International Journal of Research in Medical Sciences
Tousif M et al. Int J Res Med Sci. 2024 Jun;12(6):2179-2185
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012

DOI: https://dx.doi.org/10.18203/2320-6012.ijrms20241586

Review Article

Modulating gut microbiota in the management of type 2 diabetes mellitus: a narrative review

Meirajuddin Tousif[1]*, Maria Akhtar[2]

[1]Department of General Medicine, Sri Devaraj Urs Medical College, Karnataka, India
[2]Department of Medicine, Khaja Bandawaz Institute of Medical Sciences, Karnataka, India

Received: 07 April 2024
Accepted: 10 May 2024

***Correspondence:**
Meirajuddin Tousif,
E-mail: meirajtousif@gmail.com

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ABSTRACT

Type 2 diabetes mellitus (T2DM) represents a significant global health burden, necessitating innovative therapeutic approaches. Recent research has increasingly recognized the role of gut microbiota modulation in T2DM management, offering promising avenues for intervention. This systematic review synthesizes current literature investigating the impact of modulating gut microbiota on T2DM management. A comprehensive search of databases yielded studies examining various strategies, including probiotics, prebiotics, dietary interventions, and facal microbiota transplantation. Analysis of these interventions revealed their potential to improve glycemic control, insulin sensitivity, and inflammation markers in individuals with T2DM. Mechanistic insights elucidate how gut microbiota modulation influences metabolic pathways, immune function, and gut barrier integrity, thereby contributing to T2DM pathophysiology. Furthermore, studies highlight the interplay between gut microbiota composition and host factors such as diet, lifestyle, and genetics, underscoring the complexity of this relationship. Modulating gut microbiota presents a promising therapeutic approach in T2DM management, with potential benefits in glycemic control and metabolic health. However, further research is warranted to optimize intervention strategies, elucidate mechanistic pathways, and explore long-term effects. The aim of this review was to underscores the importance of considering gut microbiota modulation as a complementary approach in the multifaceted management of T2DM.

Keywords: Gut microbiota, Type 2 diabetes mellitus, Modulation, Probiotics, Prebiotics, Dietary interventions, Fecal microbiota transplantation, Glycemic control, Metabolic health

INTRODUCTION

Overview of type 2 diabetes mellitus (T2DM) and its global prevalence

T2DM is a chronic metabolic disorder characterized by insulin resistance and relative insulin deficiency. It represents a significant global health challenge, with its prevalence steadily increasing over the past few decades. According to the WHO, an estimated 463 million adults were living with diabetes in 2019, with T2DM accounting for the majority of cases. T2DM is associated with various complications, including cardiovascular disease, neuropathy, nephropathy, and retinopathy, leading to substantial morbidity and mortality worldwide.

Introduction and significance of gut microbiota in human health

The gut microbiota refers to the diverse community of microorganisms inhabiting the gastrointestinal tract, predominantly composed of bacteria but also including fungi, viruses, and archaea. Emerging research has highlighted the pivotal role of the gut microbiota in maintaining human health, influencing various physiological processes such as digestion, metabolism, immune function, and even neurological health. The gut

microbiota interacts with the host through complex metabolic and immunological pathways, playing a crucial role in nutrient absorption, synthesis of vitamins, and protection against pathogens.

Importance of understanding gut microbiota modulation for t2dm management

Understanding the intricate interplay between gut microbiota and T2DM pathophysiology holds immense therapeutic potential for the management of this prevalent metabolic disorder. The composition and functionality of the gut microbiota have been increasingly implicated in the development and progression of T2DM, with alterations in microbial diversity and abundance observed in individuals with T2DM compared to healthy counterparts. Therefore, elucidating mechanisms by which the gut microbiota influences glucose metabolism and insulin sensitivity, as well as exploring strategies to modulate the gut microbiota, represents a promising avenue for novel therapeutic interventions in T2DM management. This literature review aims to comprehensively analyze existing evidence regarding the role of gut microbiota modulation in T2DM, highlighting its potential implications for clinical practice and future research directions.

THE GUT MICROBIOTA COMPOSITION IN TYPE 2 DIABETES MELLITUS

Review of studies examining alterations in gut microbiota composition in individuals with T2DM compared to healthy controls

Numerous studies have demonstrated significant differences in gut microbiota composition between individuals with T2DM and healthy counterparts. For instance, a study highlighted that patient with T2DM exhibited distinct gut microbiota profiles compared to healthy individuals, indicating dysbiosis in T2DM.[1] This dysbiosis is characterized by alterations in microbial diversity and abundance, potentially contributing to metabolic dysfunction and insulin resistance observed in T2DM.

Furthermore, investigations into specific microbial taxa have provided insights into the association between gut microbiota composition and T2DM. Firmicutes, a predominant phylum in the gut microbiota, were identified as having a major abundance in both healthy individuals and those with T2DM.[2] However, the relative abundance of certain bacterial species within the Firmicutes phylum may differ between T2DM patients and healthy controls, suggesting a role in disease pathogenesis.

Moreover, studies have explored the functional alterations in the gut microbiota of individuals with T2DM. Functional dysregulation in the gut microbiota, such as changes in metabolic pathways and microbial-derived metabolites, may influence glucose metabolism and insulin sensitivity. For example, butyrate-producing bacteria were found to be negatively correlated with glycemic parameters in individuals with T2DM, indicating a potential link between gut microbiota dysbiosis and T2DM pathophysiology.[3]

Beyond compositional and functional changes, age-related factors and comorbidities, such as periodontitis, have been implicated in shaping gut microbiota composition in individuals with T2DM. Elderly T2DM and periodontitis patients exhibited distinct gut microbiota profiles compared to healthy controls, suggesting potential interactions between systemic health conditions and gut microbiota composition.[4]

Specific bacterial taxa associated with T2DM and potential mechanisms driving these associations

T2DM represents a significant health challenge globally, with its prevalence steadily increasing. Emerging research has shed light on the intricate interplay between gut microbiota and T2DM pathogenesis. Specific bacterial taxa have been implicated in the development and progression of T2DM, offering insights into potential therapeutic interventions and preventive strategies.

Recent studies have identified several bacterial taxa associated with T2DM, including but not limited to, Firmicutes, Bacteroidetes, and Actinobacteria. Notably, alterations in the relative abundance of these taxa have been observed in individuals with T2DM compared to healthy controls.[5] For instance, an overrepresentation of Firmicutes and a decrease in Bacteroidetes have been consistently reported in T2DM patients.[6] Furthermore, specific species within these taxa, such as Akkermansia muciniphila, have been found to correlate with T2DM status, highlighting the potential of targeted interventions at the species level.[7]

Additionally, reduced abundance of Roseburia intestinalis has been observed in T2DM patients, suggesting its involvement in the disease process.[8] This bacterium's depletion underscores its potential significance in T2DM and related complications.

Understanding the mechanisms driving these associations is crucial for elucidating the pathophysiology of T2DM and developing effective interventions. Several mechanisms have been proposed, including dysregulated host-microbiota interactions, alterations in gut barrier function, and microbial-derived metabolites.[9] For instance, dysbiosis-induced inflammation and insulin resistance have been attributed to the production of lipopolysaccharides by certain gut bacteria.[10] Additionally, microbial-derived short-chain fatty acids have been implicated in modulating host metabolism and inflammation, thereby influencing T2DM progression.[11]

Moreover, dietary factors play a pivotal role in shaping the gut microbiota composition, further influencing T2DM risk. High-fat diets, low in fiber, have been associated with

dysbiosis and T2DM development.[12] Conversely, dietary interventions aimed at promoting a balanced gut microbiota composition, such as increased fiber intake, have shown promise in ameliorating T2DM symptoms.[13]

IMPACT OF GUT MICROBIOTA ON GLUCOSE HOMEOSTASIS

Microbial-derived metabolites (e.g., short-chain fatty acids, bile acids) and their role in regulating glucose homeostasis

Microbial-derived metabolites, such as short-chain fatty acids (SCFAs) and bile acids, have emerged as key regulators of glucose homeostasis, a vital process for metabolic balance.

Short-chain fatty acids (SCFAs), including acetate, propionate, and butyrate, are produced through the fermentation of dietary fibers by gut bacteria. These SCFAs influence glucose metabolism by acting as signalling molecules that modulate various pathways involved in glucose regulation.[14]

SCFAs have been demonstrated to influence glucose metabolism through various mechanisms. They enhance insulin sensitivity in peripheral tissues like adipose tissue and skeletal muscle by activating AMP-activated protein kinase (AMPK), thereby promoting glucose uptake and utilization.[15] Additionally, SCFAs may inhibit hepatic gluconeogenesis by suppressing the expression of key gluconeogenic enzymes such as phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6Pase), consequently reducing hepatic glucose output.[16] SCFAs also serve as energy substrates for glycolysis, with butyrate notably utilized by colonocytes.[17] Furthermore, SCFAs influence glucose transport by enhancing the translocation of glucose transporter 4 (GLUT4) to the cell membrane, facilitating glucose uptake in adipocytes.[18] Moreover, SCFAs stimulate the secretion of incretin hormones such as glucagon-like peptide 1 (GLP-1) and peptide YY (PYY) from enteroendocrine cells, which play roles in enhancing insulin secretion and reducing gastric emptying and food intake.[19] These collective mechanisms contribute to the beneficial effects of SCFAs on glucose metabolism and insulin sensitivity.

Bile acids, synthesized in the liver and further modified by gut bacteria, have also been implicated in glucose metabolism. Bile acids interact with specific receptors, such as the farnesoid X receptor (FXR) and Takeda G-protein-coupled receptor 5 (TGR5), to regulate key metabolic processes, including gluconeogenesis and insulin sensitivity.[20] Recent studies suggest that bile acids hold therapeutic potential for treating hyperglycemia and diabetes.[21]

The intricate interplay between microbial-derived metabolites and host metabolism underscores the importance of gut microbiota in maintaining glucose homeostasis. Dysbiosis, or an imbalance in gut microbial composition, has been linked to metabolic disorders, emphasizing the significance of microbial metabolites in metabolic health.[22] Understanding the mechanisms by which these metabolites influence glucose metabolism holds promise for the development of novel therapeutic interventions for metabolic diseases.

Overview of studies investigating the influence of gut microbiota on insulin sensitivity

One seminal study demonstrated that the transfer of intestinal microbiota from lean donors to individuals with metabolic syndrome improved insulin sensitivity, highlighting the potential therapeutic implications of modulating gut microbiota composition.[23] This finding prompted further investigation into the specific microbial taxa associated with insulin sensitivity. Subsequent research identified an association between decreased insulin sensitivity and reduced abundance of certain beneficial gut bacteria, such as butyrate-producing species.[24] Conversely, an overrepresentation of opportunistic pathogens was linked to insulin resistance, suggesting a role for dysbiosis in metabolic disorders. Moreover, studies have elucidated potential mechanisms through which gut microbiota influence insulin sensitivity.[25]

Researchers demonstrated that microbial-derived metabolites, such as short-chain fatty acids (SCFAs), regulate host metabolism and insulin sensitivity.[26] SCFAs serve as energy substrates for colonocytes and exert anti-inflammatory effects, thereby modulating insulin sensitivity. Furthermore, gut microbiota can influence host metabolism through interactions with bile acids.[27] Scientists found that gut microbes regulate bile acid metabolism, impacting lipid and glucose homeostasis. Dysregulation of this pathway contributes to insulin resistance and metabolic dysfunction. Additionally, dietary interventions have been shown to modulate gut microbiota composition and improve insulin sensitivity.[28] Studies demonstrated that dietary changes, such as increased fiber intake or adoption of a Mediterranean diet, promote the growth of beneficial gut bacteria and enhance insulin sensitivity. In conclusion, a growing body of evidence underscores the intricate interplay between gut microbiota composition and insulin sensitivity. Understanding these relationships may offer novel therapeutic strategies for metabolic disorders. Further research is warranted to elucidate specific microbial mechanisms and optimize interventions targeting the gut microbiota to improve metabolic health.

MECHANISMS OF GUT MICROBIOTA MODULATION IN T2DM

Strategies for modulating gut microbiota composition

Modulating gut microbiota through dietary interventions, probiotics, prebiotics, and fecal microbiota transplantation

(FMT) presents promising strategies for T2DM management.

Dietary interventions play a crucial role in T2DM management by influencing gut microbiota composition. High-fiber diets rich in fruits, vegetables, and whole grains have been shown to promote the growth of beneficial bacteria and improve insulin sensitivity in individuals with T2DM.[29] Conversely, diets high in saturated fats and refined carbohydrates can alter gut microbiota composition, exacerbating metabolic dysfunction in T2DM patients.[30]

Probiotics, live microorganisms with beneficial effects on host health, have garnered attention for their potential role in T2DM management. Studies have demonstrated that certain probiotic strains, such as Lactobacillus and Bifidobacterium species, can improve glycemic control and reduce inflammatory markers in individuals with T2DM.[31] Probiotic supplementations may exert these effects by modulating gut microbiota composition and enhancing intestinal barrier function.[32]

Prebiotics, non-digestible fibers that selectively stimulate the growth of beneficial bacteria, offer another avenue for T2DM management. Consumption of prebiotic-rich foods, such as chicory root, garlic, and onions, has been associated with improved glycemic control and reduced risk of T2DM development.[33] Prebiotics exert their effects by promoting the growth of beneficial bacteria such as Bifidobacterium and Lactobacillus, which contribute to glucose homeostasis and insulin sensitivity.[34]

FMT has emerged as a novel therapeutic approach for T2DM management. Preliminary studies have shown that FMT from healthy donors to T2DM patients can improve insulin sensitivity and metabolic parameters by modulating gut microbiota composition.[35] FMT may restore a healthy gut microbiota profile in T2DM patients, thereby mitigating metabolic dysfunction and improving glycemic control.

Clinical evidence for gut microbiota modulation in T2DM

Clinical trials assessing gut microbiota modulation interventions in T2DM management represent a burgeoning area of research, reflecting the evolving understanding of the gut microbiome's influence on metabolic health. Studies have explored diverse interventions like prebiotics, probiotics, FMT, and intermittent fasting aiming to reshape the gut microbiota composition to ameliorate metabolic dysregulation associated with T2DM.[36] Moreover, promising outcomes from FMT in mice reveal reductions in glucose levels, improvements in insulin sensitivity, and decreased islet cell apoptosis.[37] Such findings underscore the therapeutic potential of gut microbiota modulation in T2DM management. Furthermore, a systematic review consolidates evidence from human studies, elucidating the impact of different bacterial taxa on diabetes pathogenesis.[38] This comprehensive analysis identifies potential targets for intervention and highlights the importance of personalized treatment strategies based on gut microbiome profiles. Additionally, the significance of ongoing clinical trials in elucidating the interplay between baseline microbiome composition and intervention efficacy is underscored.[39] These trials pave the way for tailored approaches to T2DM management, leveraging insights into individual gut microbiota dynamics.

CHALLENGES AND FUTURE DIRECTIONS

Current challenges and limitations in gut microbiota modulation strategies for T2DM management

Identification of current challenges and limitations in gut microbiota modulation strategies for T2DM management is crucial for developing effective therapeutic interventions. Several scientific studies have shed light on these challenges, providing insights into the complex interplay between gut microbiota and T2DM. One significant challenge lies in understanding the specific mechanisms by which gut microbiota modulates T2DM pathophysiology.[40] While research suggests a clear association between gut microbiota dysbiosis and T2DM, the precise microbial species and metabolites involved require further elucidation.[41]

Moreover, the heterogeneity of gut microbiota composition among individuals poses challenges in developing universally applicable modulation strategies.[42] What works for one person may not be effective for another due to variations in diet, genetics, and environmental factors. Additionally, the dynamic nature of gut microbiota further complicates modulation efforts, as microbial composition can change rapidly in response to various stimuli.[43]

Another limitation is the lack of robust clinical trials evaluating the efficacy and safety of gut microbiota modulation strategies for T2DM management.[44] While preclinical studies show promise, translating these findings into clinical practice remains a challenge. Furthermore, existing interventions such as probiotics and dietary modifications may yield inconsistent results due to individual variability and lack of standardization in study protocols.[45]

Addressing these challenges requires multidisciplinary approaches integrating microbiology, genetics, nutrition, and clinical research. Future studies should aim to identify specific microbial targets and develop personalized modulation strategies tailored to individual patient profiles.[46] Additionally, large-scale clinical trials with long-term follow-up are needed to establish the efficacy, safety, and optimal dosing of gut microbiota modulation interventions for T2DM management.[47]

Potential future research directions, including personalized microbiota-based therapies and microbiome-targeted pharmaceuticals

Discussion of potential future research directions in gut microbiota modulation for T2DM management holds promise for advancing therapeutic interventions. Emerging studies have highlighted avenues for personalized microbiota-based therapies and microbiome-targeted pharmaceuticals to address the complexities of T2DM. One potential future research direction is the development of personalized microbiota-based therapies tailored to individual patient profiles.[48] By leveraging advances in microbiome sequencing and analysis, researchers can identify specific microbial signatures associated with T2DM and develop targeted interventions. Personalized diets, probiotics, and FMT could be customized based on an individual's gut microbial composition, potentially leading to more effective T2DM management.[49]

Another promising direction is the exploration of microbiome-targeted pharmaceuticals aimed at modulating gut microbiota composition and function.[50] Small molecules, peptides, or biologics that selectively target key microbial species or metabolites implicated in T2DM pathophysiology could offer novel therapeutic options. These pharmaceuticals may act as adjuvants to existing treatments or as standalone therapies for T2DM.[51]

Furthermore, integrating microbiome data into precision medicine approaches could revolutionize T2DM management. By combining genetic, clinical, and microbiome information, researchers can develop predictive models to identify individuals at high risk of T2DM and tailor interventions accordingly.[52] Personalized microbiota-based therapies and microbiome-targeted pharmaceuticals could thus be prescribed pre-emptively or as part of individualized treatment plans to optimize glycemic control and improve outcomes for T2DM patients.

CONCLUSION

Extensive research underscores the significant impact of gut microbiota modulation on the management of T2DM. Key findings highlight its pivotal role in influencing inflammation, dietary interactions, gut permeability, glucose, and lipid metabolism, as well as insulin sensitivity. These insights provide a foundation for developing targeted interventions aimed at modulating the gut microbiota to prevent and manage T2DM complications. Moving forward, there are promising implications for clinical practice. Microbiome-based interventions offer the potential to complement existing T2DM therapies by providing personalized treatments that address the underlying microbial dysbiosis. By targeting the gut microbiota, clinicians may improve patient outcomes, enhance glycemic control, and mitigate the risk of T2DM-related complications. In summary, the role of gut microbiota modulation in T2DM management represents a burgeoning field with profound implications for patient care. Embracing microbiome-based interventions alongside traditional therapies holds promise for revolutionizing T2DM management strategies and improving the overall health outcomes of individuals affected by this metabolic disorder.

ACKNOWLEDGEMENTS

We would like to acknowledge the support and guidance provided by our academic advisors and colleagues who offered their insights and expertise throughout the research process.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Tousif M, Akhtar M. Modulating gut microbiota in the management of type 2 diabetes mellitus: a narrative review. Int J Res Med Sci 2024;12:2179-85.