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Review Article

# Intestinal microbiota changes after solid organ transplantation: a systematic review

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## ABSTRACT

**Introduction:** The intestinal microbiota may undergo changes after solid organ transplantation. The purpose of this systematic review was to characterize the intestinal microbiota of patients undergoing solid organ transplantation.

**Methods:** MEDLINE, EMBASE and Cochrane Library databases were searched from inception to July 21, 2017. Studies of patients undergoing solid organ transplantation that evaluated changes in intestinal microbiota composition and one of the following outcomes were included: post-transplant weight, new-onset diabetes after transplantation, delayed graft function, acute rejection, graft and patient survival, and post-transplant infections.

**Results:** Out of 765 studies found in this search, two studies (86 patients) fulfilled inclusion criteria. Both studies assessed kidney transplantation recipients, and a reduction in bacterial species diversity after transplantation was observed. Changes in intestinal microbiota were associated with acute rejection in both studies. One study reported diarrhea and urinary infections, while the other one reported urinary and respiratory infections. None of them reported other outcomes of interest.

**Conclusion:** Changes in intestinal microbiota were observed after kidney transplantation, and they were associated with higher incidence of acute rejection and infections in transplant recipients. However, data are still scarce and more studies are needed to evaluate if microbiota changes have an impact on post-transplant outcomes.

***Keywords:*** *Transplantation; intestinal microbiota; outcomes*

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The intestinal microbiota is composed mainly by bacteria, which find a favorable environment for proliferation. Deregulation of intestinal mucosal homeostasis leads to the development of diseases and detrimental conditions to the host[1,2]. These intestinal microbial communities perform some beneficial functions to their hosts, which are divided into three levels: (1) biological, as barriers against pathogenic microorganisms; (2) immunomodulatory, as a stimulus to the local and systemic immune system; and, finally, (3) nutritional and metabolic, involving the fermentation of food products and production of nutrients[3-6].

Changes in the intestinal microbiota have been reported in individuals with obesity and/or metabolic syndrome (MS)[7-9]. Obesity development is associated with specific phylum of bacteria inhabiting the human gut[8,10,11]. Thus, obese individuals may have a higher proportion of Firmicutes and a lower proportion of Bacteroides compared with individuals with healthy weight[8]. Furthermore, some authors have suggested that treatments with emphasis on balancing gut microbiota may be an alternative for obesity treatment[7-9]. Regarding MS, the intestinal microbiota has an important role in metabolic balance, affecting the absorption of glucose and lipids and intestinal motility[7].

Conversely, the intestinal microbiota may influence solid organ transplant outcomes. The gut microbiota of organ transplant recipients is expected to

undergo changes in its composition, as the majority of patients use antibiotics as prophylaxis or treatment of infections during initial hospitalization[12-16]. Since changes in the gut microbiota are associated with metabolic disarrangements in both the obese and the MS population, as described above[7-9], similar effects might be observed in organ transplant recipients. Advances in immunosuppressive therapy have improved post-transplant outcomes in recent decades, increasing both graft and patient survival[17-19]. However, organ transplant recipients continue to show higher mortality than the general population, and this fact is directly related to the increased incidence of cardiovascular disease in the post-transplant period[17,20-26]. Several factors have been associated with increased cardiovascular risk after transplantation, especially the development of MS[27-31]. It is known that weight gain is significant in transplanted patients, affecting 30-50% of these individuals[32-34]. In addition, both obesity and MS are associated with worse outcomes after transplant[34-36].

Few studies have evaluated the composition of the intestinal microbiota in organ transplant recipients. Thus, the objective of this systematic review was to characterize the intestinal microbiota in patients undergoing solid organ transplantation and its possible associations with post-transplant outcomes.

## METHODS

### *Data Sources and Search*

All studies were found using Medical Subject Headings (MeSH) and entry terms (Supplementary material) while searching MEDLINE (via PubMed), EMBASE and Cochrane Library databases, as well as gray literature (conference abstracts), from inception to July 21, 2017. All relevant articles were considered for review regardless of language.

### *Study Selection*

Studies assessing changes in the gut microbiota of transplanted patients (kidney, liver, lung, pancreas or heart transplantation) were included. Bacterial species diversity was defined according to the Shannon index, which analyzes the diversity of categorical data considering heterogeneity, variety, complexity and abundance of bacterial species in the microbiota[37].

Studies with replicated data or pediatric patients were excluded, as well as studies that assessed database populations. Two independent investigators performed study selection, initially by titles and abstracts, and subsequently by full-text assessment. Disagreements were resolved by consensus or a third investigator.

### *Data Extraction and Quality Assessment*

Data extraction was performed by two investigators according to the following data: author's name, year of publication, number of patients included, length of follow-up, demographic characteristics, number of fecal samples, microbiota features and the following post-transplant outcomes: post-transplant weight gain, new-onset diabetes after transplantation (NODAT), delayed graft function (DGF), acute rejection, graft and patient survival, and post-transplant infections (urinary tract, respiratory and intestinal infections). Both reviewers were not blinded to authors, institutions or article journals. The quality of studies was assessed using the Newcastle Quality Assessment Scale[38]. An overall score of 5 or less was considered low quality; 6 to 7 was considered moderate quality; and 8 to 9 was considered high quality. This systematic review is described according to Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines[39].

## RESULTS

Database search identified 765 studies. Of these, 48 studies were duplicated and 680 studies were excluded after an analysis of titles and abstracts. The remaining 37 studies were selected for full-text assessment, and only two of them fulfilled eligibility criteria (Figure 1). Both studies have evaluated the gut microbiota and kidney transplant. Table 1 shows demographic characteristics of the patients included in these studies and Table 2 shows the quality of the studies. Main results are described below.

Lee et al.[40] have assessed 85 fecal samples of 26 kidney transplant recipients. Samples were collected during the first 3 months after transplantation and accounted at least two per patient. The fecal microbial composition was identified by polymerase chain reaction (PCR). Reduced bacterial species diversity, according to the Shannon index, and increased amounts of Proteobacteria were found in post-transplant fecal samples compared with pre-transplant samples ($p = 0.04$). Three patients with acute rejection showed increased number of bacteria from the order Lactobacillales ($p = 0.04$) and a significant decrease in phylum Bacteroidetes ($p = 0.03$) compared with patients without acute rejection. Six patients developed diarrhea in the post-transplant period. These patients had decreased amounts of Bacteroidales, Bacteroidetes, *Ruminococcus* and *Coprococcus* compared with those without diarrhea ($p = 0.007$). Finally, patients with urinary tract infection ($n = 3$) showed increased frequency of the genus *Enterococcus* ($p = 0.005$).

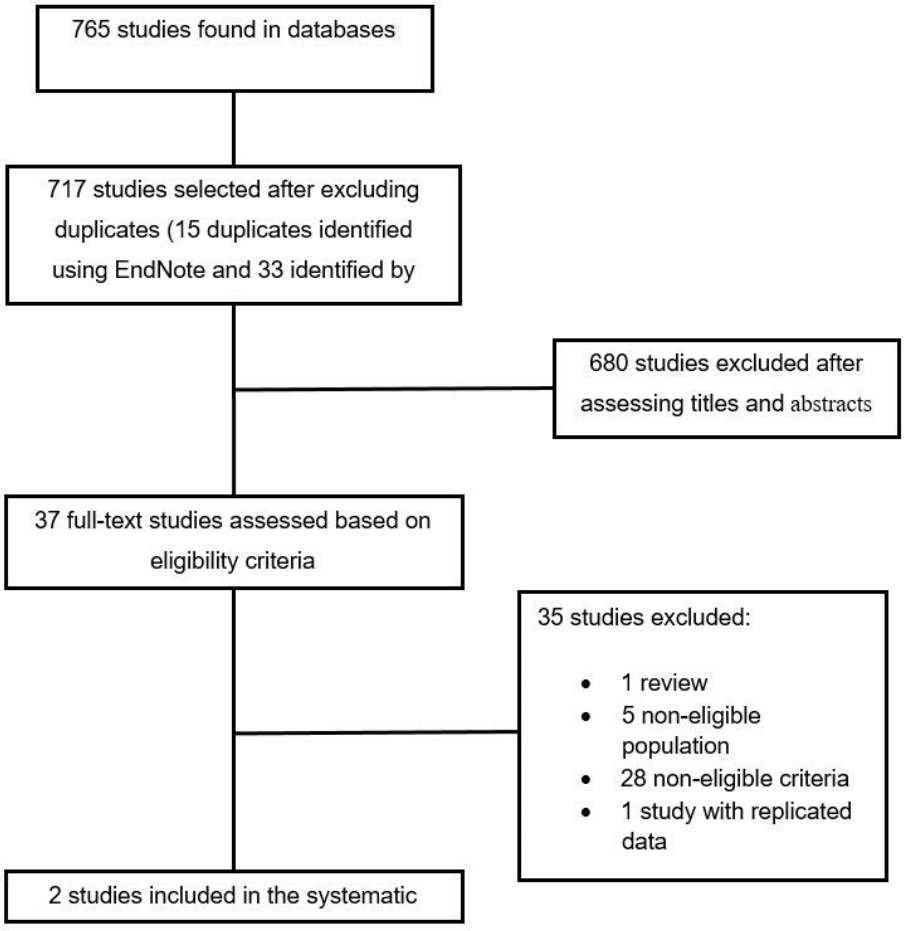


Figure 1: Identification and selection of articles included in the systematic review.

Table 1: Characteristics of patients from the included studies.

| General characteristics | Study | |
|---|---|---|
| | Lee et al.[40] | Fricke et al.[41] |
| Transplant recipients, n (%) | 26 (100) | 60 (100) |
| Men, n (%) | 13 (50) | 38 (63) |
| Women, n (%) | 13 (50) | 22 (37) |
| Age (years) | 56 (46-63) | 58 (30-79) |
| Ethnicity | | |
| White, n (%) | 16 (61) | 36 (60) |
| Hispanic, n (%) | 6 (23) | 0 |
| African American, n (%) | 4 (15) | 24 (40) |
| Type of transplantation | | |
| Living donor, N (%) | 14 (54) | N/A |
| Deceased donor, N (%) | 12 (46) | N/A |
| Organ type | | |
| Kidney, N (%) | 24 (92) | N/A |
| Simultaneous pancreas and kidney, N (%) | 2 (8) | N/A |
| Immunosuppression with tacrolimus | 26 (100) | N/A |
| Perioperative antibiotics | | |
| Cefazolin, n (%) | 21 (81) | N/A |
| Vancomycin, n (%) | 3 (11) | N/A |
| Ampicilin and Sulbactan, n (%) | 2 (8) | N/A |

N/A: Not available.

Table 2: Quality scoring based on the Newcastle-Ottawa Quality Assessment Scale.

| Study (ref) | Selection | Comparability | Outcome |
|---|---|---|---|
| Lee et al.[40] | *** | - | **** |
| Fricke et al.[41] | **** | - | **** |

Ref = reference number. Note: study groups were controlled for age, gender and donor type for assessment of comparability. * = Scores.

Fricke et al.[41] have evaluated 60 patients during the first 6 months after kidney transplant and the composition of fecal microbiota was evaluated by rectal swab. Bacterial species diversity, according to the Shannon index, decreased significantly in the first month after kidney transplant ($p = 0.01$), and this change was maintained until the assessment of the last sample at 6 months. Fermicutes phylum accounted for most bacteria observed in the microbiota of post-transplant patients. Individuals with acute rejection ($n = 4$) had a significant decrease in four bacterial groups, including *Anaerotruncus*, *Coprobacillus*, *Coprococcus* and an unknown member of the *Peptostreptococcaceae* ($p < 0.005$), compared with the 14 patients without acute rejection. Four patients had an episode of respiratory or urinary tract infection and a decrease in the amount of Fermicutes phylum, mainly from the genus *Anaerotruncus* ($p < 0.001$).

## DISCUSSION

This systematic review has revealed that the diversity of bacterial species decreases in the intestinal microbiota of kidney transplant recipients. These alterations in the number of bacteria from were associated with acute rejection, diarrhea and respiratory and urinary infections.

The human microbiota tends to change rapidly during childhood, when food is introduced, and more slowly in adult age[3]. The components of the human intestinal microbiota are constantly being modified by modern lifestyle. It is well known that factors such as host diet, age range, hygiene and use of antibiotics play a relevant role in shaping the intestinal microbiota[5,42,43].

Some key contributing factors are associated with intestinal microbiota changing patterns[44], and the use of antibiotics and immunosuppressive therapy are among the most relevant. These interventions are associated with decreased intestinal bacteria diversity and dysregulation of the immune system, and patients undergoing solid organ transplantation commonly use both. Antibiotic effects depend on composition, dosage, spectrum, route of administration and duration of treatment[45,46]. These medications are not always harmless to the transplant patient and, in most cases, their frequent use is associated with intestinal dysbiosis and production of resistant pathogens[12].

A retrospective cohort study has reported a 50% incidence of infectious episodes in kidney transplant recipients during the first months after transplantation and concluded that the most frequent infection involved the urinary tract, followed by cytomegalovirus, surgical incision and lung infections[47]. Lee et al.[48] have demonstrated that the most commonly used antibiotics for urinary infections are cefazolin and vancomycin. Kidney transplant recipients with infections tend to be older, to use more potent immunosuppression, to have received the graft from a deceased donor and to have had a longer time on dialysis[47]. In addition, female gender, prolonged use of urinary catheter, retransplantation, cold ischemia time and DGF may be risk factors for urinary tract infections[47,48]. Infections remain a recurring problem in transplanted patients, resulting in deaths with functioning graft and triggering complications that affect the quality of life of patients[49]. Based on this information, the use of antibiotics is commonly required post-transplantation, and this may be the most important factor leading to microbiota changes in these patients.

The intestinal microbiota represents a stimulus for the development of the immune system, especially the establishment of lymphoid tissues, activation of neutrophils, induction of IgA and regulation of homeostasis of intestinal T cells (regulatory T cell and T helper), which may interfere in the human susceptibility to infections and immune-mediated diseases[50,51]. When altered, the microbiota shows a reduction in the number of bacteria that favor regulatory cells or an increase in the number of cells that help the induction of immune systems in response to pathogens, leading to infections and diseases in individuals[52]. This deviation from a more tolerant immune system to the activation of effector cells may be the link between post-transplant microbiota changes and acute rejection observed in one of the studies[40,51]. However, further studies should be performed to evaluate the association of the intestinal microbiota with the mechanisms of infection development and acute rejection in transplant patients.

This systematic review has some limitations, including the scant number of studies assessing intestinal microbiota in patients after solid organ transplantation and their small sample size and clinical heterogeneity. Also, another clear limitation was the difference in the methods used in the studies for collecting microbiota samples.

## CONCLUSION

Changes in the intestinal microbiota were observed after kidney transplantation, and they were associated with higher incidence of acute rejection and infections in recipients. However, data are still scarce and more studies are needed to evaluate if microbiota changes have an impact on other metabolic and graft-related post-transplant outcomes.

### *Conflicts of Interest*

The authors declare no conflicts of interest.

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