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THE IMPACT OF THE GUT MICROBIOTA ON THE PATHOGENESIS AND MANAGEMENT OF INSULIN RESISTANCE

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ABSTRACT

Insulin resistance is a pathophysiological state, defined as a diminished biological response to insulin stimulation of target tissues, primarily the liver, muscles and adipose tissue. It has been identified as a significant factor in the development of certain diseases including type II diabetes mellitus, metabolic syndrome and obesity, and is concurrently associated with an elevated risk of cardiovascular disease and several cancers. A substantial amount of research has indicated a correlation between the occurrence of insulin resistance and imbalances in gut microbiota diversity. Intestinal dysbiosis has been demonstrated to contribute to a reduction in the synthesis of beneficial bacterial metabolites and to an increase in the production of pro-inflammatory cytokines and intestinal barrier permeability, allowing lipopolysaccharide to enter the bloodstream. These mechanisms have been shown to promote the development of inflammation and, consequently, insulin resistance. Therefore, a more profound comprehension of these processes is a matter of significance, as it may potentially facilitate the establishment of more specific and efficacious methods for the prevention and treatment of metabolic diseases.

KEYWORDS

Gut Microbiota, Insulin Resistance, Lipopolysaccharide, Probiotics, Short-Chain Fatty Acids

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1. Introduction

In recent years, the scientific community has directed a significant amount of attention towards the impact of the gut microbiota on human health. The human gut microbiota is defined as a complex, dynamic and spatially heterogeneous ecosystem populated by a myriad of microorganisms. These microorganisms interact with each other and with the human host, as well as with bacteria, fungi, archaeons and viruses. It is important to note that the genetic repertoire of intestinal microbial genes in an individual is more than one order of magnitude higher than that of the human genome (Fan & Pedersen, 2021). The intestinal microbiota is comprised of over 1,500 species, which are distributed across more than 50 different phyla (Robles-Alonso & Guarner, 2013). It has been documented that the most prevalent phyla comprise *Bacteroidetes* and *Firmicutes*, followed by *Proteobacteria*, *Fusobacteria*, *Tenericutes*, *Actinobacteria* and *Verrucomicrobia*. These seven phyla collectively constitute approximately 90% of the total microbial population in humans (Jethwani & Grover, 2019). A number of factors have been identified as being able to alter the composition and function of the gut microbiota. These factors include the mode of birth, infant feeding, lifestyle, medication, as well as genetics and age of the host (Gomaa, 2020). The gut microbiome plays a crucial role in shaping host immunity, facilitating food digestion, modulating gut endocrine activity and neurological communication, influencing drug metabolism and efficacy, detoxifying harmful substances, and generating a variety of compounds that affect the host. Therefore, it substantially contributes to the development of obesity and metabolic diseases (Fan & Pedersen, 2021). A number of molecular interactions have been identified between the microbiota and the host that lead to low-grade inflammation, fat accumulation and consequently, to insulin resistance (Boulangé et al., 2016). Insulin resistance is a condition in which target tissues in the body (primarily skeletal muscles, liver and adipose tissue) exhibit a reduced response to physiological insulin concentrations, resulting in an impaired glucose uptake and compensatory hyperinsulinemia (Freeman et al., 2025). The issue of increased prevalence of insulin resistance is becoming a matter of serious concern. The global prevalence of insulin resistance is estimated to be between 26% and 30%, with variations observed across different populations and geographical regions (Ballena-Caicedo et al., 2025).

The present review aims to provide a comprehensive overview of the current knowledge regarding the contribution of the gut microbiota to the development and modulation of insulin resistance, a pivotal precursor in the pathogenesis of type 2 diabetes. A more profound comprehension of these processes has the potential to refine existing conceptual frameworks of insulin resistance and to inform the development of more targeted preventive and therapeutic approaches for metabolic diseases.

2. Correlation between intestinal microbiota imbalances and metabolic dysregulation

Individuals with insulin resistance exhibit significant alterations in their gut microbiota composition. Studies consistently demonstrate that obese individuals and patients with insulin resistance or type 2 diabetes have lower gut microbiota diversity. Chen et al. examined the association between gut microbiome composition and insulin resistance. They found that higher richness and balance of gut microbes was linked to lower insulin resistance. The study also analyzed differences in microbiome composition between individuals and identified specific taxa, *Christensenellaceae* and *Ruminococcaceae* groups, as potential biomarkers of insulin resistance development (Chen et al., 2021). The disruption of the gastrointestinal microbiota, known as dysbiosis, has been associated with a number of human diseases, including inflammatory bowel diseases, obesity, diabetes, allergies, autoimmune and cardiovascular diseases (Gomaa, 2020). The observed correlations are the consequences of the aggravation of the systemic inflammation and adverse host metabolic regulation caused by the elevated production of pro-inflammatory cytokines and bacterial lipopolysaccharides, increased intestinal permeability facilitating bacterial endotoxin translocation, and a reduction in beneficial gut-derived metabolites, particularly butyrate (Chong et al., 2025). Butyrate, along with other short-chain fatty acids (SCFAs), namely propionate and acetate, are produced as the result of the fermentation process of indigestible carbohydrates. These metabolites have been shown to possess immunomodulatory capabilities.

For example, butyrate directly stimulates enteroendocrine L cells to secrete glucagon-like peptide-1 and peptide YY, contributing to appetite regulation, augment insulin secretion and reduction in glucose release into the bloodstream (Alqahtani, 2025). According to a systemic review by Hamari et al., increased gut-derived butyrate correlated with improved insulin secretion and β-cells performance during meal testing (Hamari et al., 2025). Most butyrate-producing bacteria are classified within the *Eubacteriales* order, notably *Faecalibacterium*, *Roseburia*, *Eubacterium*, *Anaerostipes*, *Coprococcus*, *Subdoligranulum* and *Anaerobutyricum* (Singh et al., 2023). The prevalence of these bacteria is markedly decreased in patients diagnosed with type 2 diabetes mellitus, particularly the genera *Ruminococcus* and *Subdoligranulum*, and species such as *Eubacterium rectale*, *Faecalibacterium prausnitzii*, *Roseburia intestinalis*, and *Roseburia inulinivorans* (Cunningham et al., 2021). Moreover, the composition of the gut microbiota, that affects the synthesis and impact of SCFAs, is significantly influenced by diet, age and health status (Al Bander et al., 2020). In individuals consuming a fiber-rich diet, bacteria produce large amounts of SCFAs, leading to elevated butyrate levels, thereby enhancing anti-inflammatory effects, improving insulin signaling, reducing adipose tissue accumulation and protecting against insulin resistance. However, dysbiosis caused by low-fiber or high-fat diets, aging or metabolic disorders can reduce the amount of SCFAs, lowering butyrate availability and compromising its protective effects (Khan & Jena, 2016). A high-fat diet has been reported to decrease the relative abundance of *Bacteroidetes* while increasing *Firmicutes* and *Proteobacteria*. In obese and overweight individuals, reduced microbial richness was associated with more pronounced metabolic dysregulation (Murphy et al., 2015). Furthermore, the findings of a study conducted by Lawrence et al., indicated that a plant-based diet was associated with elevated levels of carbohydrate fermentation products and an augmented abundance of saccharolytic microbes, including *Roseburia*, *Eubacterium rectale*, and *Faecalibacterium prausnitzii*, in comparison with an animal-based diet (David et al., 2014). In terms of aging, a study conducted by Salazar et al., discovered that in older adults, the abundance of *Lachnospiraceae* and *Faecalibacterium prausnitzii* is often depleted, leading to a decrease in the effectiveness of dietary fibre fermentation (Salazar et al., 2019). The diversity of the intestinal microbiota can be influenced by a number of additional factors, such as host genetics. In a study by Daria V. Zhernakova et al., it was demonstrated that host genetics regulate the genetic variation of intestinal bacteria, with observed associations between the *ABO* locus and the relative abundance of *Faecalibacterium prausnitzii* (Zhernakova et al., 2024). Polyphenols have also been shown to contribute to shifts in microbial composition. In a study by Junwen Yu et al., it was revealed that a polyphenol-rich diet increased the abundance of *Clostridiales* and *Eubacteriales*, well-known for their role in butyrate synthesis (Yu et al., 2025).

3. Immunological consequences of gut microbiota activity on insulin resistance

Alterations in the composition of the gut microbiota, along with its metabolites can have a relevant influence on the progression of inflammation leading to an increased risk of developing insulin resistance. Bacterial lipopolysaccharide (LPS) is a major component of the external membrane of Gram-negative bacteria, which plays a critical role as a protective barrier, providing the structural stability and integrity of the bacterial cell membrane. Its hydrophobic element, Lipid A, secures LPS within the membrane and carries multiple negatively charged phosphate groups, giving the bacterial surface a negative character. Immunologically, LPS functions as a potent pathogen-associated molecular pattern (PAMP). In circulation, LPS is initially bound by LPS-binding protein, simplifying its transfer to CD14. CD14 then presents LPS to the Toll-like receptor 4 (TLR4)/myeloid differentiation-2 (MD-2) receptor complex, which is expressed on immune cells such as macrophages, as well as on non-immune cells (Cani et al., 2007; Xiao et al., 2017). The receptor complex TLR4/MD-2 activates two main pathways: myeloid differentiation primary response 88 (MyD88)-dependent and MyD88-independent. In the MyD88-dependent pathway, TLR4/MD-2 recruits MyD88 and Toll-interleukin-1 receptor (TIR)-domain-containing adaptor protein (TIRAP), followed by interleukin (IL)-1R-associated kinase (IRAK) and tumor necrosis factor (TNF) receptor-associated factor 6 (TRAF6), to activate the transforming growth factor-β-activated kinase 1 (TAK1) complex and suppress transcription factors such as nuclear factor-κB (NF-κB) and activator protein-1 (AP-1), leading to a production of proinflammatory cytokines including IL-6, TNF-α and IL-1β. In the MyD88-independent pathway, TLR4-LPS complexes can be internalized into endosomes, allowing recruitment of TIR-domain-containing adaptor protein inducing interferon (IFN)-β (TRIF) and TRIF-related adaptor molecule (TRAM), followed by activation of TRAF3 and Tank binding kinase-1 (TBK1), consequently phosphorylating and activating interferon regulatory factor 3 (IRF3). This drives transcription of type I interferons (e.g., IFN-β) and the interferon-stimulated genes (Zamyatina & Heine, 2020, 2021). In addition to extracellular sensing by the TLR4/MD-2 complex, LPS can

be detected intracellularly by the cytosolic receptors caspase-4 and caspase-5. Binding of LPS to the caspase recruitment domain (CARD) of these pro-caspases triggers their oligomerization and activation, inducing cell death and inflammasome activation, resulting in secretion of IL-1β and IL-18 (Zamyatina & Heine, 2020, 2021). Slight chemical variations in LPS, such as the number and length of acyl chains or phosphate modifications, not only influence the strength of TLR4 activation, but also the intensity of inflammatory response. The longer or the more chains, the stronger cytokine production and the more intense inflammation (Maeshima & Fernandez, 2013; Xiao et al., 2017).

Under normal conditions, the intestinal barrier restricts the passage of bacterial products, including LPS, into the bloodstream, providing metabolic and immune homeostasis. However, alterations in gut microbiota composition and dysbiosis can compromise barrier integrity, increasing intestinal permeability and allowing LPS to reach circulation, leading to localized and systemic inflammation, stimulated by the releasing the proinflammatory cytokines such as TNF-α, IL-6, IL-1β, IL-18 and interferons (Al Bander et al., 2020; Cani et al., 2007). IL-6 and TNF-α have been shown to influence insulin resistance through multiple molecular mechanisms. Both cytokines can impair insulin signaling by promoting serine phosphorylation of insulin receptor substrate (IRS) proteins, reducing their ability to activate downstream effectors (Al Bander et al., 2020; Aroor et al., 2013). TNF-α activates protein kinase C (PKC) isoforms and c-Jun N-terminal kinase (JNK), which phosphorylate IRS-1 on inhibitory serine residues, impairing its interaction with the insulin receptor and reducing insulin-stimulated glucose uptake (Senn et al., 2002; Srikanthan et al., 2016). Likewise, IL-6 stimulates the mTOR/S6 kinase pathway, leading to additional inhibitory phosphorylation of IRS-1 and further attenuating insulin receptor signaling (J.-H. Kim et al., 2008; Rehman et al., 2017). Both cytokines also amplify a production of reactive oxygen species (ROS) and activate IκB kinase (IKK), promoting NF-κB-mediated transcription of pro-inflammatory genes and creating a feed-forward loop that exacerbates inflammation and insulin resistance (Srikanthan et al., 2016). Through these mechanisms, TNF-α and IL-6 disrupt the normal insulin signaling cascade at multiple levels, from the insulin receptor to IRS proteins and downstream effectors, ultimately reducing glucose uptake and contributing to systemic insulin resistance (Al Bander et al., 2020; Aroor et al., 2013; Rotter et al., 2003; Srikanthan et al., 2016). Research by Mehta et al. demonstrated that experimental endotoxemia and the resulting inflammation, induced by injecting healthy human participants with LPS, led to increased insulin resistance by suppressing insulin receptor signaling in adipose tissue without any dysfunction of pancreatic β-cells (Mehta et al., 2010). These findings are further supported by animal studies, which showed that mice injected with bacterial LPS exhibited elevated plasma insulin levels and increased adipose tissue mass, comparable to mice fed a high-fat diet. Moreover, high-fat food consumption was associated with increased circulating LPS, suggesting that diets promoting the growth of Gram-negative bacteria can intensify systemic endotoxemia. These observations indicate a strong connection between LPS exposure, adipose tissue inflammation, and the development of insulin resistance, highlighting the role of gut microbiota composition and metabolic endotoxemia in the pathogenesis of obesity-related metabolic disorders(Al Bander et al., 2020).

4. Probiotics, prebiotics and synbiotics as a therapeutic option for insulin resistance

4.1. Definition and implications

The scope and proper use of the terms probiotic and prebiotic have been thoroughly analyzed by the International Scientific Association for Probiotics and Prebiotics (ISAPP). The definition of probiotics, initially presented by the Food and Agriculture Organization of the United Nations and the World Health Organization (FAO/WHO), was subsequently updated to “live microorganisms which, when administered in adequate amounts, confer a health benefit to the host” (Hill et al., 2014). The definition of prebiotics was updated by ISAPP three years later. A prebiotic was described as "a substrate that is selectively utilized by host microorganisms, conferring a health benefit." The concept of prebiotics was expanded to include their application beyond the gastrointestinal tract and various substances other than food. For a substance to be considered a prebiotic, it must act in a selective manner, dependent on the microbiota, and have a documented positive effect on health (Gibson et al., 2017). Synbiotics are formulations that combine probiotics and prebiotics, working together to support the immune system and gastrointestinal health (Al-Habsi et al., 2024). They can be classified into two types: complementary synbiotics, which contain probiotics and prebiotics that act independently, and synergistic synbiotics, where the prebiotics are specifically selected for selective utilization by particular gut microorganisms (Lee et al., 2024).

Probiotic products may include one or more specific strains of microorganisms. The most commonly used human-derived microorganisms in probiotics include *Lactobacillus*, *Bifidobacterium*, *Lactococcus*,

Streptococcus, and *Enterococcus*. Additionally, probiotics often contain selected strains of yeast from the genus *Saccharomyces*, as well as bacterial strains from the genus *Bacillus* (Markowiak & Śliżewska, 2017). Probiotics support the host's immune system and provide protection against a variety of diseases. Their key properties, including the ability to colonize, eliminate pathogens and induce host cells, play a significant role in the management of numerous chronic conditions, thereby contributing to the overall improvement of health (M. K. Yadav et al., 2022).

Prebiotic products support the growth of various types of natural gut bacteria, with their effects being specific to individual strains and species. Prebiotics hold significant potential in shaping the composition of the gut microbiota. However, their effects may vary depending on the specific strains involved. Carbohydrate-rich foods, such as fruits, vegetables, grains and other edible plants, can serve as natural prebiotics. Meanwhile, artificially produced prebiotics include compounds such as lactulose, galactooligosaccharides, fructooligosaccharides, maltooligosaccharides, cyclodextrins and lactosucrose. Among prebiotics, fructans, such as inulin and oligofructose, are particularly notable for their high efficacy in influencing various species of probiotic bacteria (Markowiak & Śliżewska, 2017).

4.2. Modulation of glucose metabolism

Probiotics and/or prebiotics may represent a promising strategy for improving insulin sensitivity by modulating the composition of the gut microbiome. A study conducted by Yadav H et al. utilised mouse models to demonstrate that one potential antidiabetic mechanism is the increase in butyrate and SCFAs levels by certain probiotics, particularly VSL#3. That increment leads to the release of glucagon-like peptide-1 (GLP-1) from intestinal L-cells, potentially influencing glucose levels. Furthermore, VSL#3 was shown to inhibit weight gain and insulin resistance through favorable modulation of the gut microbiota composition. The administration of VSL#3 not only prevented obesity and diabetes but also proved effective in treating these conditions in several cases (H. Yadav et al., 2013). Other potential antidiabetic mechanisms of probiotics may involve a reduction in oxidative stress. In a randomized, double-blind, placebo-controlled clinical trial, patients with type 2 diabetes in the intervention group consumed 300 g/day of probiotic yogurt containing *Lactobacillus acidophilus* La5 and *Bifidobacterium lactis* Bb12, while those in the control group consumed 300 g/d of conventional yogurt for six weeks. The study revealed that probiotic yogurt significantly reduced fasting glucose levels and HbA1c, while also enhancing erythrocyte superoxide dismutase and glutathione peroxidase activity, as well as total antioxidant status, compared to the control group. These findings imply that probiotic yogurt may represent a potential therapeutic option for managing type 2 diabetes (Ejtahed et al., 2012). In the prebiotic group, inulin, has been extensively studied for its potential benefits on lipid and glucose metabolism. The research showed that incorporating inulin into the diet may serve as an effective strategy for preventing metabolic syndrome. It has been demonstrated that enriching the diet with inulin-fortified pasta improved lipid metabolism, glycogen storage, and insulin resistance in healthy young individuals. Furthermore, inulin delayed gastric emptying time, which may explain its positive impact on metabolic processes (Russo et al., 2010). Another prebiotic, starch, has been shown to have a beneficial effect on glucose tolerance in individuals with both normal and impaired glucose tolerance. These effects include a reduction in blood glucose and insulin levels, as well as improvement in glycemic control in individuals with diabetes. Studies indicate that consuming products containing moderate quantities of resistant starch and soluble fiber can enhance glucose metabolism in both normal-weight and overweight women (Behall, 2006). A subsequent study examined the effect of resistant starch on insulin levels in overweight and obese men. The results suggested that the consumption of 15-30g/day of high-amylose type 2 corn starch ameliorates insulin sensitivity in these men (Maki et al., 2012). Furthermore, a review study conducted by Kim et al. analyzed 12 studies on the application of synbiotics. In 11 of these studies, synbiotics demonstrated a positive impact on glucose metabolism. Additionally, it was observed that synbiotics had a more favorable effect in controlling glycemic levels and inflammation compared to the use of probiotics alone (Y. A. Kim et al., 2018). Probiotics, prebiotics and synbiotics play a crucial role in modulating the gut microbiota, influencing its composition and function, which may result in numerous health benefits. However, due to the specificity of the action of individual strains, further research is required to fully understand their mechanisms of action and therapeutic potential.

5. Conclusions

The gut microbiota has been demonstrated to play a significant role in the pathogenesis of insulin resistance, type 2 diabetes, and obesity. A reduction in gut microbiota diversity, including a significant decline in the number of bacteria producing short-chain fatty acids, promotes the development of chronic inflammation and impaired insulin metabolism. Alterations in the gut microbiota composition result in increased permeability of the intestinal barrier, facilitating the translocation of bacterial lipopolysaccharides into the circulation. Consequently, it activates innate immune response receptors, encompassing TLR4, leading to a substantial production of proinflammatory cytokines, such as TNF-α and IL-6. These cytokines disrupt the functioning of insulin signaling pathways at the level of its receptor and substrates, resulting in the development of insulin resistance. Environmental factors, comprising a diet rich in fiber, polyphenolic compounds and plant-based products, continue to have a notable positive impact on the composition and function of the gut microbiota. These factors contribute to the enhancement of the intestinal metabolic homeostasis through the increment of beneficial bacterial metabolites. In turn, a high-fat, low-fiber diet promotes the disruption of the gut ecosystem and exacerbates metabolic disorders. Interventions directed towards the improvement of the gut microbiota, including the utilization of probiotics, prebiotics, or synbiotics, can improve cellular insulin sensitivity and, consequently, glycemic control. This augmentation is achieved through a number of mechanisms, encompassing the stimulation of short-chain fatty acids production, a reduction in oxidative stress, and a promotion of incretins secretion. However, it should be noted that the observed effects are largely dependent on individual characteristics, doses, and the bacterial strains used. Understanding the interactions between the gut microbiome and the host could contribute to the development of even more effective strategies for the prevention and treatment of insulin resistance and metabolic diseases. Nevertheless, further, well-designed clinical studies are still required to elucidate their therapeutic potential.

Ethics Approval: The study was a descriptive one. No humans or animals were a subject of examinations.

Conflicts of Interest: No conflicts of interest to declare.

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