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REVIEW

Effect of Immunosuppressive Therapy After Liver Transplantation and the Relationship Between Changes in the Gut Microbiome and Graft Rejection

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ABSTRACT

Solid organ transplantation, particularly liver transplantation, necessitates the use of immunosuppressive therapy to prevent organ rejection. However, these agents profoundly affect the gut microbiota, whose altered state can significantly impact transplant outcomes. This review synthesizes current knowledge on the interactions between immunosuppressants and the gut microbiota and explores the mechanisms by which these interactions affect graft survival and rejection. Immunosuppressive drugs, including cyclosporine, tacrolimus, sirolimus, mycophenolate mofetil, prednisone, and azathioprine, are known to cause dysbiosis by decreasing microbial diversity and favoring pathogenic bacteria and fungi. This disruption can lead to increased susceptibility to infections, chronic inflammation, impaired drug metabolism, and direct effects on graft rejection. The review also discusses the potential of modifying the gut microbiota to improve transplant outcomes through dietary interventions, probiotics, prebiotics, and fecal microbiota transplantation (FMT). These interventions aim to restore a healthy microbial balance, enhance immune tolerance, and reduce the incidence of graft rejection. The paper highlights the need for integrated approaches that consider the microbiome's role in transplantation and outlines future directions for research and clinical practice, aiming to optimize the management of transplant recipients. By understanding and manipulating the gut microbiome, new therapeutic strategies could revolutionize transplant medicine, reducing complications and improving the quality of life for recipients.

Keywords: Gastrointestinal microbiome, graft rejection, immunosuppression therapy, liver transplantation.

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1. Introduction

In the complex interplay of human physiology, where solid organ transplantation represents a critical therapeutic strategy for end-stage organ failure, the gut microbiome emerges as a pivotal player influencing immune system responses and the overall success of transplant outcomes [1]–[3].

The human gut microbiome, an intricate ecosystem of microorganisms, has been recognized for its essential role in the development and function of the immune system. It influences systemic immunity and metabolic processes that can alter the host's response to various external stimuli, including transplanted organs [4]–[6]. This review consolidates current understandings from multiple studies that investigate the dynamic interaction between the microbiota and host immune pathways in the context of organ transplantation [7].

Immunosuppressive medications, essential for preventing organ rejection, paradoxically predispose patients to a plethora of complications, notably by altering the gut microbial composition [8]. These drugs disrupt the microbial equilibrium, potentially leading to dysbiosis, which has been implicated in the pathogenesis of infections and even cancer post-transplantation. The altered microbiota can modulate the metabolic and immunological milieu of

the gut, influencing the systemic immune response and organ tolerance [9]–[11].

Recent findings suggest a compelling correlation between gut microbiota profiles and the outcomes of kidney and liver transplants. Specific microbial signatures are associated with a higher risk of allograft rejection, indicating that the microbiome could serve as both a biomarker and a target for therapeutic modulation to improve transplant outcomes [12]–[14].

The mechanisms through which the microbiome affects immune tolerance and rejection are complex and multifaceted. Commensal bacteria can modulate the host immune system through various pathways, including producing short-chain fatty acids (SCFAs) that affect T-cell differentiation and influence the expression of major histocompatibility complex (MHC) molecules on donor organs [15]–[17].

Diet is a major modifiable factor affecting microbiota composition. Post-transplant dietary management can significantly impact the diversity and functionality of the gut microbiota, affecting the host's immune response and the integrity of the transplanted organ [18]. Understanding these dietary effects provides avenues for non-pharmacological interventions to optimize transplant outcomes [19]–[21].

Modifying the gut microbiota through dietary interventions, probiotics, and prebiotics represents a promising avenue to enhance alloimmune tolerance and reduce the incidence of graft rejection. These interventions aim to restore a healthy microbial balance, potentially reducing the need for long-term immunosuppression [22].

The potential of manipulating the gut microbiota to improve transplant outcomes is vast. Future research should focus on identifying specific microbial species that promote immune tolerance. Furthermore, developing microbial-based therapeutics could pave the way for personalized medicine strategies in organ transplantation [23].

Clinically, gut microbiota monitoring could become an integral part of post-transplant care. Regular microbiota assessments can guide immunosuppressive therapy dosages and help predict the risk of rejection or infection, thereby personalizing patient management plans [24].

Despite the promising potential, significant challenges in microbiome research need to be addressed. These include the complexity of microbiome analysis, the variability in microbiota composition among individuals, and the interplay of numerous confounding factors that influence both the microbiota and transplant outcomes [25], [26].

In this sense, the gut microbiome plays a critical and complex role in the success of liver transplants under the influence of immunosuppressive therapy. By understanding and manipulating this intricate ecosystem, we can potentially reduce graft rejection rates and improve the overall efficacy of transplant protocols [27].

This burgeoning field of research offers new insights and tools that could revolutionize the management of transplant patients. This introduction has integrated insights from multiple studies to construct a comprehensive overview of current research on the gut microbiome's impact on transplant outcomes, laying the groundwork for further discussion and investigation within the review article [28].

The primary objective of this review article is to explore and synthesize the current research on the impact of the gut microbiome on immune responses and graft outcomes in the context of solid organ transplantation, particularly under the influence of immunosuppressive therapy post-liver transplantation [10].

This article aims to delineate how modifications in the gut microbiota due to immunosuppressive drugs affect graft survival and rejection rates. Furthermore, it seeks to evaluate the potential of dietary and microbiota-targeted interventions to enhance immunological tolerance and improve overall transplant efficacy [12]–[14].

By consolidating various study findings, this review intends to highlight the gut microbiome as a critical, modifiable factor that could revolutionize transplant protocols and patient management, thereby reducing complications and improving the quality of life for transplant recipients. This comprehensive analysis will provide insights into future research directions and the development of novel therapeutic strategies based on microbiome modulation [16].

2. Methods

The research strategy employed for this study was meticulously designed to encompass an exhaustive review of literature across several distinguished databases known for their extensive collection of medical and scientific peer-reviewed publications. The databases selected for this comprehensive search included PubMed, Scopus, Scielo, Embase, and Web of Science, each renowned for their vast repository of scholarly articles. Google Scholar was also a supplementary resource for accessing the so-called gray literature, which often contains significant studies and reports unavailable in conventional academic journals. The focal point of this research was the intersection of the effect of immunosuppressive therapy after liver transplantation and the relationship between changes in the gut microbiome and graft rejection, guiding the formulation of search parameters. A carefully curated set of keywords was deployed to optimize the search, comprising terms such as "Gastrointestinal Microbiome,"; "liver transplantation,"; "Immunosuppression Therapy," and "Graft Rejection." This strategic combination of keywords was instrumental in filtering the literature to include studies directly pertinent to the research objectives. To ensure a broad yet relevant data collection, the inclusion criteria were designed to be comprehensive, welcoming a variety of study designs, including systematic reviews, case-control studies, cross-sectional analyses, case series, and scholarly reviews. Such diversity in study types aimed to capture a spectrum of evidence and viewpoints regarding the nexus between immunosuppressive therapy after liver transplantation and the relationship between changes in the gut microbiome and graft rejection. The literature review's evaluation and selection process were executed strictly with methodological rigor. This involved a dual-review system, where pairs of reviewers independently evaluated each study's title and abstract for relevance and conformity to

TABLE I: Immunosuppressants in Liver Transplantation

Immunosuppressant	Mechanism of action	Effects on intestinal microbiota and other
Cyclosporine	Binds to cyclophilin to inhibit calcineurin, thereby preventing the transcription of interleukin-2 (IL-2) and other cytokines critical for T cell activation.	Can cause dysbiosis by reducing microbial diversity; promotes overgrowth of pathogenic microbes. Side effects include nephrotoxicity, hypertension, and increased risk of infections which can complicate post-transplant outcomes.
Tacrolimus (FK506)	Inhibits calcineurin similarly to cyclosporine, thereby reducing IL-2 and other cytokines involved in immune activation. Binds to FKBP-12, forming a complex that inhibits calcineurin and thus T-cell activation by preventing IL-2 transcription.	Like cyclosporine, can lead to significant dysbiosis, favoring pathogenic bacteria and fungi. Side effects include nephrotoxicity, neurotoxicity, diabetes, and increased risk of infections, potentially leading to graft rejection.
Sirolimus	Binds to FK-binding protein-12 (FKBP-12) to inhibit the mammalian target of rapamycin (mTOR), a key regulator of cell cycle progression. Binds to mTOR complex and inhibits T-cell proliferation and response to IL-2.	Less impact on the microbiota compared to calcineurin inhibitors; may lead to mild dysbiosis. Side effects include impaired wound healing, proteinuria, and lipid abnormalities which may affect graft health.
Mycophenolate mofetil	Inhibits inosine monophosphate dehydrogenase, crucial for purine synthesis in lymphocytes, thus suppressing both T and B cell proliferation.	Can disrupt the microbiota balance, increasing susceptibility to bacterial infections. Common side effects include gastrointestinal disturbances, leukopenia, and anemia, which could indirectly influence graft rejection.
Prednisone	A corticosteroid that inhibits gene expression for cytokines, adhesion molecules, and other inflammatory agents.	May promote overgrowth of potentially pathogenic bacteria due to immunosuppression; also increases risk of peptic ulcers and bone density loss, complicating overall post-transplant management and possibly influencing graft survival.
Azathioprine	A prodrug that converts into 6-mercaptopurine, inhibiting purine synthesis and thus lymphocyte proliferation.	Impact on microbiota not as well-defined as other agents, but can lead to leukopenia and hepatotoxicity, which may exacerbate graft rejection complications.

the predefined criteria. Discrepancies between reviewers were resolved through consultation with a third independent reviewer to reach a consensus, ensuring the selection was based on solid and unbiased judgment. This detailed and systematic approach to research methodology underpins the reliability and validity of the findings presented and ensures that the conclusions drawn from this study are grounded in a comprehensive and critically evaluated body of scientific evidence related to immunosuppressive therapy after liver transplantation and the relationship between changes in the gut microbiome and graft rejection (Table I).

3. Results and Discussion

In the intricate realm of solid organ transplantation, particularly liver transplants, the gut microbiome plays a pivotal role in modulating the immune response and influencing graft outcomes. While essential for preventing organ rejection, immunosuppressive therapy significantly impacts the intestinal flora, introducing complex interactions that affect both the efficacy and complications associated with transplantation [29]–[31].

Pharmacogenomic variations can affect the pharmacokinetics and pharmacodynamics of immunosuppressants. For example, variations in the CYP450 enzymatic activity can alter the metabolism of drugs like tacrolimus and cyclosporine, impacting drug levels and potentially leading to either subtherapeutic effects or toxicity. Understanding these genetic influences is crucial for personalized medicine approaches in transplantation [32]–[34].

This discussion delves into how the gut microbiota interacts with immunosuppressive drugs, the immunological, biochemical, and microbiological dynamics involved, and the prospective interventions that could enhance patient outcomes by mitigating graft rejection [35].

The genetic background of transplant recipients can influence the composition of their gut microbiota, which in turn affects the metabolism and efficacy of immunosuppressive drugs. Research has shown that certain genetic markers are associated with variations in microbiota diversity and density, which may impact the effectiveness and side effects of immunosuppressive therapies [36]–[38].

Immunosuppressive agents, designed to inhibit the immune system's natural response to foreign bodies, inadvertently alter the gut microbiome's composition. These drugs reduce microbial diversity and can shift the balance towards an overrepresentation of pathogenic bacteria [14]. Reducing microbial diversity is critical as it is associated with increased susceptibility to infections, a significant cause of morbidity and mortality post-transplantation [5]. For instance, a decrease in Firmicutes and an increase in Proteobacteria have been linked to poorer outcomes in transplant recipients [7]–[9].

Gut microbiota-derived bile acids can modulate liver immune responses by influencing various immune cells, including Kupffer cells and hepatic stellate cells. Modified bile acid profiles due to microbiota changes can affect the liver's immunological environment post-transplant and play roles in the acceptance or rejection of the graft [15]–[17].

The gut virome, particularly bacteriophages, can influence the bacterial composition and functionality of the microbiota. Changes in the virome composition have been associated with various diseases, including those affecting transplant outcomes. The interactions between the virome and the host immune system are complex and can significantly impact the success of organ transplants [39].

The fungal components of the microbiota, or the mycobiome, also play roles in immune modulation and have been linked to outcomes in liver transplantation. The balance between bacterial and fungal communities is crucial, as dysbiosis involving fungal overgrowth (e.g., Candida species) can lead to severe complications in immunocompromised hosts [40], [41].

Integrating microbiota management into routine care involves not only monitoring and modifying bacterial populations but also considering virome and mycobiome interactions. This approach could lead to more comprehensive strategies that minimize complications and improve long-term graft survival [42].

The interaction between the gut microbiota and the immune system is mediated through various mechanisms. Microbiota-derived metabolites such as short-chain fatty acids (SCFAs) are essential in maintaining gut integrity, modulating immune responses, and promoting a tolerogenic environment crucial for the transplanted organ's survival [3], [4]. These SCFAs, particularly butyrate, propionate, and acetate, influence the differentiation of T-cells, promoting regulatory and anti-inflammatory profiles that can decrease graft rejection [43].

SCFAs, primarily butyrate, propionate, and acetate, produced by bacterial fermentation of dietary fibers, have significant immunomodulatory effects. They enhance regulatory T cell functions and can promote a more tolerogenic immune environment conducive to transplant tolerance [44]. These metabolites also strengthen the gut barrier function, reducing bacterial translocation and systemic inflammation, which are critical in preventing acute and chronic graft rejections [36]–[38].

Furthermore, the gut microbiota influences the expression of major histocompatibility complex (MHC) molecules in intestinal epithelial cells and immune cells. These molecules are vital for presenting antigens to immune cells, a process intricately linked with developing tolerance or rejection of transplanted organs18. Alterations in the gut microbiota due to immunosuppressants can lead to an imbalance in MHC molecule expression, potentially triggering an immune response against the transplanted organ [44].

Addressing these interactions through targeted interventions can significantly improve transplant outcomes. Probiotics, prebiotics, and dietary modifications are among the most promising approaches [30]–[32]. Probiotics help restore the balance of the gut microbiome by introducing beneficial bacteria, which can outcompete pathogenic bacteria and support a healthy immune system. Studies have shown that probiotics can reduce the incidence of infections in liver transplant patients and improve overall outcomes [45].

Prebiotics, which are non-digestible fibers that stimulate the growth of beneficial bacteria in the colon, also play a crucial role. By enhancing the growth of bacteria that produce SCFAs, prebiotics can help maintain gut integrity and modulate the immune system to favor tolerance, thereby reducing the risk of graft rejection [46].

Dietary management is equally critical. The type of diet affects the composition of the gut microbiota. High-fiber diets promote a diverse and stable microbiome supporting a healthy immune system33. In contrast, diets high in fat and sugar can lead to dysbiosis, which is detrimental to transplant outcomes. Nutritional interventions aimed at optimizing fiber intake and reducing unhealthy fats and sugars could thus benefit transplant recipients [47].

Additionally, novel therapeutic approaches such as fecal microbiota transplantation (FMT) are under investigation. FMT involves the transfer of stool from a healthy donor to the patient to alter the gut microbiome directly. Preliminary studies have shown promising results in reducing complications and improving the longevity of the transplanted organ [48].

Clinically, regular monitoring of the gut microbiota through non-invasive tests such as stool samples can provide valuable information on the transplant recipient's health4. Adjustments to immunosuppressive therapy based on microbiota assessments could personalize treatment plans and potentially reduce the side effects associated with these drugs [19].

The long-term effects of reduced diversity in the gut microbiota on transplant recipients are profound and multifaceted, significantly impacting both the immune system's functionality and the individual's overall health [35]. A less diverse microbiome often entails a weakened barrier against pathogenic organisms, leading to an increased rate of infections, including opportunistic infections, which are significant causes of morbidity and mortality in transplant patients [34].

Furthermore, reduced microbial diversity is associated with dysbiosis, which often triggers and sustains inflammation throughout the body. This chronic inflammation can lead to systemic issues such as inflammatory bowel disease (IBD) and potentially foster conditions that may result in graft rejection [10]. Additionally, the microbiota plays a crucial role in metabolizing many drugs, including immunosuppressants [13].

Altered microbiota may affect the metabolism and efficacy of these drugs, requiring adjustments in dosing that can complicate post-transplant management. Moreover, a healthy and diverse microbiota helps to maintain a balanced immune response; imbalances due to reduced diversity can lead to an increased incidence of acute and chronic graft rejection [40]. Disruptions in metabolic pathways influenced by the gut microbiota can lead to obesity, type 2 diabetes, and other metabolic syndromes, risk factors for cardiovascular diseases [18]–[20].

Fecal Microbiota Transplantation (FMT) can be a viable option for transplant recipients but with specific criteria and precautions. FMT is more likely to be considered for patients who experience severe dysbiosis, which conventional probiotics or dietary adjustments cannot manage [44].

Rigorous screening of fecal material for pathogens is crucial to avoid introducing new infections to the immunocompromised host. The state of immunosuppression in a transplant recipient must be carefully managed when considering FMT, as altering the microbiota can potentially impact immune system behavior [15]. Additionally, FMT must be performed under strict clinical oversight, following guidelines that consider the procedure's ethical implications and clinical safety [20].

Specific dietary changes can help optimize the gut microbiota and improve outcomes for transplant recipients. Increasing fiber intake by consuming a high-fiber diet enhances the growth of beneficial bacteria such as Bifidobacteria and Lactobacilli.

Sources include fruits, vegetables, legumes, and whole grains [28].

Reducing the intake of refined sugars and saturated fats can decrease the proliferation of pathogenic bacteria that thrive on these foods. Incorporating fermented foods like yogurt, kefir, sauerkraut, and kombucha introduces beneficial probiotics directly into the digestive system, helping to maintain a healthy microbial balance [38].

Additionally, foods rich in prebiotics, such as garlic, onions, bananas, and asparagus, provide nutrients that promote the growth of healthy bacteria in the gut. Foods containing polyphenols, found in berries, nuts, and green tea, have also been shown to increase microbial diversity by promoting the growth of beneficial bacteria [44]–[46].

By implementing these dietary strategies, transplant recipients can foster a richer, more balanced gut microbiota, which supports immune function, reduces the risk of infection and rejection, and promotes better health outcomes post-transplant [3]. These interventions, along with careful medical supervision, form a comprehensive approach to managing the health of transplant recipients through the modulation of the gut microbiome. This integrative approach is essential for enhancing immune tolerance, reducing the risk of rejection, and improving transplant recipients' longevity and quality of life [37]–[39].

Future therapies could include the use of next-generation probiotics (engineered bacterial strains with specific beneficial properties) and synbiotics (combinations of probiotics and prebiotics designed to enhance microbial colonization and benefits). These advanced formulations could more effectively restore microbiota balance and support immune regulation in transplant recipients [48].

4. Conclusion

In conclusion, the interplay between the gut microbiota and immunosuppressive therapy is a critical factor in the outcomes of liver transplants. Through a better understanding of this relationship and the implementation of targeted interventions such as probiotics, prebiotics, dietary modifications, and potentially FMT, it is possible to significantly improve the survival and quality of life of transplant recipients.

Future research should continue to unravel the complex interactions at play and develop integrative approaches considering the gut microbiome as a central element in transplant medicine. These efforts will enhance our understanding and pave the way for innovative treatments that could revolutionize the field of transplantation.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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