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MICROBIAL PARTNERS IN DISEASE: UNDERSTANDING THE ROLE OF GUT MICROBIOTA IN DIABETES

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Abstract: INTRODUCTION: Type 2 diabetes (T2DM) is a chronic metabolic disorder marked by insulin resistance and relative insulin deficiency. Diagnosis involves assessing glucose levels, managed through lifestyle changes and medication. Recent research highlights personalized treatment approaches. The gut microbiota, consisting of diverse microorganisms, influences metabolism and immunity. Dysbiosis, an imbalance in gut microbes, correlates with T2DM and metabolic dysfunction. Dysbiosis disrupts microbial metabolites, alters gut barrier function, and impacts the gut-brain axis, contributing to T2DM development. Understanding dysbiosis' role in T2DM pathogenesis is vital for developing tailored interventions targeting the gut microbiota. Further research is needed to elucidate underlying mechanisms and personalize therapeutic strategies for T2DM management. **OBJETIVE:** Analyze and describe the main aspects of microbiota in T2DM and glucose metabolism in the last years. **METHODS:** This is a narrative review, in which the main aspects of the main aspects of microbiota in T2DM and glucose metabolism in recent years were analyzed, included studies in the MEDLINE – PubMed (National Library of Medicine, National Institutes of Health), COCHRANE, EMBASE and Google Scholar databases. **RESULTS AND DISCUSSION:** Glucose metabolism is intricately regulated by various hormones and enzymes, with dysregulation implicated in metabolic disorders like type 2 diabetes (T2DM). The gut microbiota, influenced by factors such as diet and lifestyle, plays a significant role in modulating glucose metabolism through microbial-derived metabolites. Dysbiosis of the gut microbiota has been linked to insulin resistance and impaired glucose tolerance, contributing to T2DM pathogenesis. Interventions targeting the gut microbiota,

including prebiotics, probiotics, and fecal microbiota transplantation, offer promising avenues for managing T2DM by restoring microbial balance and improving metabolic health. However, gaps in understanding the gut microbiota's role and optimal therapeutic strategies necessitate further research to develop personalized interventions for T2DM prevention and treatment, including exploring the preventive potential of fecal microbiota transplantation. **CONCLUSION:** In essence, the relationship between glucose metabolism and the gut microbiota is intricate and pivotal in understanding and managing metabolic disorders like type 2 diabetes mellitus (T2DM). Dysregulation in glucose metabolism, influenced by hormonal regulation and enzymatic activity, contributes to T2DM development. Prebiotics and probiotics offer potential in modulating the gut microbiota to improve metabolic outcomes. Dysbiosis of the gut microbiota is linked to T2DM pathogenesis, with microbial-derived metabolites playing vital roles in host metabolism and inflammation. Interventions targeting the gut microbiota, including fecal microbiota transplantation, present promising avenues for T2DM management, but further research is essential to optimize these approaches. Advancing our understanding of the gut microbiota's role in T2DM and developing personalized therapeutic strategies are crucial steps in addressing this global health challenge.
Keywords: Microbiota; Dysbiosis; Diabetes; glucose.

INTRODUCTION

Type 2 diabetes (T2DM), characterized by insulin resistance and relative insulin deficiency, is a chronic metabolic disorder affecting glucose homeostasis. It is commonly associated with lifestyle factors such as poor diet, sedentary behavior, and obesity[1]. The pathogenesis of T2DM involves a complex interplay of genetic predisposition and environmental factors, leading to impaired insulin action in peripheral tissues such as muscle, liver, and adipose tissue[2]. This results in elevated blood glucose levels, contributing to long-term complications such as cardiovascular disease, neuropathy, nephropathy, and retinopathy[3]. Diagnosis of T2DM typically involves assessing fasting plasma glucose, oral glucose tolerance test, or HbA1c levels[4]. Management strategies include lifestyle modifications (dietary changes and increased physical activity) and pharmacotherapy aimed at improving insulin sensitivity, enhancing insulin secretion, or reducing hepatic glucose output. Additionally, recent research emphasizes personalized approaches to treatment considering individual patient characteristics and preferences[5].

The term "microbiota" refers to the diverse community of microorganisms inhabiting a particular environment, such as the human gastrointestinal tract, skin, oral cavity, or soil[6]. In the context of human health, the gut microbiota, comprising bacteria, archaea, viruses, fungi, and other microbes, plays a crucial role in host physiology, metabolism, and immune function[7]. The gut microbiota participates in nutrient metabolism, synthesis of vitamins and short-chain fatty acids (SCFA), modulation of immune responses, and protection against pathogenic invaders[8]. Perturbations in the composition and function of the gut microbiota, known as dysbiosis, have been associated with various health conditions, including inflammatory bowel diseases (IBD), obesity, T2DM, allergies, and neurological disorders[9]. Understanding the complex interactions between the host and its microbiota is essential for elucidating the mechanisms underlying health and disease and developing targeted interventions to

promote host-microbiota symbiosis[10].

The normal microbiota, also known as commensal microbiota or microbiome, consists of a diverse array of microorganisms that colonize various niches in and on the human body[11]. The main agents of the normal microbiota include bacteria, archaea, viruses, fungi, and protozoa[11]. In the gastrointestinal tract, bacteria dominate the microbiota, with the most abundant phyla including Firmicutes, Bacteroidetes, Actinobacteria, and Proteobacteria[12]. These bacteria play essential roles in digestion, nutrient absorption, and immune system development. In addition to bacteria, viruses such as bacteriophages are abundant in the gut microbiota and influence bacterial diversity and function[13]. Fungi are also present in the gut, although less abundant, and can interact with bacteria to influence host health[14]. Furthermore, the skin microbiota is predominantly composed of bacteria such as Staphylococcus, Propionibacterium, and Corynebacterium species, which contribute to skin barrier function and protection against pathogens. Understanding the composition and function of these main agents of the normal microbiota is crucial for comprehending their impact on human health and disease[15].

Dysbiosis refers to an imbalance or perturbation in the composition, diversity, or function of the microbial communities residing in a particular environment, most applied to the gut microbiota in the context of human health[15]. This imbalance may involve an overgrowth of harmful microorganisms, a reduction in beneficial ones, or alterations in microbial metabolic activities[16]. Dysbiosis can result from various factors, including antibiotic use, dietary changes, stress, and environmental exposures[17]. In the gut, dysbiosis has been associated with numerous health conditions, such as IBD, obesity, metabolic syndrome, autoimmune disorders, and allergic diseases[18]. The mechanisms underlying dysbiosis-mediated pathogenesis are multifaceted and involve disruptions in immune regulation, intestinal barrier integrity, and microbial-host interactions[18]. Understanding dysbiosis and its implications for host health is critical for developing targeted interventions aimed at restoring microbial balance and promoting overall well-being[19].

Dysbiosis has emerged as a potential contributor to the pathogenesis of T2DM. The gut microbiota plays a crucial role in modulating host metabolism, inflammation, and immune responses, all of which are implicated in T2DM development[20]. Dysbiosis can lead to alterations in microbial-derived metabolites, such as SCFA and bile acids, which can influence host energy metabolism, insulin sensitivity, and inflammation[21]. Additionally, dysbiosis-induced changes in gut barrier integrity may facilitate the translocation of microbial products into systemic circulation, triggering low-grade inflammation and insulin resistance[22]. Moreover, dysbiosis is associated with increased gut permeability, leading to the release of endotoxins like LPS, which can activate Toll-like receptors and exacerbate metabolic dysfunction[23]. Furthermore, dysbiosis-induced alterations in the gut-brain axis and production of neurotransmitters may influence appetite regulation and dietary behaviors, contributing to obesity and T2DM risk[24]. Understanding the intricate interplay between dysbiosis and T2DM pathophysiology is essential for developing novel therapeutic strategies targeting the gut microbiota to mitigate metabolic disturbances and improve glucose homeostasis[22,23].

OBJETIVE

Analyze and describe the main aspects of microbiota in T2DM and glucose metabolism in the last years.

SECONDARY OBJECTIVES

1. Explore the mechanisms by which dysbiosis of the gut microbiota contributes to the pathogenesis of T2DM, including insulin resistance and impaired glucose metabolism.
2. Discuss the potential impact of diet, lifestyle, and environmental factors on gut microbiota composition and its relationship to T2DM risk.
3. Examine the role of microbial-derived metabolites, such as SCFA and bile acids, in modulating host metabolism and inflammation in T2DM.
4. Evaluate the therapeutic potential of interventions targeting the gut microbiota, such as probiotics, prebiotics, and dietary modifications, for the management and prevention of T2DM.
5. Highlight gaps in current knowledge and identifying future research directions to further elucidate the complex interplay between the gut microbiota and T2DM pathophysiology.

METHODS

This is a narrative review, in which the main aspects of the main aspects of microbiota in T2DM and glucose metabolism in recent years were analyzed. The beginning of the study was carried out with theoretical training using the following databases: PubMed, sciELO and Medline, using as descriptors: "microbiota" AND "dysbiosis" AND "glucose metabolism" OR "diabetes" in the last 10 years. As it is a narrative review, this study does not have any risks. Only studies in English and Portuguese were selected

Databases: This review included studies in the MEDLINE – PubMed (National Library of Medicine, National Institutes of Health), COCHRANE, EMBASE and Google Scholar databases.

RESULTS AND DISCUSSION

Glucose metabolism is a fundamental process crucial for energy production and homeostasis in living organisms[25]. It involves a series of intricate biochemical reactions that facilitate the uptake, utilization, and storage of glucose[25]. The regulation of glucose metabolism is tightly controlled by various hormones, including insulin, glucagon, and epinephrine, as well as by several key enzymes and transporters[26]. Dysregulation of glucose metabolism is implicated in various metabolic disorders, such as T2DM, where impaired insulin secretion or action leads to hyperglycemia[27]. Understanding the molecular mechanisms underlying glucose metabolism is essential for developing targeted therapies for metabolic diseases. Research in this field continues to uncover novel insights into the complex network of pathways involved in glucose metabolism, paving the way for innovative diagnostic and therapeutic approaches[28].

Prebiotics and probiotics play pivotal roles in modulating the composition and function of the gut microbiota, thereby influencing host health and well-being[29]. Prebiotics are non-digestible dietary fibers that selectively stimulate the growth and activity of beneficial bacteria in the gut, such as Bifidobacteria and Lactobacilli, promoting their colonization and metabolic activity[30]. Common prebiotics include inulin, fructooligosaccharides, and galactooligosaccharides. Probiotics, on the other hand, are live microorganisms that confer health benefits on the host when administered in adequate amounts[31]. These beneficial microbes, typically strains of Lactobacillus and Bifidobacterium genera, contribute to gut microbial balance, strengthen the intestinal barrier, and modulate immune responses[30]. Numerous studies have demonstrated the potential of prebiotics and probiotics in managing various

gastrointestinal disorders, such as irritable bowel syndrome and IBD, as well as in enhancing immune function and preventing infections[32]. Furthermore, emerging evidence suggests their utility in mitigating metabolic disorders, including obesity and T2DM, by improving glucose homeostasis and lipid metabolism. Incorporating prebiotics and probiotics into the diet represents a promising strategy for promoting gut health and overall well-being[32].

The physiopathology of the microbiota in glucose metabolism encompasses a complex interplay between the gut microbiota and host metabolic processes, influencing systemic glucose homeostasis[33]. Dysbiosis, characterized by alterations in the composition and function of the gut microbiota, has been implicated in the development of insulin resistance and impaired glucose tolerance, predisposing individuals to T2DM[34]. Mechanistically, dysbiotic microbiota can induce metabolic endotoxemia by increasing gut permeability and translocation of bacterial products such as lipopolysaccharides (LPS), triggering chronic low-grade inflammation and insulin resistance[35]. Moreover, dysbiotic microbiota are capable of producing metabolites, such as SCFA, which can directly influence host metabolism, including glucose and lipid metabolism[34]. Conversely, restoration of a balanced gut microbiota through interventions like probiotics, prebiotics, or fecal microbiota transplantation (FMT) has shown promise in ameliorating glucose intolerance and insulin resistance in both animal models and clinical studies[35]. Understanding the intricate mechanisms underlying the crosstalk between the microbiota and glucose metabolism holds significant therapeutic potential for managing metabolic disorders like T2DM[36].

Physical exercise exerts profound effects on the composition and function of the gut microbiota, contributing to overall health and metabolic homeostasis[37]. Regular exercise has been shown to increase microbial diversity, promoting the growth of beneficial bacteria such as Bacteroidetes and Firmicutes while reducing the abundance of potentially harmful taxa[38]. Exercise-induced changes in gut microbiota are associated with improvements in gastrointestinal function, immune regulation, and metabolic outcomes[39]. For instance, exercise can enhance the production of SCFA by gut bacteria, which play a crucial role in energy metabolism and inflammation modulation[37,39]. Moreover, exercise-induced alterations in gut microbiota have been linked to enhanced insulin sensitivity, reduced systemic inflammation, and mitigated risk factors for metabolic disorders such as obesity and T2DM[39]. Collectively, these findings underscore the bidirectional relationship between physical exercise and the gut microbiota, highlighting the potential of exercise as a modifiable lifestyle factor for promoting gut health and metabolic well-being[37,38,40].

Recent research has shed light on the intricate relationship between the gut microbiota and T2DM, revealing significant alterations in composition and function in individuals with this metabolic disorder[40]. Studies have demonstrated dysbiosis in the gut microbiota of diabetic individuals, characterized by a decrease in microbial diversity, changes in relative abundance of specific bacterial taxa, and alterations in metabolic pathways[41]. These microbial changes have been associated with insulin resistance, chronic low-grade inflammation, and impaired glucose metabolism, contributing to the pathogenesis and progression of T2DM[42]. Furthermore, the gut microbiota has been implicated in modulating host energy homeostasis, gut barrier function, and immune system regulation, all of which play crucial roles in T2DM development and

complications[43]. Understanding the complex interplay between the gut microbiota and T2DM holds promise for developing novel therapeutic strategies targeting the gut microbiota to improve metabolic health in individuals with T2DM[41,42,43].

Dysbiosis of the gut microbiota has emerged as a significant contributor to the pathogenesis of T2DM, primarily through its influence on insulin resistance and impaired glucose metabolism[44]. Mechanistic studies have revealed several key mechanisms underlying this association[38]. One mechanism involves the production of microbial metabolites such as SCFAs, which can directly impact host metabolism by modulating adipocyte differentiation, insulin signaling, and glucose uptake in peripheral tissues[38]. Additionally, dysbiotic microbiota can induce metabolic endotoxemia through increased intestinal permeability, leading to the translocation of bacterial products such as LPS into the circulation. This, in turn, triggers chronic low-grade inflammation and insulin resistance by activating toll-like receptor 4 signaling pathways[44]. Moreover, dysbiosis-mediated alterations in bile acid metabolism and gut hormone secretion further contribute to disturbances in glucose homeostasis. Understanding these intricate mechanisms by which dysbiosis of the gut microbiota influences T2DM pathogenesis provides valuable insights into potential therapeutic targets for mitigating insulin resistance and improving glucose metabolism[44,45].

The composition of the gut microbiota is influenced by various factors, including diet, lifestyle, and environmental exposures, which in turn can impact an individual's risk of developing T2DM[46]. Dietary habits play a crucial role in shaping the gut microbiota, with high-fiber, plant-based diets associated with greater microbial diversity and a more favorable profile of beneficial bacteria, such as Bifidobacteria and Lactobacilli[47]. Conversely, diets high in saturated fats, sugars, and processed foods have been linked to dysbiosis, characterized by reduced microbial diversity and an increase in potentially harmful bacteria. Lifestyle factors such as physical activity levels, stress, and sleep patterns also influence gut microbial composition, with sedentary behavior and chronic stress associated with alterations in microbial diversity and function[48]. Furthermore, environmental factors including exposure to pollutants, antibiotics, and pesticides can disrupt the gut microbiota and contribute to metabolic dysfunction. Understanding the intricate interplay between diet, lifestyle, environmental factors, and gut microbiota composition is essential for elucidating their collective impact on T2DM risk and developing targeted interventions to promote metabolic health[49].

Microbial-derived metabolites, particularly SCFAs and bile acids, play integral roles in modulating host metabolism and inflammation, thus influencing the pathogenesis of T2DM[50]. SCFAs, primarily acetate, propionate, and butyrate, are produced by gut bacteria through the fermentation of dietary fibers[51]. These metabolites act as signaling molecules, binding to specific receptors such as G protein-coupled receptors and serving as energy substrates for host cells[52]. SCFAs have been shown to exert beneficial effects on glucose and lipid metabolism by enhancing insulin sensitivity, promoting energy expenditure, and reducing adipose tissue inflammation. Conversely, dysbiosis-induced alterations in SCFA production have been associated with insulin resistance and metabolic dysfunction in T2DM[52]. Bile acids, synthesized in the liver and modified by gut bacteria, also serve as signaling molecules through activation of nuclear receptors such as farnesoid X receptor and Takeda G protein-

coupled receptor 5[53]. Bile acids regulate lipid and glucose metabolism, inflammation, and gut barrier function. Dysregulation of bile acid metabolism has been implicated in the pathogenesis of T2DM and its complications[50]. Understanding the intricate interplay between microbial-derived metabolites and host metabolism is critical for developing novel therapeutic strategies targeting the gut microbiota to improve metabolic health in T2DM[52].

Evaluating the therapeutic potential of interventions targeting the gut microbiota, including probiotics, prebiotics, and dietary modifications, holds promise for the management and prevention of T2DM[54]. Probiotics are live microorganisms that confer health benefits on the host when administered in adequate amounts, whereas prebiotics are non-digestible fibers that selectively stimulate the growth and activity of beneficial bacteria in the gut[55]. Numerous studies have demonstrated the efficacy of probiotics and prebiotics in improving glucose metabolism, enhancing insulin sensitivity, and reducing systemic inflammation in individuals with T2DM or at risk of developing the disease[56]. Additionally, dietary modifications such as increasing fiber intake and consuming plant-based diets rich in fruits, vegetables, and whole grains have been associated with favorable alterations in the gut microbiota composition and improved metabolic outcomes[57]. While the precise mechanisms underlying the therapeutic effects of these interventions are still being elucidated, modulation of gut microbial diversity, production of beneficial metabolites such as SCFA, and enhancement of gut barrier function are thought to play crucial roles[54]. Further research is warranted to optimize the selection, dosage, and duration of these interventions and to better understand their long-term effects on metabolic health in T2DM[57].

Highlighting gaps in current knowledge and identifying future research directions are crucial steps to further elucidate the complex interplay between the gut microbiota and T2DM pathophysiology[58]. While significant progress has been made in understanding the role of gut microbiota in T2DM, several gaps in knowledge remain[58]. Firstly, more comprehensive studies are needed to elucidate the dynamics of the gut microbiota in T2DM progression, considering factors such as disease duration, severity, and treatment regimens[59]. Secondly, the molecular mechanisms underlying how specific microbial taxa and their metabolites influence host metabolism and inflammation require further investigation[60]. Moreover, the impact of host genetics, diet, lifestyle, and environmental factors on shaping the gut microbiota and its relevance to T2DM risk and outcomes necessitates extensive research[60]. Additionally, the development of standardized methodologies for profiling the gut microbiota and functional analysis of microbial communities will facilitate cross-study comparisons and improve reproducibility[61]. Furthermore, large-scale prospective studies and randomized controlled trials are warranted to evaluate the efficacy and safety of interventions targeting the gut microbiota in T2DM prevention and management. Integrating multi-omics approaches, including metagenomics, metatranscriptomics, metabolomics, and host-microbiome interaction studies, will provide a comprehensive understanding of the intricate mechanisms driving the gut microbiota-disease axis in T2DM[60]. Addressing these knowledge gaps and pursuing future research directions will pave the way for personalized therapeutic strategies targeting the gut microbiota to combat T2DM and its complications[59].

The future of gut-intervention therapies for

T2DM holds promise in revolutionizing the management and treatment of this metabolic disorder[60]. Targeting the gut microbiota through interventions such as probiotics, prebiotics, dietary modifications, and FMT represents a novel approach to modulating host metabolism and improving glucose homeostasis[53]. Emerging evidence suggests that these interventions can ameliorate insulin resistance, reduce systemic inflammation, and enhance metabolic health in individuals with T2DM[54]. Moreover, advancements in microbial profiling technologies and systems biology approaches will enable a deeper understanding of the complex interactions between the gut microbiota and host physiology, leading to the identification of personalized therapeutic strategies tailored to individual microbiome profiles[61]. Furthermore, the integration of gut-intervention therapies with existing pharmacological treatments holds potential for synergistic effects and improved clinical outcomes in T2DM management[62]. However, further research is needed to optimize the selection, dosage, and duration of gut-intervention therapies, as well as to assess their long-term safety and efficacy in large-scale clinical trials[63]. Overall, the future of gut-intervention therapies for T2DM is promising, offering innovative strategies to address the growing burden of this global health epidemic[62,63].

FMT has emerged as a potential prevention strategy for various conditions, including metabolic disorders such as T2DM[64]. By restoring microbial diversity and function in the gut, FMT holds promise in mitigating dysbiosis-associated metabolic dysfunction and insulin resistance, thus reducing the risk of developing T2DM[65]. Preclinical studies in animal models have demonstrated the preventive efficacy of FMT in improving glucose metabolism and reducing adiposity[64]. Additionally, observational studies in humans have shown associations between gut microbiota composition and metabolic health, supporting the rationale for FMT as a preventive intervention for T2DM[66]. However, further research is warranted to elucidate the optimal timing, dosage, and frequency of FMT administration, as well as to assess its long-term safety and efficacy in large-scale clinical trials[64]. Moreover, understanding the mechanisms underlying the preventive effects of FMT on T2DM will be essential for its translation into clinical practice[64,65,66].

CONCLUSION

In conclusion, the interplay between glucose metabolism and the gut microbiota is a multifaceted relationship with significant implications for metabolic health, particularly in the context of type T2DM. Dysregulation of glucose metabolism, influenced by factors such as hormone regulation and enzymatic activity, can lead to metabolic disorders like T2DM. Understanding the molecular mechanisms involved in glucose metabolism is crucial for developing targeted therapies. Prebiotics and probiotics have emerged as promising interventions for modulating the gut microbiota, thereby improving metabolic outcomes. Dysbiosis of the gut microbiota is implicated in T2DM pathogenesis, with microbial-derived metabolites playing key roles in modulating host metabolism and inflammation. Interventions targeting the gut microbiota, including probiotics, prebiotics, and fecal microbiota transplantation, offer potential avenues for T2DM management and prevention. However, further research is needed to optimize these interventions and elucidate their long-term effects. The future of gut-intervention therapies, including FMT, holds promise in revolutionizing T2DM management by addressing underlying microbial dysbiosis and metabolic dysfunction. Overall, advancing our

understanding of the gut microbiota's role in T2DM pathophysiology and developing personalized therapeutic strategies represent crucial steps in combating this global health epidemic.

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