	1 (5.3) 0	2 (10.5) 0	1 (5.2) 0	2 (12.5) 1 (6.25)	
Frequency of incomplete evacuation n (%) Never/ rarely Sometimes Often Always	 8 (40) 7 (35) 5 (25) 0	 10 (52.6) 6 (31.5) 2 (10.5) 1 (5.3)	 11 (57.9) 6 (31.5) 1 (5.3) 1 (5.3)	 11 (61.1) 7 (38.9) 1 (5.5) 0	 12 (63.2) 6 (31.6) 1 (5.3) 0	 10 (55.6) 8 (44.4) 1 (5.6) 0	 10 (62.5) 4 (25) 1 (6.25) 1 (6.25)	-
Frequency of sensation that stool cannot pass n (%) Never/ rarely Sometimes Often Always	 6 (30) 12 (60) 2 (10) 0	 14 (73.7) 3 (15.8) 1 (5.3) 1 (5.3)	 14 (73.7) 5 (26.3) 0 0	 13 (61.1) 5 (27.8) 1 (5.5) 0	 13 (68.4) 6 (31.6) 0 0	 9 (50.0) 8 (44.4) 1 (5.6) 0	 10 (62.5) 5 (31.25) 1 (6.25) 0	-
Laxative use n (%)	13 (65)	4 (21.1)	4 (21.1)	5 (26.3)	5 (20)*	6 (33.3)	6 (37.5)	c
Consumption of intervention (g)	-	36.7 g ± 4.03	36.7 g ± 5.06	34.6g ± 9.24	34.7 ± 11.9	-	-	-
Adherence rate to intervention % of 40 g consumed per day	-	91	92	86	87	-	-	-

Legend: Reported as mean (sd) or counts (percentage). Serum potassium reported after controlling for dietary potassium intake, serum bicarbonate level, urine output and dialysis adequacy. Serum phosphate reported after dietary phosphate, serum PTH level, urine output and dialysis adequacy. *=indicates $p<0.05$ compared to baseline.

a: Bowel habit assessed using Bristol Stool Form Scale : Compared to baseline: week 2, p=0.04; week 3: p=0.04; Week 10 p=0.04.

b: Frequency of daily bowel movement compared to baseline: week 2: p=0.03; week 3: p=0.03; week 4: p=0.04

c: Proportion using laxatives compared to baseline: week 4 : p=0.02

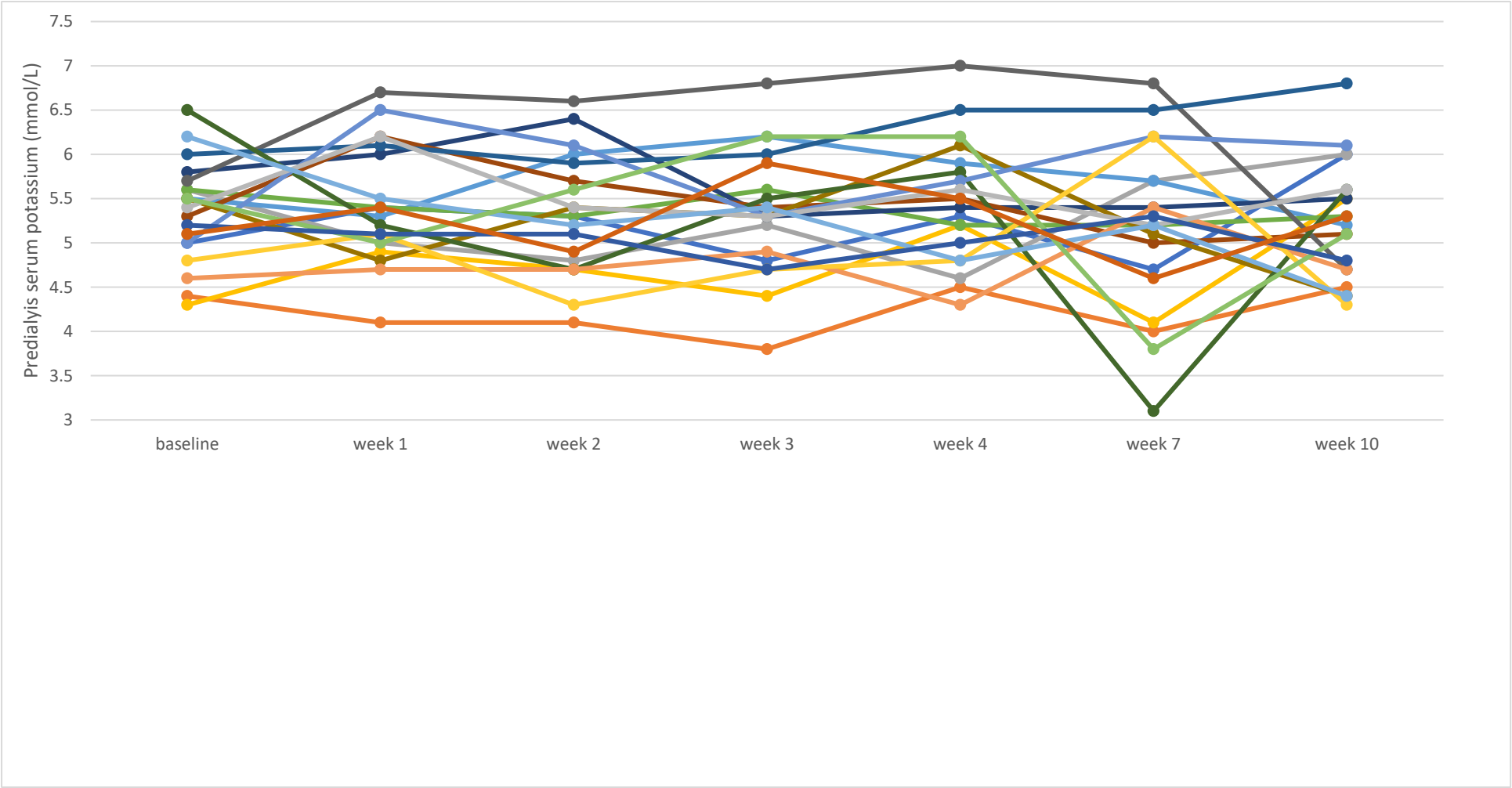
Table 3. Secondary outcomes

	Baseline	Week 4	Week 7	Week 10	P value
EQ5D5L index score	[a] 0.60 (0.51-0.74)	[a] 0.72 (0.50-0.87)	-	[a] 0.75(0.50-0.86)	0.03
EQ5D5L VAS score (range 0-100)	62.3 ± 20.2	69.2 ± 22.7	67.8 ±20.9	59.8 ± 24.1	0.27
PCS (total, umol/ L) (NR: 0.0-38.4)	167.6 ± 100.7	176.4 ± 103.9	-	155. 4 ± 105.1	0.40
PCS (free, umol/ L) (NR:0.1-2.4)	14.4 ± 14.8	17.6 ± 14.3	-	23.7 ± 18.9	0.18
IS (total, umol/L) (NR: 0.7-6.3)	136.7 ± 56.9	133.3 ± 54.8	-	111.2 ± 37.9	0.97
IS (free, umol/L) (NR:0.0-0.2)	25.6 ± 18.4	32.3 ± 20.2	-	38.1 ± 20.4	0.10
MoCA score (maximum score 30)	24.3 ± 4.3	25.2 ± 3.5	-	23.1 ± 5.1	0.05
POS-S Renal total score	16.7 ± 6.7	10.2 ± 6.0	11.7 ± 6.6	11.3 ± 9.0	0.002
POS-S Renal subscores					
Pain	1.1 ± 1.2	0.6 ± 1.0	0.8 ± 1.0	1.2 ± 1.1	0.22
Shortness of breath	1.2 ± 1.3	0.9 ± 1.2	1.1 ± 1.2	0.9 ± 1.2	0.50
Weakness	1.8 ± 1.2	1.2 ± 1.2	1.4 ± 1.2	1.4 ± 1.3	0.29
Nausea	0.8 ± 0.9	0.5 ± 0.8	0.4 ± 0.8	0.7 ± 0.9	0.25
Vomiting	0.6 ± 0.8	0.2 ± 0.4	0.2 ± 0.5	0.4 ± 0.8	0.02
Poor appetite	0.5 ± 0.9	0.2 ± 0.4	0.4 ± 0.7	0.3 ± 0.6	0.55
Constipation	1.0 ± 1.0	0.5 ± 0.7	0.7 ± 0.9	0.4 ± 0.7	0.02
Mouth problems	0.3 ± 0.7	0.3 ± 0.6	0.5 ± 0.8	0.5 ± 1.0	0.57
Drowsiness	1.2 ± 1.2	1.0 ± 1.0	1.2 ± 1.1	0.9 ± 1.0	0.70
Poor mobility	1.2 ± 1.1	1.0 ± 1.1	1.0 ± 0.9	0.8 ± 1.1	0.49
Itching	1.3 ± 1.0	0.7 ± 0.7	0.7 ±0.9	0.9 ± 1.0	0.006
Difficulty sleeping	1.4 ± 1.3	1.0 ± 1.2	1.2 ± 1.2	1.0 ± 1.0	0.42
Restless legs	1.0 ± 1.4	0.8 ± 1.0	0.8 ± 1.0	0.9 ± 1.2	0.78
Anxiety	1.3 ± 1.4	1.0 ± 1.4	0.8 ± 1.1	0.9 ± 1.1	0.20
Depression	0.8 ± 1.2	0.7 ± 1.2	0.8 ± 1.2	0.6 ± 1.1	0.51
Changes in skin	1.3 ± 1.4	0.3 ± 0.6	0.4 ± 0.7	0.4 ± 0.7	0.002
Diarrhoea	0.1 ± 0.3	0.5 ± 0.8	0.3 ± 0.7	0.1 ± 0.3	0.09

Data reported as mean and standard deviation or [a] median and interquartile range

Legend: NR: normal range; EQ-5D-5L: EuroQol 5 level Quality of Life Assessment tool ; VAS: Visual Analogue Scale; PCS: P Cresyl Sulfate; IS: Indoxyl Sulfate; MoCA: Montreal Cognitive Assessment score; POS-S Renal: Palliative Care Outcome Scale – Renal

Supplementary Table 1. Individual trend of study participant's predialysis serum potassium over study period (raw data)



Supplementary Table 2. Individual trend of study participant's predialysis serum phosphate over study period (raw data)