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ASSOCIATION BETWEEN INTESTINAL MICROBIOTA AND TYPE 2 DIABETES MELLITUS: MECHANISMS, IMPACT AND THERAPEUTIC APPLICATIONS

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Abstract: The gut microbiota plays a crucial role in the metabolic and inflammatory modulation associated with Type 2 Diabetes Mellitus (T2DM). This study reviewed recent evidence on the relationship between gut dysbiosis and the development of T2DM, exploring interventions based on microbial modulation. Using a literature review with PVO criteria, 31 articles published between 2019 and 2024 were selected from PubMed. The results indicate that intestinal dysbiosis, characterized by a reduction in butyrate-producing bacteria and an increase in inflammatory metabolites such as LPS, contributes to insulin resistance and systemic inflammation. Therapeutic interventions, such as the use of probiotics, prebiotics and fecal microbiota transplantation (FMT), have shown potential to restore eubiosis, improve insulin sensitivity and glycemic control. However, challenges such as individual variability in responses, lack of standardization and lack of longitudinal studies limit the practical implementation of these approaches. It is concluded that microbial modulation has emerged as an innovative and promising approach to the management of T2DM, especially when combined with personalized strategies and diets rich in bioactive compounds. However, robust research is needed to validate its long-term efficacy and safety in order to optimize the clinical benefits and transform the treatment of T2DM.
Keywords: intestinal microbiota, dysbiosis, Type 2 Diabetes Mellitus, microbial modulation.

INTRODUCTION

The role of the gut microbiota in human health has attracted increasing interest in recent decades, particularly in metabolic conditions such as Type 2 Diabetes Mellitus (T2DM). Recent studies highlight how gut dysbiosis is associated with chronic inflammatory processes, insulin resistance and metabolic alterations that contribute to the development and progression of T2DM. According to Sikalidis and Maykish (2020), the gut microbiota plays a crucial role in metabolic homeostasis, directly influencing metabolic health through bacterial metabolites such as short-chain fatty acids (SCFAs). This connection suggests that modulating the microbiota may represent a promising approach to preventing and managing T2DM (Garcia-Gutierrez *et al.*, 2024).

The composition of the microbiota in individuals with T2DM is often characterized by an increase in the Firmicutes/Bacteroidetes ratio and a reduction in butyrate-producing species such as Faecalibacterium prausnitzii and Roseburia (Ahmad *et al.*, 2024). In addition, bacterial metabolites such as lipopolysaccharides (LPS) and trimethylamine-N-oxide (TMAO) are implicated in systemic inflammation and insulin resistance (Adeshirlarijaney; Gewirtz, 2020). For Iatcu, Steen and Covasa (2022), these microbial imbalances can contribute to chronic complications associated with T2DM, such as increased intestinal permeability and systemic inflammation. Despite advances, there is controversy over the effectiveness of microbiota-based interventions, such as fecal transplantation and the use of prebiotics, due to variability between populations and regional factors (Ahmad *et al.,* 2024).

Although the evidence points to the importance of the intestinal microbiota in T2DM, the causal relationship has not yet been fully elucidated. According to Wu *et al.* (2023), there is a lack of longitudinal studies validating the efficacy of therapeutic strategies based on microbial modulation. In addition, the interaction between diet, genetics and microbiota remains an under-explored area. This study seeks to fill these gaps by gathering recent data that reinforce the relevance of the microbiota as a therapeutic target in the management of T2DM (Zhou *et al.,* 2022).

Research indicates that dietary interventions rich in bioactive compounds, such as polyphenols and fiber, can promote eubiosis and improve metabolic outcomes in patients with T2DM (Sharma; Jaiswal; Ravindra, 2022). In addition, probiotics and prebiotics have shown potential in restoring microbial diversity and reducing inflammatory markers (Bielka; Przezak; Pawlik, 2022). For Iatcu, Steen and Covasa (2022), strategies such as faecal microbiota transplantation (FMT) have shown promising results in reversing insulin resistance and improving quality of life, although they still face challenges in terms of standardization and safety. However, studies such as those by Garcia-Gutierrez *et al.* (2024) point out that the effectiveness of these interventions varies according to individual factors, such as microbial profile and lifestyle.

Thus, this study provides a critical analysis of the literature, evaluating emerging interventions and highlighting future directions for a personalized approach to the management of T2DM. The aim is to synthesize the existing evidence to provide a solid basis to support the use of microbial modulation as an effective approach in the management and prevention of T2DM, contributing to the development of personalized interventions that maximize the clinical benefits of this emerging therapy.

METHODOLOGY

This is a literature review developed according to the criteria of the PVO strategy, which stands for: population or research problem, variables and outcome. This strategy was used to develop the research question "How does the intestinal microbiota influence the development and progression of Type 2 Diabetes Mellitus, and what are the potential therapeutic applications for modulating the microbiota in this context?". The searches were carried out using the PubMed - MEDLINE (Medical Literature Analysis and Retrieval System Online) databases. The search terms were used in combination with the Boolean terms "AND" and "OR", using the following search strategy: (gut microbiota) AND (dysbiosis) AND ((type 2 diabetes mellitus) OR (T2DM)). From this search, 377 articles were found, which were then submitted to the selection criteria. The inclusion criteria were articles in English; published between 2019 and 2024 and which addressed the themes proposed for this research, review-type studies, meta-analysis and randomized clinical trials. The exclusion criteria were: duplicate articles, available in abstract form, which did not directly address the proposal studied and which did not meet the other inclusion criteria. After applying the search strategy to the database, a total of 55 articles were found. After applying the inclusion and exclusion criteria, 31 articles were selected from the PubMed database to make up this study's collection.

DISCUSSION

COMPOSITION OF THE INTESTINAL MICROBIOTA AND METABOLIC HEALTH

The gut microbiota is predominantly composed of four main bacterial phyla: Actinobacteria, Bacteroidetes, Firmicutes and Proteobacteria. Among them, the ratio of Bacteroidetes to Firmicutes emerges as an important marker of metabolic health (Woldeamlak; Yirdaw; Biadgo, 2019). In obese individuals, a relative increase in Firmicutes and a decrease in Bacteroidetes is observed, indicating that changes in this ratio can directly influence carbohydrate metabolism and the expression of obesity-related genes (Martínez-Lopez *et al*., 2022).

In addition, a reduction in butyrate-producing bacteria, a short-chain fatty acid with anti-inflammatory and intestinal barrier-protecting properties, is associated with the development of T2DM. In these individuals, the presence of Lactobacilli and opportunistic pathogens is often increased (Woldeamlak; Yirdaw; Biadgo, 2019; Martínez-Lopez *et al*., 2022). Reduced microbial diversity in patients with T2DM, characterized by the loss of beneficial bacteria and an increase in opportunistic pathogens, reinforces the association between gut dysbiosis and insulin resistance (Liu *et al*., 2023). Studies indicate that this loss of microbial diversity contributes significantly to the development of T2DM (Liu *et al*., 2023; Gradisteanu Pircalabioru *et al*., 2022).

MICROBIOTA AND INFLAMMATION

Chronic low-grade inflammation, mediated by lipopolysaccharides (LPS) from Gram-negative bacteria, plays a central role in the pathogenesis of T2DM. These LPS activate pattern recognition receptors, such as TLR-4, which contribute to insulin resistance, especially in high-fat diets (Cani *et al*., 2019).

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For Kumar *et al*. (2022), intestinal dysbiosis is strongly associated with increased systemic inflammation in patients with T2DM. Microbial alterations promote the translocation of LPS into the bloodstream, activating pro-inflammatory pathways that aggravate insulin resistance. This process highlights the microbiota as a key mediator of chronic inflammation in T2DM (Kumar *et al*., 2022).

Short-chain fatty acids (SCFA), produced by intestinal bacteria, play significant roles in modulating inflammation and maintaining metabolic homeostasis. While butyrate is essential for intestinal mucosal integrity and protection against inflammation, acetate and propionate modulate the inflammatory response and insulin sensitivity (Xu, *et al*., 2024). These metabolites have distinct effects on lipid and glucose metabolism and are essential for intestinal health (Ballan; Saad, 2021).

Therapeutic interventions using probiotics and prebiotics have also shown potential to reduce chronic inflammation and improve insulin sensitivity. Prebiotic supplementation, for example, contributes to a more balanced microbial composition and a less intense inflammatory response in individuals with T2DM (Huda; Kim; Bennett, 2021).

THERAPEUTIC INTERVENTIONS

Studies indicate that modulating the intestinal microbiota through prebiotics, probiotics and synbiotics shows promising results in the management of T2DM. Probiotic supplementation has been shown to be effective in reducing glucose and glycated hemoglobin levels (Liu *et al.* , 2024), although results from clinical trials are sometimes inconclusive, reinforcing the need for further studies into the efficacy of different probiotic strains (Ayesha, 2023; Baars, 2024). Prebiotics have been shown to promote the growth of beneficial bacteria, such as Bifidobacterium, improving glucose tolerance in animal models (Woldeamlak; Yirdaw; Biadgo, 2019). (2023), strategies based on probiotics and prebiotics have shown promising results in restoring microbial diversity and reducing inflammatory markers. Supplementation with Lactobacillus and Bifidobacterium has been effective in improving insulin sensitivity and glycemic control in patients with T2DM. These findings reinforce the importance of interventions that promote eubiosis for metabolic management (Wang *et al*., 2023).

Metformin, a conventional treatment for T2DM, has also been associated with beneficial changes in the microbiota, including an increase in the population of Akkermansia muciniphila, a bacterium with positive effects on glycemic control (Martínez-Lopez *et al*., 2022). However, antibiotic therapy, such as the use of vancomycin, has shown controversial effects, including reducing the abundance of Firmicutes and improving glucose tolerance in mice, while results in humans remain uncertain (Martínez-Lopez *et al*., 2022).

DIET AND FECAL MICROBIOTA TRANSPLANTATION (FMT)

Diet plays a crucial role in modulating the gut microbiota, with significant impacts on host metabolism. However, dietary responses vary between individuals, highlighting the need for personalized approaches (Ayesha, 2023). According to Vitetta, Gorgani, Vitetta and Hendson (2023), the combination of fiber-rich diets and fecal microbiota transplantation (FMT) has significant potential in modulating the gut microbiome in individuals with T2DM. These interventions not only improve microbial diversity, but also promote the production of beneficial metabolites, such as short-chain fatty acids, contributing to the control of insulin resistance and the reduction of inflammation (Vitetta, Gorgani, Vitetta, Hendson, 2023).

Fecal microbiota transplantation (FMT) has been explored as a promising therapeutic strategy, showing potential to restore the microbiota and improve insulin sensitivity in patients with T2DM (Gradisteanu Pircalabioru *et al*., 2022; Kaul *et al*., 2024). However, the FDA has issued warnings about the potential risks of infections associated with FMT, reinforcing the need for further studies to ensure its safety and efficacy (Martínez-Lopez *et al*., 2022).

CRITICAL AND COMPARATIVE ANALYSIS

The relationship between the gut microbiota and type 2 diabetes (T2DM) is widely recognized as central to the modulation of metabolic health. Gut dysbiosis, characterized by an imbalance in bacterial populations, is strongly associated with the development and worsening of T2DM. This metabolic dysregulation includes chronic inflammation and insulin resistance, two critical factors in T2DM (Tanase *et al*., 2020; Alagiakrishnan; Halverson, 2021).

Therapeutic advances suggest that the manipulation of the microbiota through prebiotics, probiotics and symbiotics shows promising results. Prebiotics such as fructooligosaccharides and β-glucans have been shown to improve glycemic levels by modulating the microbiota and promoting the production of short-chain fatty acids such as butyrate and propionate (Iatcu; Hamamah; Covasa, 2024). Probiotics have also shown significant benefits, including a reduction in lipid levels and improved glycemic control (Kaul *et al*., 2024; Martínez-Lopez *et al*., 2022).

However, methodological challenges remain. Studies with small samples and limited duration make it difficult to generalize the results, while the lack of standardization in interventions complicates comparison between studies (Xu *et al*., 2024), (Huda; Kim; Bennett, 2021). In addition, publication bias can limit conclusions about the effectiveness of these interventions (Mlynarska *et al*., 2024).

Despite progress in understanding the relationship between gut microbiota and T2DM, important gaps remain. The lack of high-quality longitudinal studies limits the validation of interventions such as fecal microbiota transplantation (FMT). The absence of standardized guidelines for performing FMT, including donor selection and administration methods, is a significant obstacle (Martínez-Lopez *et al*., 2022; Xu, 2024).

In addition, the impact of enteric viruses, archaea and fungi on the gut microbiome is still poorly understood, due to the scarcity of reference data and testing difficulties (Huda; Kim; Bennett, 2021). The complexity and dynamism of the microbiome make it difficult to identify specific bacterial strains or combinations that are most effective for the management of T2DM (Xu, *et al*., 2024).

Finally, inter-individual variability in the response to interventions such as prebiotics and probiotics remains a challenge, highlighting the need to personalize therapies (Iatcu; Hamamah; Covasa, 2024).

IMPLICATIONS FOR PRACTICE AND FUTURE RESEARCH

The gut microbiota is a crucial factor for metabolic homeostasis, playing a central role in glucose and lipid metabolism, as well as in the response to antidiabetic drugs. Therapeutic strategies aimed at modulating the microbiota, including the use of prebiotics, probiotics and dietary interventions, offer promising opportunities for the management of T2DM (Al Bataineh *et al*., 2023; Mlynarska *et* al., 2024).

However, the lack of standardized protocols and longitudinal studies limits the practical implementation of these approaches. Future research should focus on understanding the causality between changes in the microbiome and the development of T2DM, as well as assessing the long-term efficacy and safety of interventions (BAARS *et al*., 2024; Su *et al*., 2022).

Manipulation of the microbiota, whether through dietary therapies or BMT, must also consider the associated risks, such as infections and individual variations in response to interventions (Martínez-Lopez *et al*., 2022). Establishing clear guidelines and investigating the interaction between microbiota, metabolism and cardiovascular health can contribute to more effective and personalized treatments (Ballan; Saad, 2021).

Modulating the intestinal microbiota has emerged as an innovative and promising approach to treating T2DM. Prebiotics, probiotics and synbiotics show significant potential in improving insulin resistance, glycemic control and overall metabolic health. Despite this, more studies are needed to standardize interventions and assess their long-term safety and efficacy (Iatcu; Hamamah; Covasa, 2024; Chen *et al*., 2024).

FINAL CONSIDERATIONS

The gut microbiota plays a central role in metabolic homeostasis and in modulating inflammatory processes associated with Type 2 Diabetes Mellitus (T2DM). This study reviewed the relationship between gut microbial composition and the progression of T2DM, highlighting the therapeutic potentials of microbial modulation. Evidence indicates that interventions such as probiotics, prebiotics, symbiotics and fecal microbiota transplantation (FMT) have shown promising results in improving insulin resistance, glycemic control and overall metabolic health.

However, challenges remain, including inter-individual variability in therapeutic responses, a lack of standardization in intervention protocols and the absence of longitudinal studies validating their long-term effectiveness. In addition, important gaps remain regarding the impact of components of the microbiome, such as archaea and fungi, on metabolic health and the progression of T2DM.

These findings reinforce the need for personalized strategies for the management of T2DM, taking into account the individual characteristics of the microbiome, lifestyle and diet. Future research should focus on developing standardized guidelines for interventions, as well as exploring integrative approaches that combine microbiota-based therapies with conventional treatments such as metformin.

Finally, modulation of the gut microbiota is emerging as an innovative and promising approach to the management of T2DM, contributing to more effective and personalized treatments. However, robust validation of their safety and efficacy is essential if these strategies are to be widely incorporated into clinical practice. This line of research has the potential to transform the treatment of T2DM, promoting significant benefits for patients' metabolic health and quality of life.

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