Prebiotic Supplementation in Kidney Transplant Recipients for Preventing Infections and Gastrointestinal Upset: A Randomized Controlled Feasibility Study

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Objectives: Modulating the large intestinal microbiome of kidney transplant recipients (KTRs) may reduce infectious complications. The aim of this study is to assess the feasibility of a randomized controlled trial of prebiotics in reducing infections and gastrointestinal symptoms in KTRs.

(Design) and Methods: Acute KTRs were recruited to a double-blind, placebo-controlled, randomized trial at a single kidney transplant center. Patients were provided with prebiotics or placebo for 7 weeks. The primary outcome was feasibility, defined as recruitment of ≥80% of eligible people within 6 months. Secondary outcomes included adherence and tolerability, participant retention in trial, proportions of participants providing serum and stool specimens, self-reported quality of life, gastrointestinal symptoms, and infection events.

Results: During the 7-week period, 72 patients met eligibility criteria, of whom 60 (83%) consented to participate (mean ± standard deviation age 53 ± 12 years; 62% males). Fifty-six (78%) participants were randomized (27 interventions and 29 controls). Although participants receiving intervention experienced reduced gastrointestinal symptoms (−0.28 [interquartile range, IQR −0.67 to 0.08] vs. −0.07 [IQR −0.27 to 0], $P = .03$), both control and intervention groups were similar in adherence (67% vs. 72%, $P = .36$), tolerability (56% vs. 62%, $P = .64$), quality of life (−0.2 [IQR −0.6 to 0] vs. −0.2 [IQR −0.8 to 0], $P = .82$), and infection events (33% vs. 34%, $P = .83$). Blood and stool samples were collected from ≥90% of participants in both groups.

Conclusions: It is feasible to recruit and retain acute KTRs in a randomized, placebo-controlled trial examining the effect of prebiotics on infections and gastrointestinal symptoms. This study also showed that prebiotics significantly reduced gastrointestinal symptoms.

Keywords: Feasibility Study; Gastrointestinal Intolerance; Gastrointestinal Microbiota; Infections; Kidney Transplantation; Randomised Controlled Trial

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Location-identifying information: Study was undertaken at the Princess Alexandra Hospital kidney transplant ward (Brisbane, Queensland, Australia). Eligible participants were limited to those who received a kidney transplant with the Queensland Kidney Transplant Service.

Ethical approval was granted through the Metro South Human Research Ethics Committee (HREC/2020/QMS/51887) and The University of Queensland Human Research Ethics Committee, and each participant gave written informed consent. This study was registered with the Australian New Zealand Clinical Trials Registry on the 19 June 2018 (ACTRN12618001057279).

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Introduction

KIDNEY TRANSPLANT RECIPIENTS experience infections approximately 6-11 times more frequently than the general population.[1,2] In addition, gastrointestinal symptoms are a frequently reported outcome by kidney transplant recipients, and has been associated with impaired quality of life (QOL) and increased morbidity, healthcare resource utilization, and allograft complications.[3] The increase in gastrointestinal symptoms may be due to a range of factors including donor-derived infections, immunosuppressive therapy, nosocomial infections, and perioperative infections.[4,5] At the same time, there is increasing evidence suggesting that post-transplant, the large intestinal (gut) microbiota of recipients is altered.[6–8] Various factors may influence the structural and functional characteristics of the gut microbiota including age, medications, medical conditions, and diet.[9,10] In kidney transplant recipients, these factors are in turn thought to drive a cascade of metabolic abnormalities, including uremic toxin production, inflammation, immunosuppression as well as insulin resistance, ultimately leading to increased risk and severity of infections.[11,12]

Because the diversity of the gastrointestinal microbiota—and its inherent functionalities—may be modified by diet, nutritional interventions such as prebiotics (food sources that promote the growth of beneficial intestinal micro-organisms), probiotics (live micro-organisms that confer health benefits when ingested), and synbiotics (combined prebiotics and probiotics) have been hypothesized to offer therapeutic opportunities to mitigate infectious complications in transplant recipients.[9,10,13-16] In a small, pilot, randomized controlled study of 43 kidney transplant recipients where participants commenced either probiotics or placebo before surgery and continued for 4 months following transplantation, those randomized to receive probiotics reported a significantly reduced incidence and severity of post-transplant diarrhea, but the results from this study remain unpublished.[17] Furthermore, a meta-analysis of 4 studies (3 randomized controlled trials and 1 historically controlled trial) involving 246 liver transplant recipients has shown that administration of synbiotics resulted in appreciably lower rates of overall infection (relative risk [RR] 0.21, 95% confidence interval [CI] 0.11-0.41, I^2 = 1%), urinary tract infection (RR 0.14, 95% CI 0.04-0.47, I^2 = 0%), and intra-abdominal infection (RR 0.27, 95% CI 0.09-0.78, I^2 = 0%).[16] The limitations of this review were that of moderate heterogeneity of the prebiotic and probiotic interventions, small sample sizes, short follow-up durations, restriction to only liver transplant recipients, inclusion of a nonrandomized controlled trial, and low certainty of evidence.

Given the paucity of evidence supporting the use of prebiotics, probiotics, or synbiotics in reducing infectious complications and gastrointestinal intolerance in kidney transplant recipients, this study explored the feasibility of conducting a randomized, double-blind, placebo-controlled trial of the effect of prebiotic supplementation on the incidence of infections and gastrointestinal symptoms in kidney transplant recipients.

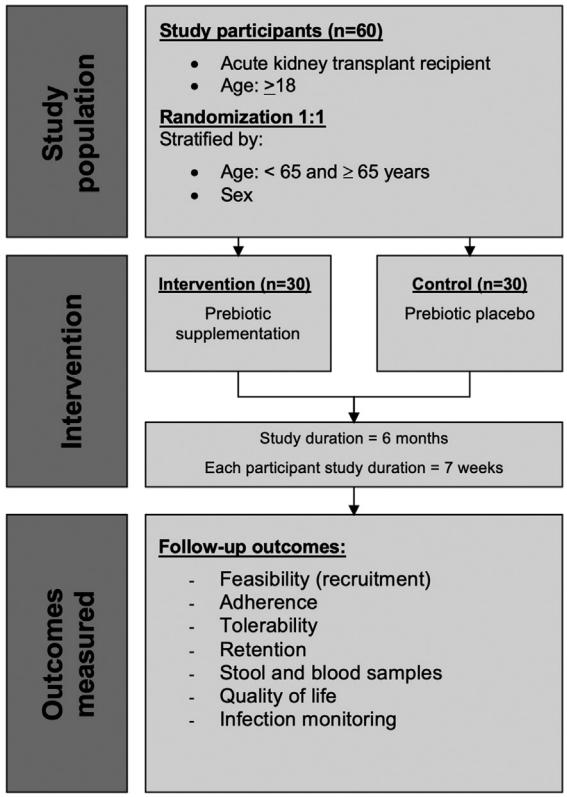

Figure 1. Summary of patient flow throughout the PREBIOTIC trial.

Methods

Study Design

This PREBIOTIC (Prospective Randomized Evaluation of preBiotic supplementation in solId Organ Transplant recipients to prevent Infectious Complications) Feasibility Study was a single-center randomized, double-blind, placebo-controlled, parallel group study (Fig. 1). All participants received either green banana–resistant starch (intervention) or waxy maize (placebo) for 4-6 weeks. Informed consent was obtained from all participants. The clinical and research activities being reported are consistent with the Principles of Declaration of Istanbul as outlined in the "Declaration of Istanbul on Organ-Trafficking and Transplant Tourism," the International Committee of Harmonization, Good Clinical Practice guidelines, and Consolidated Standards of Reporting Trials guidelines.[18,19]

Participants

Participants were recruited between October 22, 2020 and May 11, 2021 at a single kidney transplant center. To be eligible to participate in this trial, participants were those who received a kidney transplant at the same kidney transplant center, aged ≥18 years, and able to provide informed consent. Patients were excluded from participation if they had received radiation to the bowel or had a large bowel resection, had medically diagnosed and active inflammatory bowel disease, were unwilling or unable to meet the requirements of the protocol, and had other medical or social reasons impacting their ability to undertake the trial.

Intervention and Control

The active intervention in this study was green banana–resistant starch. This is a functional food product resistant to small intestinal digestion by the structure of the starch granule. When resistant starch reaches the large intestine, it is hydrolyzed and fermented by the resident bacteria, generating a range of beneficial changes including a laxative effect which promotes regularity, and promotes changes in the large intestinal (gut) microbiota in favor of "beneficial microbes" that provide goods and services that improve gut function and health.[20] The placebo (control) in this study was waxy maize, which is a starch that is readily digested by salivary and pancreatic amylases and the resulting products absorbed in the small intestine, rather than reaching the large intestine.

Study Procedure

This trial consisted of 2 arms: (1) green banana–resistant starch (prebiotic supplement) and (2) waxy maize (matched, identical placebo). Patients were given information about the study while an inpatient in the transplant ward. They were given the opportunity to ask questions, to take the information home with them when they left hospital, and to discuss it with friends, family, or others. They were able to inform researchers about whether or not they wished to participate at one of their routine clinic visits in the early postdischarge period. This ensured that the patients were well, stable, and able to fully consider their participation in the study. On the day that participants were consented and enrolled into the study (usually between day 5 and day 12 following kidney transplantation), they were commenced on study powder (either prebiotic or placebo) and continued this treatment for 7 weeks. The initial dosage was 7.5 g daily for the first 2 weeks, thereafter increasing to 15 g daily for the final 5 weeks of the study. The intervention and control products were powders suspended in water. Participants were encouraged to take their study powder suspension with their breakfast.

All kidney transplant recipients received induction therapy, consisting of basiliximab, tacrolimus, mycophenolate sodium, and methylprednisolone, and perioperative antibiotic prophylaxis with piperacillin/tazobactam. All recipients received maintenance tacrolimus, mycophenolate sodium, and prednisolone, and trimethoprim/sulfamethoxazole for Pneumocystis jiroveci pneumonia prophylaxis.

Participants were randomly assigned in a 1:1 ratio to receive either prebiotic or placebo. The randomization schedule was prepared by a researcher not involved with treatment allocation and involved stratification factors of age (<65 years, ≥65 years) and sex. A blinded allocation list was maintained in an Excel spreadsheet on a secure server in a folder not accessible to trial staff involved in recruitment. Participants, caregivers, treating physicians and surgeons, laboratory staff, and members of the study team were blinded to the treatment.

Outcomes

The primary outcome was feasibility, which was assessed as the ability to successfully recruit 60 patients within 6 months. Feasibility was also assessed as the proportion of eligible patients who agreed to take part in the study.

The secondary outcomes included adherence (if 80% or more of the weight of the prescribed study therapy was consumed by participants), tolerability (proportion of patients who continue the prebiotic supplementation), gastrointestinal symptoms (measured using the Gastrointestinal Symptom Rating Scale [GSRS][21] score between baseline and the end of study), retention (proportion of participants who remained in the PREBIOTIC study for the entire study period), laboratory testing of stool samples (proportion of participants providing 2 stool samples at baseline and at the end of the study), laboratory testing of serum indoxyl sulfate and *p*-cresyl sulfate (proportion of participants providing 2 stool samples at baseline and at the end of the study), QOL (measuring the change in the EuroQol- 5 Dimension (EQ-5D) score between baseline and the end of study), and clinical outcomes (proportion of patients who developed at least one infectious event requiring admission or antimicrobial therapy).[22] A serious adverse event was defined as any event that suggested a significant hazard, contraindication, side effect, or precaution, including fatal or life-threatening events, permanent disability incidents, and experiences requiring in-patient hospitalization. All serious adverse events were documented and reported to the ethics committee for review.

Statistical Analysis

Data were presented as frequencies (percentages) for categorical data, mean ± standard deviation for continuous normally distributed data, or median [interquartile range] for continuous non-normally distributed data. In addition, CIs were presented for all descriptive statistics. Analysis was performed on an intention-to-treat basis. Missing data (planning to impute) were reported formally for all variables under consideration. Baseline characteristics were compared between groups using *t*-test or appropriate nonparametric tests such as the Mann-Whitney test for continuous variables and chi-squared tests for categorical variables. The null hypothesis was rejected at the 0.05 level.

Table 1. Baseline Characteristics of Participants in the Feasibility Study

Characteristics	Overall*, n (60)	Intervention Group, 27 (%)	Control Group, 29 (%)
Age (y), mean ± standard deviation	53.4 ± 11.7	52.9 ± 12.1	54.7 ± 10.9
Male sex	37 (62%)	17 (63%)	18 (62%)
Body mass index (kg/m^2), mean ± standard deviation	28.0 ± 3.9	28.6 ± 4.0	27.3 ± 3.8
Primary kidney disease			
Glomerulonephritis	21 (35%)	11 (41%)	9 (31%)
Genetic kidney disease	6 (10%)	1 (4%)	5 (17%)
Diabetic kidney disease	13 (22%)	5 (19%)	8 (28%)
Reflux nephropathy	6 (10%)	3 (11%)	2 (7%)
Renovascular disease	4 (6%)	2 (7%)	1 (3%)
Other	10 (17%)	5 (19%)	4 (14%)
Graft number			
1	55 (92%)	24 (89%)	27 (93%)
≥2	5 (8%)	3 (11%)	2 (7%)
Ethnicity			
Caucasian	50 (83%)	25 (93%)	22 (76%)
Aboriginal and Torres Strait Islander	2 (3%)	0 (0%)	2 (7%)
Asian	3 (5%)	1 (4%)	2 (7%)
Other	5 (8%)	1 (4%)	3 (10%)
Cytomegalovirus (donor/recipient)			
Positive/negative	12 (20%)	8 (30%)	3 (10%)
Positive/positive	18 (30%)	8 (30%)	9 (31%)
Negative/negative	11 (18%)	2 (7%)	8 (28%)
Immunosuppressant combination			
Tacrolimus + mycophenolate sodium + prednisolone	60 (100%)	27 (100%)	29 (100%)
Induction antimicrobial use			
Piperacillin/tazobactam	60 (100%)	27 (100%)	29 (100%)
Prophylactic antimicrobial use			
Trimethoprim/sulfamethoxazole	60 (100%)	27 (100%)	29 (100%)

*Includes n = 4 (participants not randomized).

The statistical analyses were performed using Stata (version 14, 2016; StataCorp, College Station, TX).

Results

Characteristics of Participants

The PREBIOTIC Feasibility Study commenced recruiting on October 22, 2020 and was completed on May 11, 2021 with follow-up completed on June 18, 2021. The baseline characteristics of the participants are reported in Table 1. Of the 60 participants who consented and completed their baseline visit, 37 (62%) were men and had a mean ± standard deviation age of 53 ± 12 years. The most common kidney failure etiology was glomerulonephritis (35%). Baseline characteristics were well balanced across the 2 groups. The study flow diagram is depicted in Figure 2. The number of missing figures for each of the questions in the GSRS and EQ-5D surveys are found in Supplementary Tables 1 and 2, respectively. All recipients received an immunosuppression regimen of tacrolimus, mycophenolate sodium, and prednisolone. Supplements were not observed to have any effects on immunosuppression dosages or tacrolimus levels. Mycophenolate sodium dosage remained at 720 mg twice daily for all participants throughout the study.

Primary Outcome

During the 7-week study period, 72 patients met study eligibility criteria, of whom 60 (83%, 95% CI 73-91) consented to participate. Fifty-six (78%, 95% CI 66-87) participants were subsequently randomized (27 interventions and 29 controls).

Secondary Outcomes

Participants receiving intervention and control, respectively, displayed similar adherence (67% vs. 72%, $P = .36$), tolerability (56% vs. 62%, $P = .64$), and QOL (median −0.2 [interquartile range, IQR −0.6 to 0]) (Table 2). The median [IQR] change in the GSRS score from baseline to the end of the trial was −0.28 [−0.67 to 0.08] for participants who took intervention and 0.07 [−0.27 to 0] for those who took control ($P = .03$). The proportion of patients who remained in the PREBIOTIC study for the

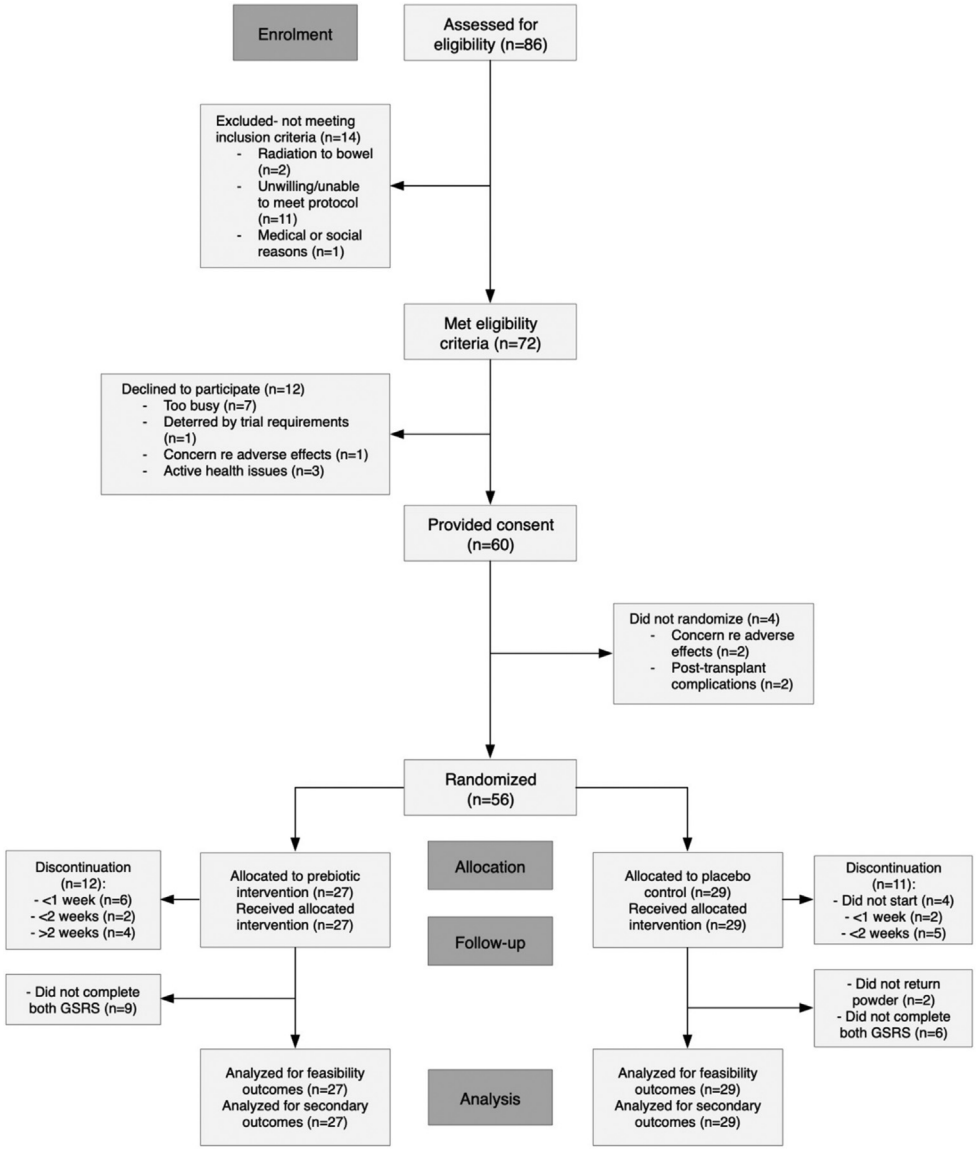

Figure 2. Overall study design.

entire period (retention) was 100% for participants in either treatment group. Blood and stool samples were collected from ≥90% of participants in both the intervention and control groups at both baseline ($P = .96$) and at completion of the study ($P = .60$ and $P = .34$, respectively). The median [IQR] change in QOL during the study was comparable between the intervention group (−0.2 [−0.6 to 0]) and controls (–0.2 [−0.8 to 0]; $P = .82$).

Among the 56 kidney transplant recipients randomized in this study, 19 experienced 22 infectious events over a median follow-up period of 1.8 months (Supplementary Table 3). The proportion of patients who developed at least one infectious event was 33% for participants who took intervention and 34% control ($P = .83$).

Six out of 27 (22%) participants taking intervention were hospitalized and experienced gastrointestinal and skin adverse events. Six out of 29 (21%) participants taking control were hospitalized and experienced cardiovascular, gastrointestinal, and skin adverse events (Supplementary Table 4).

Discussion

This study evaluated the feasibility of conducting a double-blind, placebo-controlled randomized study of the effect of prebiotic supplementation on infections and gastrointestinal symptoms in kidney transplant recipients. Eighty-three percent of eligible participants consented to this study. After randomization, only 78% of eligible participants were willing to participate. The time to recruitment was 7.5 months, slightly longer than the prespecified period of 6 months. Additionally, this study found that those taking prebiotic supplementation experienced fewer gastrointestinal symptoms but

Table 2. Feasibility and Tolerability Outcomes After Randomization

Outcome	Overall	Intervention Group (n = 27)	Control Group (n = 29)	*P*-Value
Feasibility*	56/72 (78%)			
Adherence†	39/56 (72%)	18/27 (67%)	21/29 (72%)	.36
Tolerability‡	33/56 (59%)	15/27 (56%)	18/29 (62%)	.64
Tolerability§: GSRS score change, median (IQR)	−0.15 (−0.42 to 0.04)	−0.28 (−0.67 to 0.08)	−0.07 (−0.27 to 0)	.03
Retention‖	56/56 (100%)	27/27 (100%)	29/29 (100%)	
Laboratory testing¶				.96
Stool testing (pre)	54/56 (96%)	26/27 (96%)	28/29 (97%)	
Stool testing (post)	53/56 (95%)	26/27 (96%)	27/29 (93%)	.60
Laboratory testing**	54/56 (96%)	26/27 (96%)		.96
Blood testing (pre)			28/29 (97%)	
Blood testing (post)	52/56 (93%)	26/27 (96%)	26/29 (90%)	.34
Consumer-centered outcomes††: EQ-5D score change, median (IQR)	−0.2 (−0.6 to 0)	−0.2 (−0.6 to 0)	−0.2 (−0.8 to 0)	.82
Clinical outcomes‡‡	22/56 (39%)	9/27 (33%)	10/29 (34%)	.83

GSRS, Gastrointestinal Symptom Rating Scale; IQR, interquartile range.

*The proportion of eligible patients who agree to take part in the study.

†The proportion of participants adherent to prescribed study therapy (intervention or placebo) over the period of study (80% of prescribed therapy).

‡The proportion of patients who continue the prebiotic supplementation.

§The changes in the Gastrointestinal Symptom Rating Scale score from baseline compared with the score at the time of the completion of the PREBIOTIC trial.

‖The proportion of patients who remain in the PREBIOTIC study for the entire study period.

¶The proportion of participants providing 2 stool samples at designated times (during the first week and between week 4 and week 8 post-kidney transplant).

**The proportion of participants providing 2 blood samples of serum indoxyl sulfate and *p*-cresyl sulfate at designated times (during the first week and week 8 post-kidney transplant).

††The changes in the overall quality of life score (measured by EQ-5D survey) from baseline compared with the score measured at the completion of the PREBIOTIC trial.

‡‡The proportion of patients who develop at least one infectious event.

comparable QOL and infection episodes. Participants demonstrated moderate adherence and tolerance in both groups, and ≥90% of participants were able to provide the required blood and stool samples at the appropriate time points.

The primary outcome of recruiting at least 80% of eligible people to participate in the trial was met, although the early withdrawal of 4 participants between consent and randomization reduced the proportion of patients randomized to 78%. Subsequent retention of participants in the trial was 100% suggesting that participants did not find the study requirements onerous or off-putting. However, the study was not able to be completed within 6 months, primarily due to temporary interruptions caused by the Christmas holiday period and a 2 weeks of COVID outbreak in the hospital in April 2021.[23] Overall, these results suggest that conducting a prebiotic trial in kidney transplant recipients is feasible.

An important finding in this study was that there was a significant reduction in the mean GSRS score in the intervention group compared with controls. Although probiotics and synbiotics have shown to reduce the incidence of diarrhea and abdominal pain in solid organ transplant recipients, there is limited research that has examined the role of prebiotics with respect to its effects on gastrointestinal symptoms in kidney transplant recipients as well as in other settings.[16,17] It is also important to note that there was moderate adherence and tolerability in participants of both the intervention and control group. Thirty percent and 24% of intervention and control participants, respectively, stopped the supplement during the first or second week of the trial, due to poor taste, altered gastrointestinal function following transplantation especially constipation, concomitant medication use, competing activities, and high pill burden early on.

This feasibility study also revealed several considerations and adaptations that can improve a future large-scale trial. First, the generalizability of the study sample could be improved by recruiting participants in other kidney transplant units across Australia and other countries. A second consideration may be to seek participant feedback in terms of the need to alter the texture of the prebiotic and control powders, as this may potentially improve adherence and tolerability. A third adaptation to this study may be to commence the treatment when participants have fully recovered from their transplant surgery, for example, 2 months following the surgery, or perhaps to consider

giving the prebiotic therapy prior to surgery such as that what has been used in another trial, although this remains unpublished.[17] In that context, and in consideration of the fact that 4 participants dropped out between consent and randomization suggests that the consenting process may need to be reviewed and that the time period between consent and randomization may have been too long. At times, it took up an additional 10 days to randomize the patients, due to intercurrent illness and onset of unanticipated rejection.

The strengths of this PREBIOTIC trial include its randomized, double-blinded, placebo-controlled trial design and the fact that we assessed feasibility prior to committing to a full-scale trial. Balanced against these strengths, the PREBIOTIC trial was constrained by a relatively small sample size and study duration thus limiting meaningful analysis of some outcomes such as infection. The single-center trial design also limited generalizability of the study findings. A formal process evaluation to better understand the barriers and enablers was also not undertaken. Furthermore, this current trial did not specifically analyze the gut microbiota changes that occurred as a result of prebiotic supplementation. However, as blood and stool specimens were collected, these samples will be analyzed in the next study to examine whether there are associations between the gut microbiota changes and improvements in gastrointestinal intolerance, and will be done as a future study.

In conclusion, the PREBIOTIC feasibility trial demonstrated that it is feasible to recruit and retain acute kidney transplant recipients in a randomized, placebo-controlled trial of the effect of prebiotic supplementation on infections and gastrointestinal symptoms. Prebiotic supplementation significantly reduced gastrointestinal symptoms and participants demonstrated moderate adherence and tolerability. Approaches to improve adherence and tolerability should be undertaken prior to embarking on a larger scale randomized controlled trial.

Practical Application

Modulating the gastrointestinal microbiota via prebiotics may reduce infections and gastrointestinal symptoms in kidney transplant recipients. A larger scale randomized controlled trial to assess the efficacy and safety of prebiotics in kidney transplant recipients may be warranted.

Credit Authorship Contribution Statement

Samuel Chan: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing, Visualization, Project administration, Funding acquisition. **Carmel M. Hawley:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data curation, Writing – review & editing, Project administration, Funding acquisition. **Elaine M. Pascoe:** Conceptualization, Methodology, Validation, Formal analysis, Data curation, Writing – review & editing. **Christopher Cao:** Formal analysis, Writing – review & editing, Visualization. **Scott B. Campbell:** Conceptualization, Methodology, Investigation, Writing – review & editing. **Katrina L. Campbell:** Conceptualization, Methodology, Validation, Writing – review & editing. **Ross S. Francis:** Investigation, Writing – review & editing. **Rachael Hale:** Validation, Formal analysis, Investigation, Project administration. **Nicole M. Isbel:** Writing – review & editing. **Mark Morrison:** Conceptualization, Methodology, Validation, Writing – review & editing, Funding acquisition. **David W. Johnson:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data curation, Writing – review & editing, Funding acquisition.

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Supplementary Data

Supplementary data related to this article can be found at https://doi.org/10.1053/j.jrn.2022.02.006.

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