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Pain Interference in End Stage Kidney Disease is Associated with Changes in Gut Microbiome Features Before and After Kidney Transplantation

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Abstract

Purpose: Characterize associations between gut microbiome features and pain interference before and after kidney transplantation.

Design: Longitudinal, repeated measures study of 19 living-donor kidney transplant recipients, collecting fecal specimens and pain interference data pretransplant and 3 months posttransplant.

Methods: We assessed fecal microbial community structure with shotgun metagenomic sequencing; we used pain interference scores derived from the Patient-Reported Outcomes Measurement Information System-57.

Results: We measured a reduction in the Shannon diversity index in both groups after transplantation but observed no significant differences between groups at either time point. We did observe significant differences in fecal microbial Bray-Curtis similarity index among those reporting pain interference pretransplant versus no pain interference at 3-months posttransplant ($R = .306$, $p = .022$), and between pain interference groups posttransplant ($R = .249$, $p = .041$). Pairwise models showed significant differences between groups posttransplant in relative abundances of several taxa, including a 5-fold reduction in *Akkermansia* among those with pain interference and a higher relative abundance of taxa associated with chronic inflammation in those with pain interference posttransplant. Functional gene analysis identified two features that were significantly enriched in those with pain interference, including a peptide transport system gene.

Conclusion: Gut microbiota community structure differs between groups with and without pain interference at 3 months after kidney transplantation. Several taxa involved in intestinal barrier integrity and chronic inflammation were associated with posttransplant pain.

Keywords

Kidney transplantation; pain; microbiome; symptom science

Background

Pain, a common debilitating symptom among kidney transplant recipients (KTRs), is among the most common and undertreated symptoms after kidney transplantation (Lambourg et al., 2021). Despite improvements in symptom burden after transplantation, a substantial proportion of KTRs report persistent pain (Tonelli et al., 2011). A recent meta-analysis reported that among KTRs, overall prevalence of chronic pain, defined as pain lasting longer than 90 days, was 46% (Lambourg et al., 2021). The most prevalent and debilitating types of pain among KTRs include musculoskeletal and neuropathic pain (Lambourg et al., 2021). The sources are multifactorial and often associated with the transplant surgery, dysregulation of key biological pathways, bone mineral disorders secondary to decreased kidney function, and comorbidities such as obesity and diabetes (Roy et al., 2020). There is a notable gap in our understanding of the effects and trajectory of pain after kidney transplantation, clinical and environmental exacerbating factors, and potential underlying mechanisms.

Pain interference (PI) measures the consequences of pain on aspects of a person's life, including the extent to which pain prevents participation in social, cognitive, emotional, physical, and recreational activities (Tang et al., 2019). Chronic pain after kidney transplantation has been shown to worsen health-related quality of life (HRQoL) and medication/treatment adherence, reduce productivity at work and school, and increase risk of rejection, graft loss, and mortality (Lockwood et al., 2019; Weisbord, 2016). Compared to pain in other stages of chronic kidney disease, pain after kidney transplantation is poorly characterized (Lambourg et al., 2021). To date, only two studies have examined trajectories of symptom burden, including chronic pain, after kidney transplantation. Taylor et al. (2021) observed that a slight majority of KTRs experienced a decrease in symptom burden over time; however, symptom scores plateaued at 3 months posttransplant. The greatest improvements were seen among younger, non-Latinx White men (Taylor et al., 2021). Amro et al. (2016) assessed symptom burden over 5 years after kidney transplantation and found improvement in some symptoms often associated with uremia; improvement in other symptoms remained ambiguous (Amro et al., 2016). These data support the need for more longitudinal assessments in racially and ethnically heterogeneous populations, using repeated measurements of pain and associated symptoms, to better understand the dynamic nature of pain and potential underlying mechanisms.

Microbiomics, the Brain–Gut Microbiome Axis, and Chronic Pain

The brain–gut microbiome axis, a bidirectional communication pathway between the gut and the brain via a diverse set of pathways, such as the central and enteric nervous systems, is a potential mechanism to explain the relationship between kidney disease and chronic pain (Martin et al., 2018). Symbiotic microbiota in the human gastrointestinal tract provide critical immunologic, metabolic, and endocrine regulatory functions for homeostasis of the human body (Martin et al., 2018; Ursell et al., 2012). Microorganisms in the gut synthesize neurotransmitters and short-chain fatty acids, as well as neuroactive cytokines and chemokines. These chemicals mediate central nervous system homeostasis via the vagal pathway or by crossing the blood–brain barrier directly into the brain (Sherwin et al., 2016).

Recently, researchers observed associations between microbiome features in the gut and nonvisceral chronic pain in fibromyalgia (Minerbi et al., 2019) as well as pain associated with osteoarthritis (Boer et al., 2019; Wang et al., 2017) and chemotherapy (Ramakrishna et al., 2019; Song & Bai, 2021). Microbiome features may differ depending if pain is visceral, inflammatory, or neuropathic. Studies observed decreased relative abundance of the genera *Bifidobacterium* and *Lactobacillus*, and increased *Firmicutes*:*Bacteroidetes* ratios at the phylum level in visceral pain, however, the role of the microbiome in other pain types is emerging (Guo, R., Chen, L. H., Xing, C., & Liu, T.; 2019; Rea, O'Mahoney, Dinan, & Cyan, 2017). Moreover, because most pain studies utilized 16s ribosomal RNA sequencing, little is known about the microbe-associated functional genes that may contribute to pain. Shotgun metagenomic sequencing provides information at the taxonomic level (who is there) and the functional gene level (what they are doing); thus, our study provides additional information on the contribution of functional changes in the gut microbiome on PI.

The dynamic temporal relationships between kidney function, chronic pain, and gut microbiome features in people with end-stage kidney disease who receive a kidney transplant are unknown. Accurately phenotyping pain in end-stage kidney disease, before and after transplantation, and investigating underlying mechanisms is essential to developing novel multimodal patient-centered pain interventions. Such interventions may include modifying gut microbiome features through pre-/probiotics, diet, mindfulness, and physical activity.

Study Objectives

The primary objective of this pilot study was to characterize microbial community structure before and after kidney transplantation and determine relationships between microbial diversity and features (i.e., microbial taxa, functional genes, and pathways) and PI. A secondary objective was to characterize differences in demographic factors, renal function (serum creatinine, serum blood, urea nitrogen, and estimated glomerular filtration rate), and HRQoL between PI groups (with PI vs. without PI).

Methods

Participant Recruitment

We enrolled a heterogeneous sample of adults scheduled to receive a living-donor kidney transplant (LDKT; $N = 19$). Eligibility criteria included (1) being 18 years or older, (2) receiving a kidney transplant from a live donor, (3) speaking English, and (4) being willing to sign informed consent. Exclusion criteria were (1) receiving a multiorgan transplant, (2) a previous transplant, (3) history of autoimmune disease requiring high-dose corticosteroids (e.g., >30 mg/day), (4) history of chronic gastrointestinal disease (e.g., irritable bowel syndrome), (5) history of antibiotic use or infection in the previous 3 months, or (6) being unwilling/unable to collect fecal specimens. Participants were recruited at the Kidney Transplant Clinic at the University of Illinois Hospital & Health Sciences System. The study was conducted in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use's Good Clinical Practice

international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects. Immunosuppression regimens differ based on individuals' immunological risk. Those at high risk receive more potent induction immunosuppression at time of surgery, then receive similar maintenance (long-term) immunosuppression as those at low risk. For induction immunosuppression, study participants at low immunological risk received basiliximab (20 mg on Day 0 and Day 4); participants at high immunological risk received thymoglobulin (dose varied) or alemtuzumab (30 mg once).

The study protocol was approved by the Office for the Protection of Research Subjects at the University of Illinois Chicago (IRB 2017–0534).

Study Design

Using a longitudinal, observational, repeated measures design, we collected patient-reported outcomes surveys (measuring PI and HRQoL) and fecal specimens for microbiome feature analysis (Shannon diversity index, Bray-Curtis similarity index, and differential abundances of microbial taxa and functional genes) from 19 LDKT recipients at two time points: within 4 weeks pretransplant and at 3 months posttransplant. Participants completed the surveys on the same days they collected fecal specimens; they were instructed to answer questionnaires based on how they were feeling at the time. To reduce the incidence of missing pretransplant samples, we included only patients who were scheduled for LDKT, as these surgeries are scheduled in advance.

Measures

Demographic variables included age, sex assigned at birth, race and ethnicity, and education. Clinical variables included origin of kidney disease, dialysis status, type of dialysis, body mass index, and measures of kidney function (serum creatinine, serum blood, urea, nitrogen, and estimated glomerular filtration rate). All demographic and clinical variables were obtained from the electronic medical record.

Pain Interference—PI was measured at two time points (pretransplant and 3 months posttransplant) using the Patient-Reported Outcomes Measurement Information System-57 (PROMIS-57, Version 2.1) (Chen et al., 2018; Tang et al., 2019). PROMIS-57 contains a fixed number of items from seven domains (Pain Intensity, Depression, Anxiety, Physical Function, Fatigue, Sleep Disturbance, and Ability to Participate in Social Roles and Activities), with eight questions per domain plus a 0 to10 numeric rating scale for pain intensity. PROMIS-57 (Version 2.1) has been validated for use in KTRs (Tang et al., 2019). We used the HealthMeasures Scoring Service to convert raw scores into T-scores (HealthMeasures, 2022b) and classified PI into two categories—"pain interference" (pain T-scores 55) and "no pain interference" (pain T-scores < 55)—based on guidelines for interpreting PROMIS scores on the HealthMeasures website (HealthMeasures, 2022a).

Health-Related Quality of Life—HRQoL was measured using the disease-specific Kidney Disease Quality of Life Short Form (KDQoL-SF; Version 1.3). The core of the KDQoL-SF is the generic 36-Item Short Form Health Survey used in the Medical Outcomes

Study (Tarlov et al., 1989), which is a psychometrically sound generic HRQoL instrument. The KDQoL-SF includes eight subscales derived from the generic core, (e.g., General Health, Vitality, Social Functioning, Role-Emotional, and Mental Health) that result in two distinct composite scores: a Physical Composite Score and Mental Composite Score (Hays et al., 1994). In addition to the generic core measures, the KDQOL-SF includes 43 kidney disease-specific items (Vindigni & Surawicz, 2015), resulting in subscales evaluating health-related concerns of people with kidney disease specific (e.g., Symptoms/Problems, Burden of Kidney Disease, Effects of Kidney Disease). Scores are standardized to a range of 0 to 100, with 0 indicating the worst possible HRQoL and 100 indicating the best.

Fecal Sample Collection, Preparation, and Sequencing

Fecal Sampling—After consenting to participate, each participant was trained to use the home-based fecal specimen collection kit, which contained one 9- by 12-inch clasped return envelope, one fecal swab collection and preservation tube with a sterile fecal specimen collection swab (Norgen Biotek Corp., ON, Canada), two feces catchers (Zymo Research, Tustin, CA, United States), one pair of latex-free gloves, one biohazard bag, and a sample request form. The Norgen Biotek fecal sample collection system allows fecal specimens to be collected at home and maintained at room temperature for up to 2 years. Written instructions with images were provided for the fecal collection procedure. Participants were contacted the week before each scheduled study visit to remind them of the upcoming appointment and review the sample collection procedure. Participants collected specimens at home prior to the upcoming pretransplant or posttransplant study visit. Upon arrival at the clinic, specimens were immediately stored at −80 °C until DNA extraction and sequencing were performed.

DNA Extraction, Preparation, and Sequencing—Genomic DNA was extracted from fecal specimens using a Maxwell RSC instrument (Promega Corporation, Madison, WI, United States) for automated nucleic acid recovery. Libraries were prepared using a Nextera library preparation kit (Illumina, San Diego, CA, United States) according to manufacturer instructions. Five control specimens were used. Libraries were pooled and sequenced on an Illumina MiniSeq sequencer; based on the relative abundance of reads generated, specimens were repooled and sequenced on a high-output 300-cycle kit implemented on an Illumina NextSeq500 sequencer. Extraction, library preparation, and sequencing were performed at the Genome Research Core of the Research Resources Center at the University of Illinois Chicago.

Taxonomic Profiling—Raw reads were mapped to the National Center for Biotechnology Information nucleotide database using Centrifuge (Buchfink et al., 2014). Taxonomic annotations for each read were obtained using a least common ancestor algorithm and then summarized across all reads to create counts per taxon. Raw counts were normalized to percentages for relative abundance.

Functional Profiling—Raw reads were mapped to the Swiss-Prot protein database using DIAMOND (Buchfink et al., 2014; The UniProt Consortium, 2016). Gene ortholog annotations were then assigned using the consensus of aligned references and then

summarized across all reads to create counts per ortholog for each sample. Higher-level summaries of ortholog functions were created using the Kyoto Encyclopedia of Genes and Genomes (KEGG) BRITE hierarchical annotation (Kanehisa et al., 2017). Raw counts were normalized to percentages for relative abundance.

Statistical Analyses

Descriptive statistics—including mean (standard deviation), median (range), and frequency (percentage)—were performed for demographic, clinical, and patient-reported outcome variables.

Differential Analyses of Microbial Taxa—Differential analyses of taxa as compared with experimental covariates were performed using the software package edgeR (Version 3.28.1) on raw sequence counts (McCarthy et al., 2012). Prior to analysis, the data were filtered to remove (a) any sequence counts annotated as chloroplast or mitochondria in origin, and (b) taxa that had less than 1,000 total sequence counts, summed across all specimens, or were present in less than 30% of specimens. Data were normalized as counts per million. Trimmed mean of M values (TMM) normalized data were then fit using a negative binomial generalized linear model using experimental covariates, and statistical tests were performed using a likelihood ratio test (i.e., glmFit and glmLRT functions in edgeR). Post hoc pairwise tests were performed using the exactTest function in edgeR. Adjusted p values (q values) were calculated using the Benjamini-Hochberg false discovery rate (FDR) correction (Benjamini & Hochberg, 1995). Significant taxa were determined based on an FDR threshold of 5% (0.05).

Alpha Diversity Analyses—Shannon indices were calculated with default parameters in R using the vegan library (Version 2.5–6) (Oksanen et al., 2018). Prior to analysis, the data were rarefied to a depth of 100,000 counts per sample. The resulting Shannon indices were then modeled with the sample covariates using a generalized linear model assuming a Gaussian distribution. Significance of the model (analysis of variance, or ANOVA) was tested using the F test. Post hoc pairwise tests were performed using the Mann-Whitney test. Plots were generated in R using the ggplot2 library (Wickham, 2009).

Beta Diversity/Dissimilarity Analyses—Bray-Curtis indices were calculated with default parameters in R using the vegan library (Version 2.5–6) (Oksanen et al., 2018). Prior to analysis, the normalized data were square root transformed. The resulting dissimilarity indices were modeled and tested for significance with the sample covariates using the permutational multivariate analysis of variance (PERMANOVA) test (also known as ADONIS). Additional comparisons of the individual covariates were also performed using analysis of similarities (ANOSIM). Plots were generated in R using the ggplot2 library (Wickham, 2009).

Differential Analyses of Functional Gene Orthologs—Differential analyses of functional gene orthologs (i.e., microbial community genes with putative identical functions) as compared with experimental covariates were performed using edgeR (Version 3.28.1) on raw sequence counts (McCarthy et al., 2012). Prior to analysis, the data were filtered to

remove any functional gene ortholog that had less than 100 total sequence counts summed across all specimens or was present in less than 30% of specimens. For functional gene summaries, summarized data were filtered to remove any functional gene group (i.e., pathway, module, or BRITE category) that had less than 1,000 total sequence counts or was present in less than 30% of specimens. As with the differential analysis of bacterial taxa, functional gene orthologs or groups were normalized to counts per million using TMM normalization. The normalized data were fit using a negative binomial generalized linear model using the experimental covariates and tested using a likelihood ratio test. Post hoc pairwise tests were performed using the exactTest function in edgeR. Adjusted p values (q values) were calculated using the Benjamini-Hochberg FDR correction (Benjamini & Hochberg, 1995). Significant functional gene orthologs or groups were determined based on an FDR threshold of 5% (0.05).

Results

Sample Characteristics

The sample was racially and ethnically diverse: 47% Black/African American, 37% White, 11% Latino/Hispanic, and 5% Asian by self-report. Most participants were men and on hemodialysis, and equal proportions received the high-risk immunosuppression protocol (Table 1).

Fecal Microbiome and Pain Interference

We noted a reduction in the Shannon diversity index in all fecal specimens over time regardless of PI status (Figure 1). Using PERMANOVA, which quantifies multivariate community-level differences between groups, we saw statistically significant differences in the Bray-Curtis (dis)similarity indices of individuals with versus without PI. Within this analysis, we observed no significant between-group differences in the Bray-Curtis index of fecal specimens at baseline (pairwise ANOSIM; Figure 2). Significant differences in the Bray-Curtis index were observed among those who reported PI at pretransplant versus at 3 months posttransplant, indicating a shift in community diversity among those with PI ($R = .306$, $p = .022$), but not among those who reported no PI at pretransplant versus at 3 months posttransplant ($R = -.072$, $p = .764$). Moreover, Bray-Curtis indices were significantly different between PI groups at 3 months posttransplant ($R = .249$, $p = .041$).

Taken together, these findings suggest that the community structure of the gut microbiome of participants with no PI was more stable. Pairwise models adjusted for FDR ($p < .05$) showed significant differences in the relative abundances of several taxa between those with PI versus no PI at 3 months posttransplant (Figure 3). Notably, there was a 5-fold reduction of bacteria from the genus *Akkermansia* among participants with PI, versus those without, at posttransplant. Several taxa associated with conditions involving chronic inflammation (e.g., *Mobiluncus*, *Enterococcus*, *Actinotigum*) were enriched among the PI group (Horton et al., 2018; Murphy & Frick, 2013; Schwebke et al., 1996).

Functional Genes

Two functional genes (K19229, sapD-cationic peptide transport system ATP-binding protein; K07076, uncharacterized protein) appeared in greater abundance (greater than 5-fold and greater than 3-fold, respectively) in those reporting baseline PI versus no PI. No between-group differences were noted at posttransplant or in modules or pathways in pairwise comparisons.

Pain Interference, Kidney Function, and HRQoL

Several between-group differences in mean scores of kidney function were observed, though none reached statistical significance. Notably, mean estimated glomerular filtration rates were slightly lower in participants reporting PI (vs. no PI) at baseline and posttransplant (8.65 vs. 11.54 ml/min/1.73 m^2 and 45.76 vs. 58.40 ml/min/1.73 m^2, respectively). Mean serum creatinine was similar in both groups at baseline and posttransplant, and mean serum blood urea nitrogen levels normalized in both groups by 3 months posttransplant (Table 2).

At baseline, 58% ($n = 11$) of participants reported PI. At posttransplant, 21% reported improvements in PI, whereas 37% ($n = 7$) continued to report PI. Differences in HRQoL were observed between those with and without PI. Those reporting PI at baseline were significantly more likely to report lower scores on the subdomain Burden of Kidney Disease prior to transplant, reflecting lower quality of life (19.89 vs. 62.50, $p = .001$). Improvements in KDQoL-SF subscales were seen at 3 months posttransplant in both groups. Statistically significant differences were observed between groups in several KDQoL-SF subdomains, including Symptom/Problems, Effects of Kidney Disease, Burden of Kidney Disease, and Energy/Fatigue. Improvements in the Physical Composite Score were seen among those with no PI. Table 2 summarizes the kidney function and HRQoL measures.

Several PROMIS-57 domains, including Fatigue and Depression, had statistically significant differences in mean scores pre- and posttransplant.

Discussion

This study leveraged the kidney transplant model to better understand the relationship between kidney function, gut microbiome features, and PI in a population with end-stage kidney disease before and after a LDKT. A key finding was differences in multiple microbiome features, specifically the Bray-Curtis (dis)similarity index, and relative abundance of several taxa at the genus level between people who reported PI versus those who did not. These features/microbiota taxa may serve as useful biomarkers or targets for patient-centered interventions.

Pain Interference and Gut Microbiome

Most participants reported PI at baseline, and a nontrivial number of participants reported PI remaining at 3 months posttransplant. Consistent with previous reports (Amro et al., 2014; Kimmel et al., 2008; Nourbala et al., 2007), pain had a significant negative impact on participants' ability to participate in everyday physical and social activities, and a negative impact on HRQoL. Deficits related to pain have serious consequences at the individual

and societal level, as evidenced by the disparate scores between PI groups on the Effects of Kidney Disease subscale of the KDQoL-SF, which captures how much kidney disease interferes with daily life, takes up time, causes frustration, or makes the respondent feel like a burden. Similar differences were seen between PI groups on the PROMIS-57 subscales for Physical Functioning and Satisfaction With Participation in Social Role and Responsibilities. It should be noted that recipients of living-donor transplants often spend less time on dialysis pre-transplant and have lower symptom burden (de Groot et al., 2013; Meier-Kriesche et al., 2004); thus, the effects of PI may have been attenuated in this study. Future studies should include recipients of kidneys from deceased donors.

Research identifying associations between gut microbiota features and posttransplant outcomes is underway. Most of this research centers on transplant-specific outcomes, such as graft loss, immunosuppression dosing, and posttransplant infections (Bartman et al., 2015; Fricke et al., 2014; Lee et al., 2015; Lee et al., 2014; Zaza et al., 2017). One study of 61 KTRs characterized differences in microbial structure of pre- and posttransplant fecal specimens and found that a reduction in diversity of the gut microbiota was associated with organ rejection and posttransplant infections (Fricke et al., 2014). Another study, with 26 participants, found distinct differences in structure and composition of the gut microbiota communities between KTRs who experienced acute rejection, urinary tract infections, and posttransplant diarrhea and those who did not (Lee et al., 2014). For example, at the genus level, *Bacteroides*, *Ruminococcus*, *Coprococcus*, and *Dorea* were significantly lower among individuals with posttransplant diarrhea versus those without. Moreover, multiple studies have shown gut microbiota are involved in immunosuppressant drug metabolism (Lee et al., 2015; Zaza et al., 2017). Despite these important advancements in our understanding of the associations of the microbiome with patient outcomes after kidney transplantation, the relationships between kidney function, gut microbiome features, and PI before and after LDKT were previously unknown.

Generally, reductions in microbiota diversity have been associated with chronic diseases, including those involving pain (Ardalan & Vahed, 2017; Kau et al., 2011). Among this study's participants, a reduction in the Shannon diversity index was noted in all fecal specimens over time regardless of PI status, likely due to prophylactic antibiotics/antivirals, potent immunosuppression, and trauma from the surgical procedure itself. These findings are consistent with previous research (Ahmad & Bromberg, 2016; Ardalan & Vahed, 2017; Lee et al., 2015; Lee et al., 2014). Differences in Bray-Curtis similarity indices, which demonstrate dissimilarity between specimens, were observed in pairwise comparisons between participants with no PI at baseline and those with PI at 3 months posttransplant. We also observed significant differences in beta diversity between PI groups at posttransplant. Taken together, these findings demonstrate that the community structure of gut microbiota differs between KTRs with PI versus those with no PI; this may indicate less resilience of the gut microbiome after transplantation among those experiencing PI.

A key finding of this pilot study was the relationship between the genus *Akkermansia* and PI before and after kidney transplantation: We noted a 5-fold reduction in *Akkermansia* in the PI group versus those without. *Akkermansia* is well-known for its probiotic effects and has been implicated in other pain conditions (Boer et al., 2019; Cruz-Aguliar et al., 2019; Wang

et al., 2017). It plays an important role in mediating systemic inflammation by maintaining the integrity of the intestinal barrier and preventing translocation of neurotoxic metabolites (Anders et al., 2013; Chelakkot et al., 2018). It also is important in regulating tryptophan metabolism along the kynurenine pathway, a key metabolic pathway in the brain–gut microbiome axis (Yin, et al., 2021). Because of its probiotic properties, *Akkermansia* may serve as a target for intervention.

We identified other taxa at the genus level that were at increased relative abundances in the PI group and have been associated with inflammation. *Murdochiella* are gram-positive bacteria that were at greater than 6-fold higher abundance in the PI group. These bacteria have been isolated from patient wounds and produce significant amounts of lactic acid and moderate amounts of acetic, butyric, and succinic acid (Victoria et al., 2022). The genus *Actinotignum* has been identified as a pathogen and implicated for its role in invasive and urinary tract infections (Karu et al., 2016). Interestingly, while the genus *Mobiluncus* is often associated with bacterial vaginosis, its role is not clearly understood. Recent case studies of *Mobiluncus curtisii* bacteremia in men have suggested a possible intestinal origin (Arries & Ferrieri, 2022). Further investigation of these genera as potential mediators of pain in chronic kidney disease is warranted.

Kidney Function and Gut Microbiome

We were unable to detect any statistically significant differences in estimated glomerular filtration rate, serum creatinine, or blood urea nitrogen between PI groups at baseline or 3 months posttransplant. This is consistent with previous studies, and suggests that surrogate markers of kidney function may not correlate with gut microbiome features (Fricke et al., 2014). However, given the small sample size and numerous confounding factors in this population, these findings should be confirmed.

Functional Genes

Only two functional genes were differentially abundant by PI group: K19229 and K07076. K19229 is a cationic peptide transport system ATP-binding protein that is part of a complex that includes sapA (K19226), sapB (K19227), sapC (K19228), and sapF (K19230). Researchers have shown that expression and trafficking of ATP-binding cassette transporters can be modified by pain and/or opioid pharmacotherapy (Yang et al., 2018); more research is needed to understand the role of K19229 in kidney disease. K07076 is annotated as an uncharacterized protein; this makes it hard to determine its role in the microbiome and relationship to PI. The relatively few functional gene differences between groups may reflect functional redundancy in microorganisms in the mammalian gastrointestinal tract (e.g., Ferrer, et al., 2013), leading to greater numbers of differentially abundant features observed in taxonomic analysis.

Limitations

First, the small sample size may not be sufficiently powered to detect statistically significant differences in some variables. However, we did see statistically significant effects between PI scores and several gut microbiome features. Second, factors involved in chronic kidney disease and kidney transplantation are complex, and we could not control for all potential

confounders. However, during the screening process, we controlled for a number of important covariates (e.g., recent antibiotic use) known to affect the microbiome. Finally, we collected no data on diet, an important mediator of the microbiome. Future studies should be designed to simultaneously control for multiple key factors (e.g., diet, age, concomitant medications) that mediate microbiome composition and function.

Conclusion

This study provides data on changes in the gut microbiome as a mechanism for pain before and after kidney transplantation. The results support recent evidence that symptom burden, specifically burden related to PI, remains for a nontrivial number of KTRs and extend previous findings to include the relationship between microbiome features and PI after restoration of kidney function via a LDKT. These findings support the need for a sufficiently powered study in a larger KTR population with high symptom burden (e.g., deceased-donor recipients). Rigorous symptom phenotyping after kidney transplantation is needed. Once the relationship between gut microbiome features and PI is further confirmed, patient-centered interventions to optimize the microbiome can be developed and tested.

Implications for Nursing

These findings may provide motivation for KTRs experiencing pain to participate in lifestyle modification-based interventions (e.g., diet modification, mindfulness, exercise) to promote optimal gut microbiome health to reduce pain. Nurses will play a critical role in developing patient-centered interventions and educational resources to aid KTRs in optimizing their gut microbiome health.

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Clinical Implications:

Findings may motivate kidney transplant recipients to participate in lifestyle interventions that promote gut microbiome health to reduce pain.

Key Practice Points:

- Pain is a common and debilitating symptom among those receiving kidney transplantation, and significantly impairs an individual's ability to participate in and enjoy usual physical and social activities.

- One potential mechanism to explain the relationship between kidney disease and chronic pain is the bidirectional communication pathway between the gut microbiome and the brain that is known as the brain-gut-microbiome-axis (BGMA).

- Several fecal microbiota taxa involved in intestinal barrier integrity and chronic inflammation were associated with pain at 3-months post-transplant.

- The gut microbiome is a modifiable target for patient-centered interventions that involve diet, mindfulness, and physical activity.
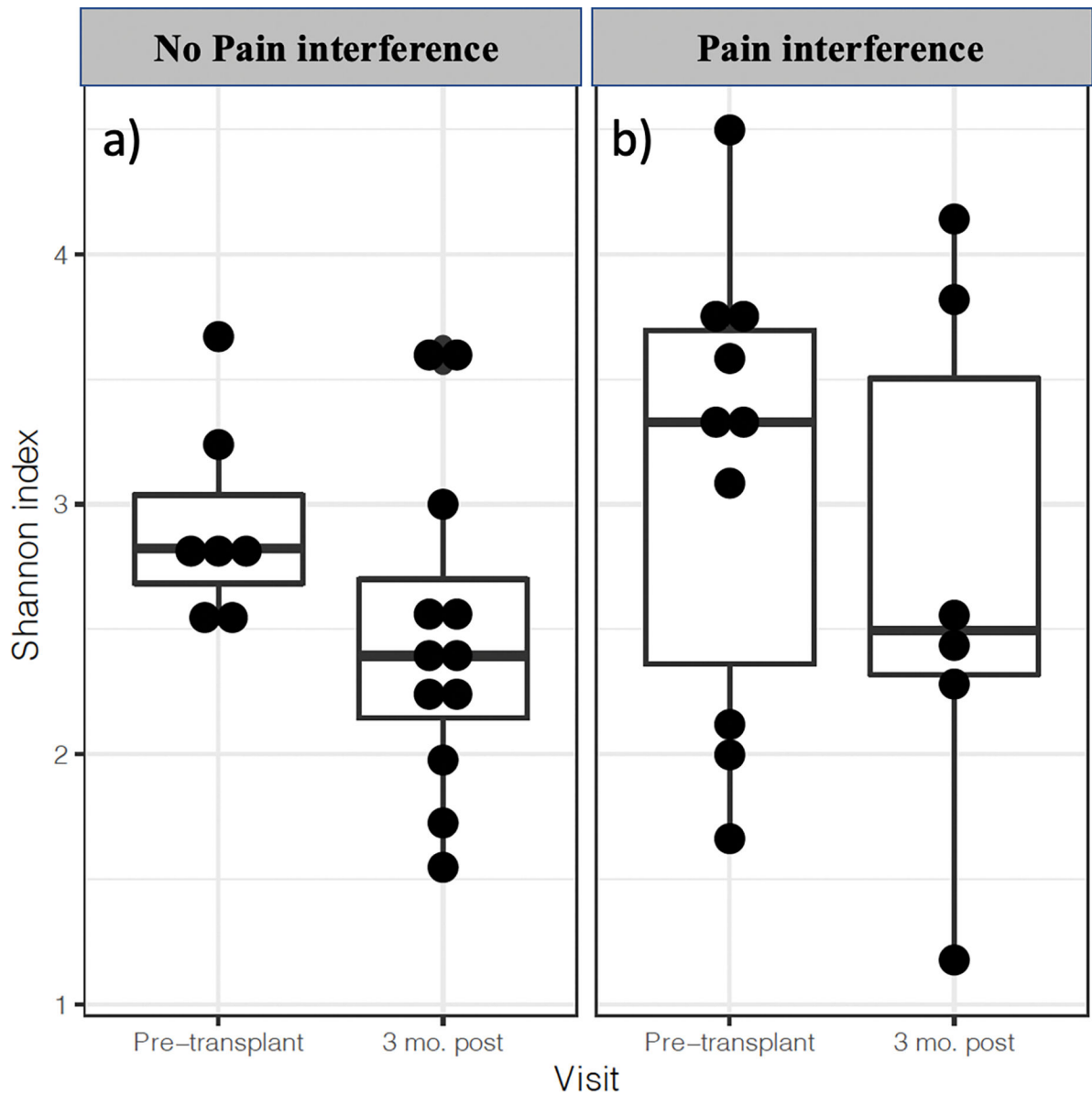
Figure 1.
Shannon diversity index in pain interference group by visit (genus level). We observed reductions in Shannon indices in both groups, though differences were not statistically significant at either timepoint. The median Shannon index and interquartile range, a) for those with no pain interference at baseline vs. 3 month was 2.82 (IQR 2.52–3.67) vs. 2.39(IQR 2.09–2.80) respectively, and b) for those with pain interference was 3.33 (IQR 3.09–3.58) vs. 2.50 (IQR 2.28–3.82), respectively.
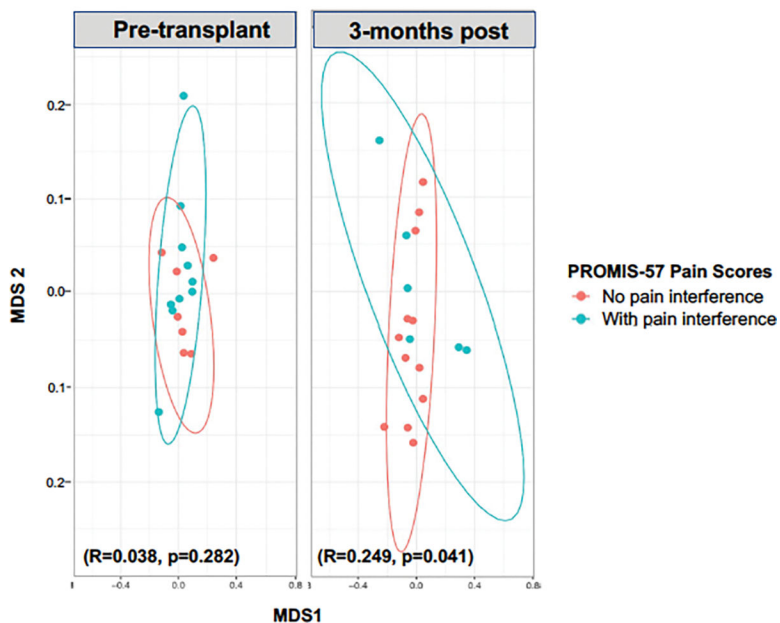
Figure 2.

Multidimensional scaling plot of fecal microbial community in study participants at (a) baseline and (b) 3 months posttransplant. Samples are color coded by Patient-Reported Outcomes Measurement Information System-57 (PROMIS-57) pain scores. *R* and *p* represent results of analysis of similarities (ANOSIM) analysis. Shotgun metagenomic analysis of fecal microbial community data are reported at the genus level.
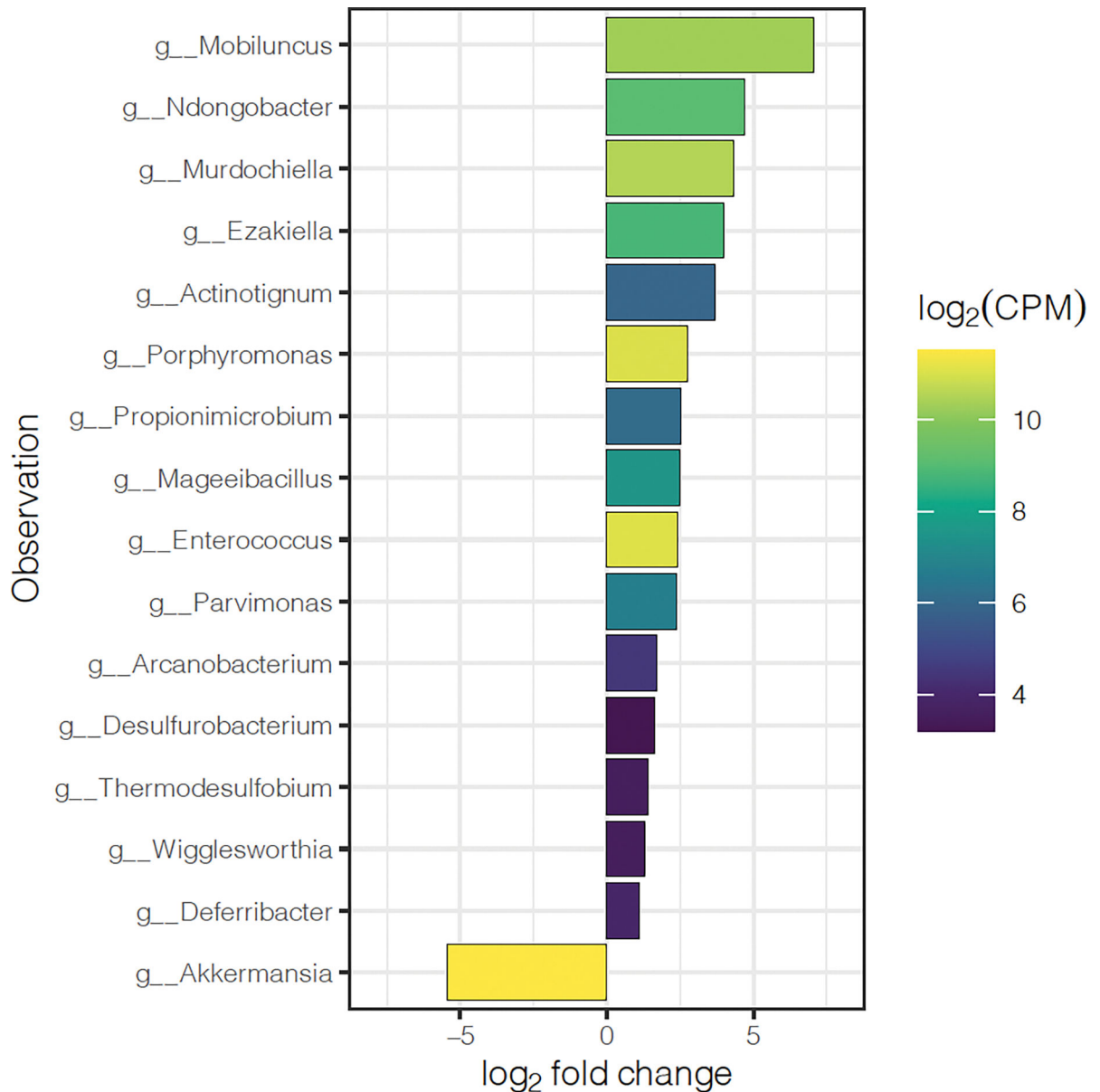
Figure 3.
False discover rate (FDR) corrected pairwise comparison of differential abundances of taxonomic composition in feces among adults reporting with PI vs. no PI at 3-months post-transplant. Statistically significant differences in the relative abundance of several microbial taxa between those with PI vs. no PI at 3 months post-transplant were found. There was a 5-log fold reduction of microbiota from the genus *Akkermansia* among those with PI. A higher abundance of several microbial taxa associated with conditions involving chronic inflammation (e.g. *Mobiluncus, Enterococcus, Actinotigum*) were found in those reporting PI at 3-months.

Table 1.

Sample characteristics by baseline pain interference groups

Variables	Total (n=19)	With pain interference (n=11)	No pain interference (n=8)
Continuous M(SD)			
Age, years	46.47(10.97)	49.27(7.31)	42.63(14,27)
Body Mass Index, kg/m^2	34.90(9.89)	37.29(9.00)	31.62(10.72)
Discrete n(%)			
Sex at birth			
Male	12(63)	7(37)	5(26) [**]
Female	7(37)	4(21)	3(16)
Race/ethnicity			
Black	9(47)	4(21)	5(26)
White	7(37)	5(26)	2(11)
Hispanic/Latino	2(11)	1(5)	1(5)
Asian/PI	1(5)	1(5)	0(0)
Education			
High school or less	5(26)	3(16)	2(11)
Trade school	4(21)	3(16)	1(5)
Some college	5(26)	2(11)	3(16)
College and beyond	5(26)	3(16)	2(11)
Dialysis status (Yes)	13(68)	7(37)	5(26)
Dialysis type			
Not yet on dialysis	7(37)	4(21)	3(16)
Hemodialysis	9(47)	5(26)	4(21)
Peritoneal dialysis	3(16)	2(11)	1(5)
Cause of kidney disease			
Hypertension	4(21)	1(5)	3(16)
Diabetes	5(26)	4(21)	1(5)
Glomerular disease	5(26)	4(21)	1(5)
Other	5(26)	2(11)	2(16)
High immunologic risk	9(47)	4(21)	5(26)

[**]
p<0.01

Legend: M, Mean; SD, standard deviation; cause of kidney disease glomerular disease includes: focal segmental glomerulosclerosis, IgA nephropathy, membranous nephropathy, chronic tubulointerstitial disease. Other includes: unknown etiology, polycystic kidney disease, ectopic kidney, congenital anomaly, Goodpasture syndrome.

Table 2

Pairwise Comparisons of Kidney Function and Health-Related Quality of Life by Pain Interference (N=19)

Variable	Pre-Transplant		3 Months Post-Transplant	
	Pain Interference (n=11)	No Pain Interference (n=8)	Pain Interference (n=7)	No Pain Interference (n=12)
Kidney function M (SD)				
Serum creatinine (mg/dL)	8.04 (0.97)	8.06 (1.67)	1.41 (0.10)	1.74 (0.20)
Blood, Urea, Nitrogen (mg/dL)	54.82 (4.75)	47.0 (6.04)	20.00 (2.48)	20.17 (2.07)
Estimated glomerular filtration rate (mL/min/1.73m2)	8.65 (3.48)	11.54 (1.59)	45.76 (5.16)	58.40 (4.34)
KDQoL-SF domains M (SD)				
Symptoms/Problems	66.55 (18.21)	78.60 (25.65)	77.40 (9.15)	90.47 (8.70) **
Effects of Kidney Disease	46.89 (31.93)	69.92 (23.80)	66.07 (19.80)	90.63 (9.78) **
Burden of Kidney Disease	19.89 (30.25)	62.50 (17.41) **	45.54 (14.46)	82.29 (24.26) *
Sleep	58.41 (23.70)	63.44 (29.88)	50.71 (19.46)	63.96 (18.41)
Overall Health	50.91 (4.56)	65.00 (7.79)	68.57 (5.53)	79.17 (3.58)
General Health	35.91 (5.13)	51.25 (7.06)	57.14 (18.45)	70.83 (16.10)
Energy/Fatigue	34.55 (19.55)	52.08 (17.50)	47.12 (17.76) *	71.25 (18.72) *
SF-12 Physical Health Composite	37.32 (9.16)	43.61 (52.70)	36.40 (5.10) **	48.83 (9.01) **
SF-12 Mental Health Composite	43.91 (9.77)	51.14 (10.60)	51.55 (9.43)	54.86 (5.48)
PROMIS 57 domains M (SD)				
Pain interference	60.10 (1.68)	42.28 (1.58) **	59.01 (1.08)	42.72 (1.36) **
Fatigue	59.67 (2.21)	48.40 (3.59) *	56.63 (2.88)	46.55 (2.79) *
Anxiety	52.28 (3.53)	43.65 (3.68)	47.06 (3.94)	44.88 (2.53)
Depression	47.06 (3.94)	44.88 (2.53)	46.77 (3.66)	43.11 (2.14)
Sleep disturbance	53.93 (3.40)	50.09 (3.18)	55.66 (4.14)	49.13 (2.94)
Physical function	40.88 (2.09)	47.53 (2.04) *	37.97 (1.86)	50.62 (2.21) **
Satisfaction with participation in social roles	47.49 (2.65)	52.04 (3.36)	43.19 (1.87)	55.41 (2.43) **

*
$p < 0.05$

**
$p < 0.001$; higher scores on KDQoL-SF indicate better quality of life; lower scores on PROMIS-57 indicate lower severity of the selected domain, with the exception of physical health and satisfaction with participation in social roles, where lower scores indicate higher severity.

Legend: M, Mean; SD, standard deviation; KDQoL-SF, Kidney Disease Quality of Life Short Form; PROMIS, Patient-Reported Outcomes Measurement Information System.