The Role of Gut Microbiota in Kidney Transplantation

Subjects: Transplantation

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Kidney transplantation improves quality of life, morbidity, and mortality of patients with kidney failure. However, integrated immunosuppressive therapy required to preserve graft function is associated with the development of post-transplant complications, including infections, altered immunosuppressive metabolism, gastrointestinal toxicity, and diarrhea. The gut microbiota has emerged as a potential therapeutic target for personalizing immunosuppressive therapy and managing post-transplant complications.

kidney transplantation gut microbiota immunosuppressive therapy

1. Introduction

Despite advances in surgical techniques, immunosuppressive therapy, and post-transplant surveillance protocols, long-term allograft survival remains challenged by several complications. KTRs can develop T-cell-mediated rejection (TCMR) and/or antibody-mediated rejection (ABMR), potentially leading to allograft failure [1]. Episodes of allograft rejection, immunosuppressive medications, and the accumulation of uremic retention solutes increase the risk of cardiovascular diseases. Moreover, immunosuppressives such as calcineurin inhibitors and corticosteroids induce metabolic complications that increase the risk of developing post-transplant diabetes. KTRs may also suffer from infectious complications, diarrhea, and cancer [2]. Hence the search for strategies that improve these patients' quality of life, graft survival, and life expectancy. The gut microbiota has emerged as a potential target to personalize immunosuppressive therapy and manage post-transplant complications.

2. Uremic Retention Solutes

Gut-derived uremic toxins trimethylamine N-oxide (TMAO), p-cresyl sulfate (pCS), p-cresyl glucuronide (pCG), indoxyl sulfate (IxS), and indole-3-acetic acid (IAA) have been identified to play a role in inflammation, metabolic function, cardiovascular disease, and fibrosis in CKD patients [3]. Several gut bacteria that have been found to increase after KT and are associated with post-transplant complications produce gut-derived uremic toxins precursors. Among these bacteria, *Enterobacteriaceae*, *Enterococcaceae*, *Clostridiaceae*, and *Bacteroides* sp. produce IAA, *E. coli* produces both IAA and indole, and *Clostridium tertium* and *Bacteroides* sp. produce *p*-cresol [4]. Studying these uremic toxins and their association with kidney function and graft outcome is an open area in KTRs.

TMAO plasma concentrations have been associated with an increased risk of graft failure and proposed as a potential biomarker of graft function in KTRs [5]. Other studies have reported increased serum pCS and IxS in KTRs with advanced CKD stages [6]. The treatment with a synbiotic (Probinul Neutro, CadiGroup, Rome, Italy), mainly containing *Lactobacillus* and *Bifidobacterium* spp., decreased plasma *p*-cresol in KTRs after 15 and 30 days of administration. Although the study included a small population (n = 36), the results indicate that gut microbiota interventions could reduce uremic toxicity in KTRs [7].

Liabeuf et al. reported no association between serum IxS levels and adverse outcomes post-transplantation, including graft loss, cardiovascular events, and mortality in a cohort of 311 KTRs [8]. Similarly, a study on the same cohort reported no association between serum-free and total IAA with adverse outcomes of graft loss, cardiovascular events, and death following KT [9].

3. Allograft Function

Delayed graft function is a common post-transplant event that can expose the patient to a longer uremic period and increase the risk of gut dysfunction, systemic inflammation, and allograft rejection [10]. Kim et al. showed that six-month allograft function was associated with a similar pre-transplantation microbial structure between donor and KTR, especially in genetically unrelated pairs such as spousal donor and recipient. The microbial distance in unrelated pairs was a better predictor of the eGFR than the number of human leukocytes antigen mismatches and incompatibility. This may indicate that microbial similarity between donors and KTRs could, to some extent, compensate for the disadvantages of genetic disparity and influence the criteria for living donor selection. Furthermore, a similar microbial structure between donor–KTR could potentially reduce the risk of infections, as microbial dissimilarity was associated with an increased post-transplant infection rate [11].

4. Allograft Rejection

Immune tolerance is crucial to ensure graft function and survival of transplant recipients. T-lymphocyte peripheral tolerance is the primary mode of tolerance to transplanted organs. It eliminates activated T-cell clones in the periphery via apoptosis, develops T-lymphocyte anergy, and suppresses alloreactive T lymphocytes by Tregs [12].

Members of the gut microbiota, such as *Clostridia*, *Bacteroides fragilis*, and *Bacteroides thetaiotaomicron*, have been found to modulate Tregs differentiation [13]. $CD4^+$ Tregs, regulatory B cells, and dendritic cells (DCs) secrete IL-10 that inhibits APC activity and promotes the conversion of T cells into T regulatory type 1 cells (T_R1s). T_R1s are able to suppress the pro-inflammatory activities of both APC and effector T cells. Furthermore, in the presence of IL-10, naive $CD8^+$ T cells can be converted into $CD8^+$ Tregs that inhibit effector T cells. $CD4^-CD8^-$ Tregs induce effector T-cell apoptosis via the CD95-CD95L pathway and by downregulating the expression of DCs molecules CD80 and CD86, consequently inhibiting the ability of DCs to stimulate pro-inflammatory responses. Tolerogenic DCs inhibit effector T-cell proliferation and differentiation into Th1 and Th17 cells [14].

The gut microbiota and derived metabolites can also modulate host inflammatory response through microbiota–cytokine interactions [15]. Schirmer et al. observed that interindividual variation in cytokine response to various microbial stimulations was linked to specific commensal bacteria and microbial functions in healthy individuals. For instance, a higher abundance of *Roseburia* was associated with lower IL-6 levels, and a higher abundance of *Bilophila* and *Odoribacter* was associated with lower TNFα levels. Furthermore, lower IL-17 production was linked to a higher abundance of *Faecalibacterium* and *Atopobium*, whereas *Escherichia*, *Anaerotruncus*, *Coprobacillus*, and *Clostridium* higher abundance was linked to increased production of IL-17. These results suggest that modulating cytokine expression by microbial interventions may have therapeutic value in KTRs. However, microbiota–cytokine interactions should be evaluated in KT, given the stimulus-specific and/or cytokine-specific nature of these interactions [16].

To date, few studies have addressed the potential association between gut microbiota and allograft rejection in KTRs. Wang et al. analyzed the gut microbial community of KTRs with ABMR compared to KTRs who did not develop graft rejection. ABMR was related to lower microbial richness and decreased relative abundance of *Clostridia*, *Paraprevotellaceae*, and *Faecalibacterium*, as well as increased abundance of *Enterococcaceae*, *Coprobacillus*, and *Enterobacter*, among other taxa. These microbial changes are likely associated with ABMR because recipients with a recent history of infection, antibiotic usage, gastric/colon resection, and non-infectious diarrhea were excluded from the study. However, immunosuppressive therapy could have contributed to the alterations observed. *Clostridiales* was proposed as a potential biomarker of ABMR after KT, but further studies are needed to validate its use as a diagnostic tool [17].

Lee et al. also reported alterations in the gut microbiota of KTRs associated with acute rejection (AR). During the first three months post-transplantation, three patients of the studied cohort were diagnosed with ABMR, TCMR, and mixed ABMR-TCMR, respectively. A lower abundance of Clostridiales, Bacteroidales, *Eubacterium dolichum*, and *Ruminococcus,* and a higher abundance of Lactobacillales, *Enterococcus*, *Anaerofilum*, and *Clostridium tertium* characterized the gut microbiota of AR patients compared to those who did not develop AR. It should be noted that AR patients received antibiotic therapy to treat *Clostridioides difficile* infection (CDI), Enterococcus UTI, *Escherichia coli* UTI, and *Klebsiella*/*Serratia* UTI before AR. It is then difficult to determine whether the observed microbial alterations are related to AR or the result of antibiotic therapy [18].

Another study analyzed the pre-and post-transplant rectal microbiota of four KTRs who experienced rejection compared to KTRs who did not experience rejection or other adverse events. A decreased abundance of *Anaerotruncus*, *Coprobacillus*, *Coprococcus*, and an unknown member of *Peptostreptococcaceae* correlated with the development of future rejection events [19]. However, these results require further validation in a larger cohort to assess the potential of gut microbial taxa as biomarkers of rejection events.

5. Immunosuppressants Metabolism

Current clinical guidelines recommend combining immunosuppressive medications as maintenance therapy, including a calcineurin inhibitor and an antiproliferative agent with or without corticosteroids [20]. Recent data

suggest the impact of the gut microbiota on the most prescribed immunosuppressive medications: MMF and TAC.

The use of MMF has been correlated to a lower diversity of the gut microbiome [21], post-transplant diarrhea, and impaired quality of life in KTRs [22]. The gut microbiome can also metabolize MMF, thereby influencing drug dosage. MMF is converted to its active form, mycophenolic acid (MPA), by plasma and tissue esterases and inactivated by hepatic glucuronidation to MPA glucuronide. MPA glucuronide is then excreted in the urine and bile. If secreted into the gastrointestinal tract through the ATP-binding cassette subfamily C member 2 protein, bacteria expressing beta-glucuronidase enzymes can cleave the glucuronic acid (GA) of MPA glucuronide to produce free MPA and GA. The resulting GA is a carbon source for bacterial metabolism, and MPA undergoes enterohepatic recirculation, which has been related to gastrointestinal toxicity [23][24]. Hence, the management strategies for gastrointestinal complications include MMF dose reduction or discontinuation, which can lead to an increased risk of allograft rejection [25].

TAC is a macrolide of the calcineurin inhibitor family that binds to the FK506-binding protein, forming a complex that inhibits calcineurin phosphatase, ultimately blocking T-cell activation. Despite its efficacy in avoiding TCMR and ABMR, TAC decreases eGFR and promotes glucose intolerance, new-onset diabetes, and hypertension [20][26]. TAC has also been associated with gastrointestinal symptoms in KTRs, including diarrhea, nausea, and vomiting [22]. Its antimicrobial activity can disrupt the gut microbial community, and recent data indicate a bidirectional relationship as gut bacteria metabolize TAC.

Lee et al. observed that the fecal abundance of *F. prausnitzii* was positively correlated with the one-month TAC dose required to maintain therapeutic levels in KTRs. This suggested a possible role of *F. prausnitzii* influencing TAC levels, but the underlying mechanisms were not identified [26]. A follow-up study found that *F. prausnitzii* and other commensal bacteria, mainly belonging to Clostridiales, metabolize TAC into a less effective immunosuppressive metabolite (M1). M1 is a C9 keto-reduction product, uniquely synthesized by gut bacteria and 15-fold less immunosuppressive than its parent in inhibiting T-lymphocyte proliferation in vitro. However, the authors observed no correlation between Clostridiales abundance (including *F. prausnitzii*) and M1 production in stool samples from KTRs undergoing oral TAC therapy [27]. In a subsequent study, the group showed active metabolism of TAC in KTRs by evaluating the pharmacokinetics of M1 after oral administration of TAC. M1 was detected within the first four hours of administration, with concentrations reduced by at least five-fold compared to parent TAC. These results could explain the interpatient variability in TAC therapeutic level requirements and suggest that changes in the gut microbiota might impact TAC trough variability [28].

6. Post-Transplant Infection

Urinary tract infections remain among the most frequent complications affecting post-transplant patients [29]. A pilot study reported an increased fecal abundance of *Enterococcus* correlated with the development of *Enterococcus* UTI in KTRs.

Fricke et al. described alterations in the rectal microbiota of KTRs associated with urinary and upper respiratory tract infections during the first six months post-transplantation. A potential role in predicting post-transplant infection events was attributed to *Anaerotruncus* as it significantly decreased in 4 KTRs with infection compared with 14 KTRs without post-transplant adverse events. Nonetheless, the value of these microbial alterations as diagnosis markers requires further evaluation in a larger population [19].

Another study serially profiled fecal specimens from KTRs within the first three months after transplantation. The authors observed 1% *Escherichia* gut abundance associated with the future development of *Escherichia* bacteriuria. Female gender was also a predictor of future *Escherichia* bacteriuria. Likewise, 1% *Enterococcus* gut abundance was associated with the future development of *Enterococcus* bacteriuria, independent from other factors such as gender, antimicrobial treatment, and immune maintenance therapy. The phylogenetic analysis showed a close relationship between the same subject's urine and fecal strains of *E. coli*, *Enterococcus faecalis*, and *Enterococcus faecium*. The similarity of *E. coli* strains was supported by detecting uropathogenic genes and beta-lactams, sulfonamides, and trimethoprim resistance genes in paired urine and fecal specimens associated with *E. coli* bacteriuria. These results suggest that an overgrowth of enteropathogenic bacteria could influence UTI development in KTRs [30].

In a follow-up study, the group found that a high abundance of *Faecalibacterium* and *Romboutsia* was significantly associated with a lower risk of developing *Enterobacteriaceae* bacteriuria and *Enterobacteriaceae* UTI. On the other hand, increased Lactobacillus abundance was associated with an increased risk of developing *Enterobacteriaceae* bacteriuria and *Enterobacteriaceae* UTI [31]. These results are promising for developing personalized UTI treatments such as *Enterobacteriaceae*-reducing probiotics.

Analyzing the previous cohort, the authors suggested a possible protective role of butyrate-producing bacteria in developing respiratory viral infections. A fecal abundance of butyrate-producing bacteria higher than 1% was associated with a decreased risk of developing respiratory viral infections in the first two years post-transplantation and CMV viremia in the first-year post-transplantation [32]. Butyrate has important roles in immunomodulation, maintenance of the intestinal barrier, and protection against bacterial and viral infections. Another study in allogeneic hematopoietic stem cell patients indicated that a high intestinal abundance of butyrate-producing bacteria at the time of engraftment conferred protection against viral lower respiratory tract infections [33]. However, these studies could not determine a causal relationship between butyrate-producing bacteria and protection against respiratory viral infections.

7. Post-Transplant Diarrhea

Post-transplant diarrhea increases the risk of graft failure, death-censored graft survival, and patient death. Despite being a common complication, the etiology of post-transplant diarrhea is not identified in most cases, and it is frequently associated with intestinal drug toxicity if infections are excluded. A retrospective study reported that over 80% of KTRs were diagnosed with unspecified non-infectious diarrhea, with greater incidence in patients following

TAC and MMF combined therapy [34]. Recent data suggest alterations in the gut microbiome of KTRs as a potential non-infectious etiology of post-transplant diarrhea.

In a pilot study, Lee et al. observed a lower gut microbial diversity and a decrease in the relative abundance of *Bacteroides*, *Ruminococcus*, *Coprococcus*, and *Dorea* to be associated with the development of diarrhea within the first-month post-transplantation [18]. Analyzing a different cohort, the group found that the development of post-transplant diarrhea was associated with gut dysbiosis instead of infectious etiologies. The gut microbiota of KTRs with diarrhea was characterized by a decreased abundance of *Ruminococcus*, *Coprococcus*, *Dorea, Faecalibacterium*, and *Bifidobacterium*, as well as an increased abundance of *Escherichia* and *Enterococcus*. The potential role of these taxa on post-transplant diarrhea was also suggested by the gut microbial analysis of two KTRs with a history of CDI and who underwent fecal microbial transplantation (FMT). The patients had persistent diarrhea despite testing negative for *C. difficile* before FMT. After FMT, the resolution of diarrhea correlated with an overall increase in the abundance of the taxa previously identified as significantly lower in diarrheal specimens and an overall decrease in the abundance of the taxa identified as significantly higher in diarrheal specimens [35]. These results indicate that restoring the gut microbial community imbalance could successfully manage post-transplant diarrhea.

A further study by the group reported a lower abundance of *Ruminococcus*, *Anaerostipes*, *Fusicatenibacter*, *Eubacterium*, *Ruminiclostridium*, *Dorea*, and *Bifidobacterium* associated with non-infectious diarrhea episodes in KTRs. Moreover, prolonged diarrhea was associated with higher beta-glucuronidase activity, indicating that the toxicity from the free MPA in the colon could contribute to the diarrhea episodes, though these results require further validation. Four genera were positively correlated with beta-glucuronidase activity: *Subdoligranulum*, *Coprococcus*, *Tyzzerella*, and an unspecified *Erysipelotrichaceae* [36]. These studies denote a potential relationship between the gut microbiota and the development of post-transplant diarrhea up to three months after KT.

8. New Onset Diabetes (NODAT)

NODAT develops in approximately 20% of KTRs in the first year after transplantation and has been identified as an adverse effect of immunosuppressive treatment, including corticosteroids, cyclosporin, TAC, and sirolimus [26][37]. Lecronier et al. observed alterations in the gut microbiota associated with the development of NODAT after KT by comparing pre- and post-transplant fecal samples from KTRs. An increase in *Lactobacillus* sp. relative abundance and a decrease in *Akkermansia muciniphila* were associated with NODAT presentation. The same microbial changes were observed in patients with pre-transplant diabetes but not in patients without diabetes either before or after KT, suggesting a potential role for these taxa in the future development of NODAT. It should be noted that the results were obtained by qPCR of targeted bacterial species. Other taxonomic changes may be revealed through metagenomic analyses. Moreover, other factors could contribute to NODAT presentation, such as immunosuppressive medications and increased body mass index of the patients following KT, because obesity is a

known risk factor for diabetes. Additional studies should validate the possible role of gut microbiota in NODAT development in KTRs [37].

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