Revista Portuguesa de Diabetes. 2024; 19 (1): 20-31

The Hidden Link Between Gut Microbiota and Vascular Dysfunction in Diabetes

A Ligação Oculta Entre a Microbiota Intestinal e a Disfunção Vascular na Diabetes

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Abstract

Recent diabetes research has unveiled novel pathways offering potential therapeutic interventions to slow the disease's progression and alleviate associated health complications. Particularly, advancements in high-throughput multi-omics technologies over the past two decades have spotlighted the gut microbiota, a rich ecosystem of microorganisms in the digestive tract, as a pivotal area of study. This body of research has established a link between dysbiosis, an imbalance in these microbial communities, and various diseases, including metabolic disorders. This review focuses on the crucial role of the gut microbiota in obesity and diabetes, highlighting its emergence as a promising target for treatment strategies. By detailing the alterations in gut microbiota and associated metabolites in obesity and diabetes, along with the therapeutic potential of fecal microbiota transplantation in these diseases, we underscore the complexity and potential of targeting these microbial communities for health benefits. As we look to the future, the importance of translating this knowledge into clinical applications becomes paramount, setting the stage for innovative treatments that harness the power of the gut microbiota to combat diabetes and other metabolic diseases.

Keywords: alterations in gut microbiota; obesity; diabetes (type 1 and 2); fecal microbiota transplantation

Resumo

Estudos recentes sobre a diabetes revelaram numerosas vias que oferecem potenciais intervenções terapêuticas para atrasar a progressão da doença e aliviar as complicações de saúde associadas. Nas últimas duas décadas os avanços nas tecnologias multi-ómicas de elevado rendimento destacaram a microbiota intestinal, um ecossistema rico em microrganismos no trato intestinal, como uma área de estudo fundamental. Este corpo de investigação estabeleceu uma ligação entre a disbiose, um desequilíbrio nessas comunidades microbianas, e várias doenças, incluindo distúrbios metabólicos. Esta revisão centra-se no papel crucial da microbiota intestinal na obesidade e na diabetes, destacando a sua emergência como um alvo promissor para a intervenção terapêutica. Ao detalhar as alterações na microbiota intestinal e nos metabolitos associados na obesidade e na diabetes (tipos 1 e 2), juntamente com o potencial terapêutico do transplante de microbiota fecal nestas doenças, sublinhamos a complexidade e o potencial de modular estas comunidades microbianas para obter benefícios para a saúde. Ao olhamos para o futuro, a importância de traduzir este conhecimento em aplicações clínicas torna-se primordial, preparando o terreno para tratamentos inovadores que aproveitem o poder da microbiota intestinal para combater a diabetes e outras doenças metabólicas.

Palavras-chave: alterações na microbiota intestinal; diabetes (tipos 1 e 2); transplante de microbiota fecal

> INTRODUCTION

Over the past few decades, type 2 diabetes (T2D) research has extensively explored mechanisms such as insulin resistance, glucose utilization, beta cell failure, and chronic low-grade inflammation. [1] Building upon this foundation, a significant evolution in diabetes treatment has recently emerged through the study of the glucagon-like peptide-1 (GLP-1) and its receptor. GLP-1, an incretin hormone, plays a crucial role in enhancing insulin secretion in a glucose-dependent manner, thus improving glycemic control. [2] The development and use of GLP-1 receptor (GLP-1R) agonists have revolutionized diabetes management, not only addressing blood glucose levels but also contributing to weight loss and potentially ameliorating beta cell function. [3,4] Interestingly, GLP-1 is produced and secreted by the L cells located in the gut, in response to food intake. [2,5] This con-

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Recebido/Received: 08/04/2024; Aceite/Accepted: 29/04/2024.

nection between GLP-1 and the gut highlights the gut's significant role not only in nutrient absorption but also in metabolic regulation and the potential for therapeutic interventions targeting the gut in diabetes management. Building upon the concept that the gut plays a critical role in T2D management, it is noteworthy to mention that numerous studies have established a link between GLP-1R agonists and changes in the composition of gut microbiota. [6-10] These effects are attributed to the agonists' ability to modify gastric emptying rates and gut transit timing, as well as to alterations in the gut's internal milieu, such as pH and nutrient availability. For an in-depth exploration of this topic, we refer to another review. [11] Furthermore, recent findings suggest a link between metformin, a leading oral anti-diabetic drug, and the gut microbiome. [12] While the intricacies of this relationship demand further elucidation, the authors suggested that metformin's therapeutic efficacy might hinge on its ability to modulate the gut microbiome. Specifically, by increasing the abundance of certain beneficial bacterial strains that generate health-promoting short-chain fatty acids (SCFAs), such as butyrate and propionate, along with a metabolite known as agmatine. [12] Although it remains premature to definitively assert that these microbiota-mediated shifts underpin the advantageous impacts of metformin and GLP-1R agonists on T2D management, this hypothesis suggests an additional mechanism through which these antidiabetic agents may exert their regulatory influence over T2D.
While the significant biological and potential therapeutic roles of gut microbiota in various disorders are increasingly recognized, the regulatory approval of such interventions remains sparse. To date, the U.S. Food and Drug Administration has only approved one oral-fecal microbiota product. This treatment is used to prevent the recurrence of *Clostridioides difficile* infection in patients previously treated with antibacterial agents for recurrent infection episodes. [13] As the scientific community continues to unravel the multifaceted roles of the gut microbiota in health and disease, the anticipation grows for an expanded arsenal of microbiota-based therapies. These would not only target recurrent infections but also address a broader spectrum of diseases where dysbiosis plays a critical role, marking a new period in medical treatment and patient care. [14] Consequently, the paramount challenge we face today is to elucidate the intricate interactions between the gut microbiota and its host that govern the initiation and progression of metabolic disorders. This pursuit not only holds the promise of uncovering novel therapeutic strategies but also aspires to achieve treatments that are both highly efficacious and minimally detrimental in terms of side effects.

> MICROBIOTA

The human microbiota comprises all microorganisms living within our bodies, orchestrating a delicate balance between health and disease. [15,16] These microbial communities, distinct in their composition and localized within various ecosystems such as the gut, oral cavity, respiratory system, and skin, play pivotal roles in our physiological processes. [16,17] The advent of microbiota research has unveiled the critical role of microbiota in health and disease, particularly pointing to the gut microbiota's fundamental importance in maintaining overall health. [17,18] The human gastrointestinal tract is home to a vast and diverse microbial community, composed of about 100 trillion microorganisms, which surpasses the microbial richness of any other body region. This rich mosaic nestled within our gut comprises bacteria, archaea, fungi, viruses, and protozoa, and forms a complex ecosystem that interacts with its host in numerous ways. [17,19,20] These diverse populations of microorganisms can either be harmful or beneficial to the host, thus negatively or positively impacting health. [15,21] For this reason, numerous researchers are seeking to identify a unique health versus disease signature within these microbial communities. [22-24] This quest, however, has proven to be challenging due to the diversity of the microbiome and the individualized nature of microbial compositions influenced by environmental factors, and the dynamic interactions between microbial communities and the host's physiology. Each of these elements contributes to the intricate puzzle researchers are striving to solve, in the hope of harnessing the microbiota's potential to revolutionize medicine.

> GUT MICROBIOTA

Hippocrates, acclaimed as the father of Western medicine, recognized the link between gut health and systemic health, a notion increasingly validated by modern science, stressing the timeless wisdom that all disease begins in the gut. Emerging research defines the gut as a central regulator of host physiology with gut dysbiosis emerging as an obesogenic/diabetogenic factor and bariatric surgery reversing the dysbiosis pattern, highlighting gut health's role in obesity and diabetes management. [20,25-27] It has been postulated that dysfunctional gut microbiota fosters an imbalance detrimental to host health and underpins the connection to the patho-

genesis of prevalent metabolic disorders, including obesity, T2D, non-alcoholic liver disease, cardio-metabolic diseases, and malnutrition. Moreover, this imbalance is also associated with inflammatory bowel disease. [20,21]
Beyond its well-established role in food digestion, the gut microbiome is involved in regulating gut endocrine functions, protecting against pathogens, and orchestrating immune and neurological responses. [20,28] Furthermore, the gut microbiome modifies drug action, eliminates toxins, and produces several metabolites that significantly impact the host's metabolism. [17,20,21] One of the open questions in the field is: How does gut microbiota influence overall organism's health? Although various mechanisms have been proposed to explain this complex interaction, the precise pathways remain a subject of ongoing research. A compelling and simplified hypothesis centers on the interplay between beneficial and harmful microbial species that influence host health, primarily through the differential immune responses elicited in the host due to the production of unique bacterial metabolites that cross from the gut into the bloodstream. [29,30] Interestingly, this variation can be explained by differences in how these bacterial communities metabolize the nutrients consumed by the host, as well as their distinct effects on the intestinal barrier's integrity. [31,32] Importantly, beneficial bacteria are capable of producing metabolites that offer health advantages to the host. [33,34] Alterations in the integrity of the gut mucosa barrier are associated with chronic inflammation and the onset and progression of metabolic diseases. [35,36]
The effect of a high-fat diet on the gut microbiota composition is among the most studied in the field, displaying severe shifts in microbial signatures. [37] This emphasizes the critical role of diet in shaping gut microbiota and its consequential effects on host health and disease susceptibility. Demonstrating an altered bacterial signature in association with a disease is one thing; asserting that this alteration causes the disease is another. The chicken-and-egg dilemma persists, we are yet to ascertain whether changes in the gut microbiota are a precursor to disease or a consequence thereof. The use of germ-free animals and the transfer of bacterial cultures to such mice have been pivotal in unraveling the interactions between gut microbiota and host health. Fecal microbiota transplantation (FMT), wherein microbiota from healthy individuals is transferred to metabolically compromised recipients, has shown promise. [38] Such interventions enhance insulin sensitivity and mitigate weight gain in recipients, providing a window into the potential causative roles of microbiota in disease. [39-41] Nonetheless, these findings, while groundbreaking, highlight the complexity of establishing clear causal relationships.

> INTERPLAY BETWEEN GUT MICROBIOTA AND METABOLIC DISORDERS

Obesity

Obesity, a prevalent global health challenge, is a risk factor for T2D, with both conditions intertwined through shared molecular pathways, namely insulin resistance and a state of subclinical chronic inflammation. [42,43] In the evolving research of obesity's etiology, the gut microbiota, along with their metabolically active byproducts, have emerged as novel players in modulating host biological functions that include appetite control and body weight regulation. [44-47] A landmark discovery in this area was the evidence that the transplantation of gut microbiota from obese donors could induce weight gain in otherwise lean mice, casting a spotlight on the gut microbiome's role in obesity's onset and progression. [16,20,48] Subsequent studies have elucidated that obese individuals typically display reduced diversity in their fecal bacteria composition. This loss of microbial diversity was correlated with an array of metabolic disturbances, including elevated levels of body fat, dyslipidemia, impaired glucose metabolism, and increased inflammation. [16,20,49] These findings suggest a potential avenue for therapeutic interventions targeting the microbiome to combat obesity and its related metabolic sequelae.
The narrative of gut microbiota's role in obesity further unfolds with specific bacterial phyla emerging into the spotlight, specifically, there is an increase in butyrate-producing *Firmicutes* and a decrease in *Bacteroidetes*. Moreover, higher levels of *Eubacterium ventriosum* and *Roseburia intestinalis* are linked to obesity. In contrast, butyrate producers such as *Oscillospira spp.* and *Methanobrevibacter smithii* were associated with leanness. [50-52]
Adding another layer to this intricate story, the gut microbiota of obese individuals is more efficient at extracting energy from their food compared to non-obese individuals. [16,53,54] This enhanced ability to harvest energy from the diet impacts the host's energy balance. Thus, not only the composition but also the functionality of the gut microbiota are key factors in obesity development. [55]
One particular bacteria present in our guts, *A. muciniphila*, has gained increasing attention for its beneficial health effects. [56] First, studies in rodents have demonstrated

that treatment with *A. muciniphila* can reduce obesity and associated conditions, including glucose intolerance, insulin resistance, liver steatosis, and gut permeability. [57,58] Second, even pasteurizing *A. muciniphila* exerts positive effects on fat accumulation, insulin resistance, and glucose tolerance, also in rodent models. [59] Most importantly, in a randomized, double-blind, placebo-controlled trial, administering supplements of either live or heat-inactivated *A. muciniphila* to overweight and obese participants resulted in decreased insulin levels, improved insulin sensitivity, and beneficial changes in blood indicators of liver dysfunction and inflammation. [60] These findings, although from a study involving a small group of participants, collectively highlight the potential of *A. muciniphila* as a promising therapeutic agent in the battle against obesity and its metabolic complications.

Building on the narrative that the composition and functionality of the gut microbiota are pivotal in the development of obesity, FMT emerges as a novel and promising approach. Interestingly, FMT from both mice and humans submitted to bariatric surgery into germ-free recipients results in weight loss by mechanisms that remain to be elucidated. [26,40,61] Although FMT is a promising therapeutic option for obesity, further investigation is required to define which and how specific gut bacterial signatures mechanistically control obesity. Such insights are essential for developing targeted interventions that utilize microbiota to combat health issues associated with obesity. [20]

Type 1 Diabetes

Dysbiosis of gut bacteria is linked to T1D pathogenesis, with a growing number of studies suggesting that alterations in gut microbiota composition increase susceptibility to and progression of T1D. [62-66] Individuals with T1D exhibit distinct gut microbiota differences compared to healthy individuals, with variations in specific phyla, displaying higher levels of *Christensenella* and *Bifidobacteria*. [17,66,67] Additionally, these individuals tend to have diminished levels of bacteria that produce SCFAs, which are essential for mitigating chronic inflammation and maintaining intestinal homeostasis. [17] Moreover, other studies report lower levels of *R. faecis*, *F. prausnitzzi*, and *Intestinimonas* in individuals with T1D compared to healthy counterparts. [17,68] This accumulating evidence highlights the importance of the gut microbiota in T1D, pointing towards its potential as a target for therapeutic interventions to improve disease outcomes. [17,69]

T1D, an autoimmune condition, results from the immune system attacking insulin-producing beta cells, leading to chronic inflammation within these cells, therefore impairing insulin production and blood glucose regulation. The gut microbiota's interaction with the immune system can exacerbate this inflammation, central to T1D's pathogenesis. This dysregulation highlights the intricate interplay between our microbiome and immune health in the context of autoimmune diseases. [17]

In a recent clinical trial, researchers explored the effects of autologous, using the patient's microbiota, versus allogeneic, using microbiota from healthy donors, FMT on the progression of beta cell loss of function. Interestingly, the trial found that participants receiving autologous FMT experienced a preservation of beta cell function for 12 months after undergoing three consecutive FMT procedures. This effect was notably distinct from the outcomes observed with allogenic FMT from healthy donors, which had previously shown promise in slowing beta cell function decline in other major studies. The beneficial impact of autologous FMT was linked to significant changes in the mucosal microbiota of the small intestine, suggesting that reintroducing one's microbiota could beneficially modify the immune response initiated in the gut. [70] These findings highlight the potential of autologous FMT in managing beta cell function and emphasize the need for further research in larger trials to fully understand the mechanisms involved.

Type 2 Diabetes

Regarding T2D, similar to the other metabolic disorders here explored, the development of this condition has been connected to variations in gut microbiota composition. [22,71-73] For instance, one study showed that individuals with T2D tend to have an increased abundance of certain groups of bacteria, including *Bacteroidetes and Proteobacteria*, alongside a decrease in *Firmicutes*. [16,17,19,71] However, some studies have found the opposite trend, an increase in both *Firmicutes* and *Proteobacteria* and a decrease in *Bacteroidetes* in individuals with T2D compared to those without the condition. [74] Meanwhile, other study has not observed any significant differences in the microbiota composition among subjects. [75] The observed disparities in microbial compositions across studies could be explained by substantial interindividual variation, thought to stem from various factors including age, diet, health status, genetic predispositions, environmental conditions, and medication use. Consequently, a cautious approach is warranted when comparing findings across different studies, bearing in mind these potential sources of variation.

Metabolites produced by the gut microbiota, such as

SCFAs, trimethylamine-N-oxide (TMAO), and those derived from tryptophan, have been associated with the development of T2D. [19,20] SCFAs play a crucial role in regulating glucose metabolism and insulin sensitivity via several signaling pathways. [17] SCFAs can stimulate the release of GLP-1 and peptide YY, which enhance insulin secretion and decrease glucagon levels. [17,19,76] Additionally, butyrate, a specific type of SCFAs, contributes to the maintenance of the intestinal epithelial barrier. Noteworhty, the barrier is frequently compromised in individuals with T2D, largely due to inflammation. [17,19,77,78] Therefore, a decrease in SCFAs-producing bacteria, those belonging to the phylum *Firmicutes* may contribute to the onset of T2D. [17,19] TMAO, another relevant metabolite formed in the liver from trimethylamine, a product of the metabolization of nutrients by gut microbiota, has been associated with an increased risk of T2D. TMAO has the potential to block hepatic insulin signaling and trigger inflammation in the adipose tissue, therefore exacerbating insulin resistance. [19,79]

While several mechanisms have been proposed to explain the connection between gut microbiota and T2D, including the regulation of inflammation, gut permeability, SCFAs production, modulation of bile acid metabolism, and effects on incretin hormones — more studies are needed to fully understand these complex interactions. Each of these pathways suggests that the gut microbiota plays a multifaceted role in influencing glucose metabolism, insulin sensitivity, and overall metabolic health. However, the precise mechanisms and their relative contributions to the pathogenesis of T2D remain to be fully elucidated, underscoring the need for further research in this promising area. [17] Understanding the interrelationship between T2D and the gut microbiota is imperative for the development of personalized therapeutic strategies aimed at effectively managing this condition and mitigating its associated complications.

> TYPE 2 DIABETES AND ITS COMORBIDITIES: FOCUS ON VASCULAR ALTERATIONS

Elevated blood glucose levels, a hallmark of T2D, result in substantial organ damage over time. This includes vascular alterations divided into macrovascular diseases, such as cardiovascular disease (CVD), cerebrovascular disease, and peripheral arterial disease, and microvascular diseases, such as diabetic nephropathy, retinopathy, and neuropathy. [80-82] The endothelium, critical for vascular functions, thus becomes a focal point in T2D progression. From the onset of T2D, endothelial function is compromised, significantly associated with negative health outcomes. The exact cause of this impairment involves both the direct effects of hyperglycemia on endothelial cells and indirect impacts through growth factors, cytokines, and vasoactive substances. [83,84] The initial dysglycemia leads to functional and structural alterations in the vessel wall, ultimately resulting in diabetic vascular complications. [84]

Building on the understanding that gut microbiota significantly impacts key diabetes markers, namely insulin resistance, glycemic control, body weight, and hepatic lipid accumulation, it is plausible to anticipate that these microbial communities also contribute to endothelial dysfunction and subsequent diabetic-associated vascular complications. Nevertheless, direct studies linking changes in the gut microbiota to vascular alterations in the context of T2D are limited. Notably, the role of gut microbiota in endothelial dysfunction has been confirmed in other diseases, underscoring its potential impact on vascular health, a topic that will be explored in the following section.

> CONTRIBUTION OF GUT MICROBIOTA TO ENDOTHELIAL DYSFUNCTION

The endothelium, a monolayer of endothelial cells lining the inner surface of blood vessels, supports various functions crucial for vascular health and systemic physiological balance. [85-88] Emerging evidence suggests that the gut microbiota plays a role in endothelial dysfunction, which is crucial for maintaining vessel integrity and overall body function, although the studies remain limited. [85,89] Importantly, endothelial function is a critical indicator of CVD risk, particularly relevant as cardiovascular diseases are the leading causes of mortality worldwide. [88] Unfortunately, in individuals with diabetes, this risk is further exacerbated. [90] The underlying pathology in diabetes is complex, involving impaired signal transduction, reduced nitric oxide (NO) availability, a critical factor for endothelial health, increased oxidative stress, and heightened release of endothelium-derived constricting factors. [90-92]

Given the vascular endothelium's role as a critical regulator of exchanges between the vascular wall and surrounding tissues, it is notably sensitive to various endogenous mediators, including those derived from the microbiota. [85,88] The gut microbiota and their metabolites can impact the endothelium within the circulatory system via two main pathways. [85,88] Firstly, they can stimulate the enteric nervous system, influencing brain centers that regulate cardiovascular functions. [93-95] Secondly, in T2D certain deleterious gut microbiota profiles and metabolites compromise gut integrity, resulting

in a leaky gut. This enables their entry into the bloodstream, where they come in contact with components of the circulatory system like the blood vessel wall, heart, and blood cells, leading to negative outcomes. [85,88,95] Therefore, interventions aimed at restoring a healthy gut microbiota have been proposed as strategies to ameliorate vascular dysfunction. [96]

Regarding specific metabolites, SCFAs are known to have protective effects on endothelial function. [97] Conversely, metabolites like TMAO and uremic toxins, both produced by gut microbiota, are harmful to endothelium function. [85,88]

TMAO is produced by gut microbiota, through the metabolization of dietary precursors such as choline, carnitine, and phosphatidylcholine. These dietary precursors are firstly converted into trimethylamine, which is subsequently absorbed into the bloodstream and transported to the liver, where it undergoes oxidation catalyzed by the enzyme flavin-containing monooxygenase 3 to form TMAO. [98–100] TMAO is associated with endothelial dysfunction and higher CVD risk, serving as a biomarker for overall cardiovascular health. [101,102] High TMAO levels activate NF-▫B, which triggers the upregulation of inflammatory signals and facilitates leukocyte adhesion to endothelial cells. [103,104] Furthermore, studies have demonstrated a correlation between elevated TMAO levels and both endothelial dysfunction and atherosclerosis. [105] Additionally, mice fed a choline-rich diet and exhibiting high TMAO levels displayed significant endothelial damage, dyslipidemia, and hyperglycemia. [106] Furthermore, TMAO downregulates the expression of IL-10, an anti-inflammatory cytokine that protects the endothelium from oxidative stress and induces reactive oxygen species (ROS) production while decreasing NO levels, which collectively damage vascular function. [107,108] Finally, concluding the discussion on the harmful impacts of elevated TMAO levels, one study indicated that high TMAO impairs the ability of damaged endothelial cells to self-repair, leading to permanent endothelial dysfunction. [109] Importantly, studies in humans disclosed that high TMAO levels are associated with an increased risk of T2D. [110-114]

Other metabolites that negatively impact endothelial function include uremic toxins, which are metabolic byproducts from the breakdown of aromatic amino acids, such as tyrosine, phenylalanine, and tryptophan by the gut microbiota. [109,115,116] In the clinic, some uremic toxins are considered a predictive biomarker for coronary atherosclerosis. [116] These toxins induce endothelial dysfunction by activating NF-kB signaling. As a transcription factor, NF-kB upregulates the production of intercellular adhesion molecule 1 and monocyte chemoattractant protein-1, which are critical for cell-cell interactions and the recruitment of inflammatory cells, respectively. [117,118] Additionally, these toxins inhibit NO synthesis and elevate ROS levels, altogether contributing to endothelial dysfunction and atherosclerosis. [119]

This section summarized the role of gut microbiota metabolites, including TMAO and uremic toxins, in endothelial dysfunction (Figure 1). These findings highlight the complex interplay between gut health and diseases associated with endothelial dysfunction, emphasizing the potential for microbiota-targeted interventions to mitigate these deleterious effects.

> CONCLUSION AND FUTURE PERSPECTIVES

As we reflect on the advancements and ongoing challenges within the field of gut microbiota and its impact on diabetes, it is clear that while significant strides have been made in understanding the intricate relationship between gut microbiota and diabetes, critical questions remain unanswered. These include discerning whether alterations in the microbiome are a cause or consequence of diabetes, defining the precise molecular mechanisms through which gut microbiota influence diabetes progression, and elucidating how changes in gut microbial ecology and successful engraftment post-transplantation impact metabolic outcomes in patients with obesity and/or diabetes. Furthermore, there is a pressing need to better define the optimal fecal microbial preparation, dosing, frequency, and method of delivery for FMT. These open questions highlight the importance of future studies to unravel the complex interactions at play, a crucial step for translating microbiota-based interventions into safe and effective treatments for diabetes and potentially revolutionizing global metabolic health. However, the road ahead requires that the effectiveness and safety of any microbiota-based intervention be rigorously established through comprehensive clinical trials before its clinical use can be endorsed. The coming years promise to unveil exciting insights that will undoubtedly contribute valuable pieces to the complex puzzle of diabetes management. Looking ahead, with diabetes prevalence escalating worldwide, the rapidly expanding domain of microbiota interventions, including the use of prebiotics, probiotics, and FMT, holds the promise of gaining regulatory approval for diabetes treatment (Figure 2). Nevertheless, it is crucial to emphasize that no microbiota-based intervention should be endorsed for clinical use until its effectiveness and safety have been rigorously established through comprehensive clinical trials. <

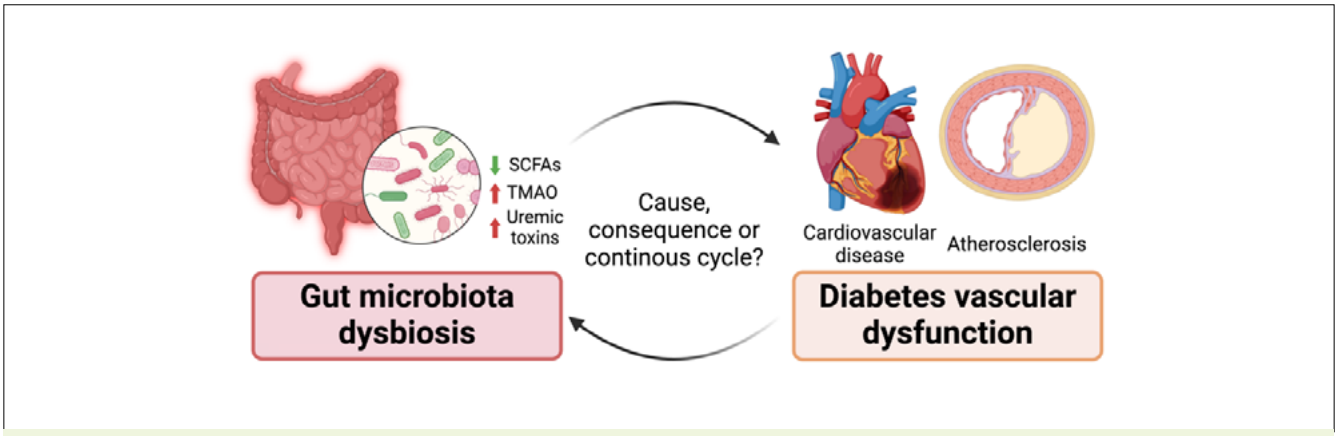

Figure 1 - Gut Metabolites and Vascular Health: Drivers, Effects, or an Endless Loop? Interactions between gut metabolites and cardiovascular diseases represent a complex feedback loop, where the decrease in short-chain fatty acids (SCFAs) producing bacteria and the increase in the production of trimethylamine-N-oxide (TMAO) and uremic toxins exacerbate endothelial dysfunction, and disease states can in turn influence metabolite production. Created with BioRender.com.

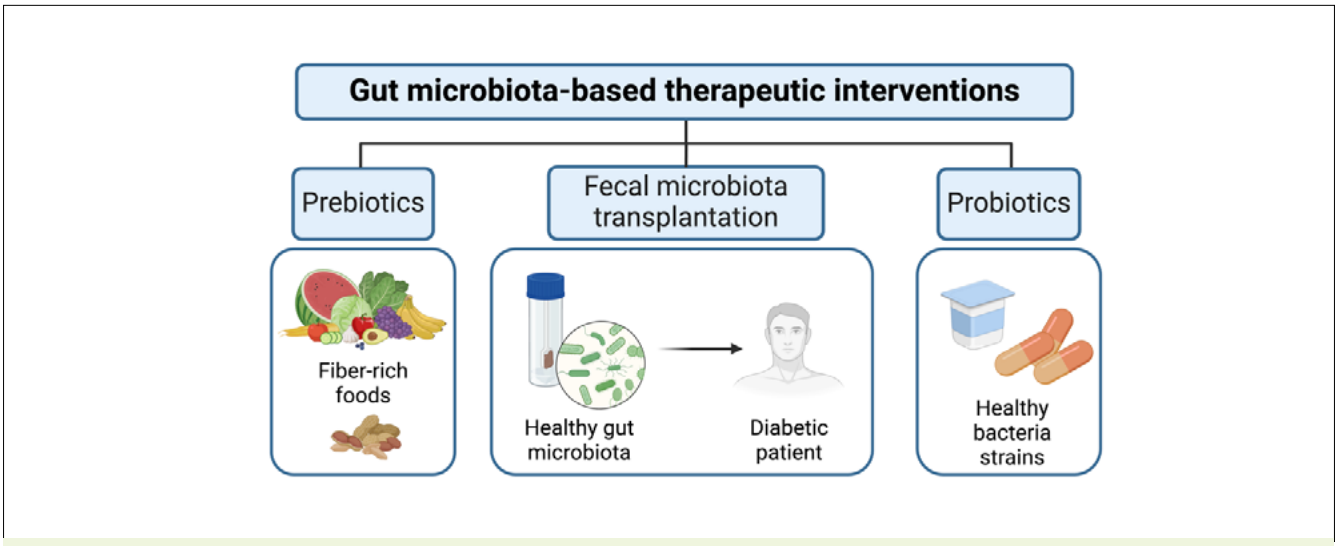

Figure 2 - Future Directions in Gut Microbiota-Based Therapeutic Interventions. This figure illustrates three promising avenues for gut microbiota-based therapies aimed at combating metabolic diseases, highlighting the potential of prebiotics, fecal microbiota transplantation (FMT), and probiotics. Prebiotics, such as fiber-rich foods, nurture beneficial gut bacteria, fostering a healthy microbiome. FMT, transferring gut microbiota from healthy to metabolically compromised individuals, shows promise in resetting dysbiotic gut communities. Probiotics, including certain foods rich in probiotics and supplements containing healthy bacterial strains, aim to directly augment beneficial gut flora. While these interventions offer exciting prospects for future treatments, extensive research and rigorous clinical trials are essential to fully understand their efficacy, safety, and long-term impacts on human health. Created with BioRender.com.

Conflicts of interests/*Conflitos de interesses*:
The authors declare that they have no conflicts of interests./*Os autores declaram a inexistência de conflitos de interesses.*

Acknowlegments – Funding/*Agradecimentos – Financiamento:*
This research was funded by Fundação para a Ciência e a Tecnologia (2022.05764.PTDC) and by the European Commission CORDIS Pas Gras Project (101080329). We express our sincere apologies to those authors whose significant contributions to the field could not be cited within this review due to space limitations. Our admiration goes out to all those who have advanced this field of study./*Esta investigação foi financiada pela Fundação para a Ciência e a Tecnologia (2022.05764.PTDC) e pelo Projeto CORDIS Pas Gras da Comissão Europeia (101080329). Expressamos as nossas sinceras desculpas aos autores cujas contribuições significativas para a área não puderam ser citadas nesta revisão devido a limitações de espaço. A nossa admiração vai para todos aqueles que avançaram esta área de estudo.*

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