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THE ROLE OF GUT MICROBIOTA, FIRMICUTES/BACTEROIDETES RATIO, AND SHORT-CHAIN FATTY ACIDS IN THE PATHOGENESIS OF TYPE 2 DIABETES MELLITUS

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Abstract
This study aims to understand the role of gut microbiota imbalance, specifically an increased ratio of Firmicutes to Bacteroidetes, in the pathogenesis of type 2 diabetes mellitus (T2DM). Using systematic literature review and thematic analysis. Data were collected from various scientific sources, including journal articles indexed in PubMed, Scopus, and ScienceDirect, this study explores how gut dysbiosis contributes to insulin resistance, impaired glucose metabolism, and chronic inflammation. The results show that changes in microbiota composition result in increased energy extraction from food, impaired gut barrier integrity, and altered production of short-chain fatty acids (SCFAs) such as butyrate, which play a role in glucose homeostasis and inflammation regulation. These findings also emphasize the potential of probiotic, prebiotic, and dietary modification interventions to restore microbiota balance, improve insulin sensitivity, and reduce oxidative stress. Overall, this study highlights the urgency of a personalized approach in the management of T2DM through modulation of the gut microbiota based on the latest clinical and mechanistic evidence.

Keywords: gut microbiota, short-chain fatty acids, *type 2 diabetes mellitus*

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INTRODUCTION

Recent studies highlight the critical role of gut microbiota composition in the pathogenesis of type 2 diabetes mellitus (T2DM). Dysbiosis, particularly an elevated Firmicutes/Bacteroidetes ratio, has been associated with metabolic dysfunction, including insulin resistance and impaired glucose homeostasis (Allin et al., 2018; Gurung et al., 2020). These microbial imbalances may contribute to T2DM by altering host metabolism, promoting low-grade inflammation, and disrupting intestinal barrier integrity (Wu et al., 2020). Additionally, gut bacteria-derived short-chain fatty acids (SCFAs), such as butyrate and propionate, play a dual role in diabetes—modulating immune responses and improving insulin sensitivity, yet their depletion has been linked to disease progression (Huang et al., 2020; Mollica et al., 2017). Understanding these mechanisms provides valuable insights for developing microbiota-targeted interventions, including probiotics, prebiotics, and personalized dietary strategies, to manage or prevent T2DM (Sircana et al., 2018; Xiao et al., 2023).

Managing the ration of Firmicutes to Bacteroidetes not only influences body composition and metabolic health but also affects oxidative stress levels within individuals suffering from type 2 Diabetes Mellitus. This microbial imbalance often leads to increased stress on metabolic pathways essential for the effective processing of glucose, which further exacerbates insulin resistance. An optimal gut environment characterized by a balanced Firmicutes to Bacteroidetes ratio may help lower oxidative stress, thereby potentially slowing down the progression of diabetes related complications (Ohtani, 2019). Moreover, this balance could enhance the presence of beneficial bacterial metabolites that help maintain the integrity of the gut barrier, thereby reducing the risk of inflammation-induced metabolic disturbances. By focusing on microbiota composition, it might be possible to develop dietary or probiotic-based interventions aimed at restoring microbial equilibrium, offering a promising adjunctive strategy for improving glucose metabolism and overall metabolic health in individuals with diabetes.

METHOD

This research method employed a qualitative approach through systematic literature review and thematic analysis. Data were collected from various scientific sources, including journal articles indexed in PubMed, Scopus, and ScienceDirect, published in the past 15–20 years that addressed the relationship between gut microbiota, the Firmicutes/Bacteroidetes ratio, short-chain fatty acids (SCFA) production, inflammation, and the pathogenesis of type 2 diabetes mellitus (T2DM). The search process was conducted using keywords such as gut microbiota, Firmicutes/Bacteroidetes ratio, SCFA, insulin resistance, and type 2 diabetes mellitus. Articles were selected based on inclusion criteria such as topic relevance, methodological quality, and the explanation of biological mechanisms. Studies with limited data or high bias were excluded. The obtained data were then analyzed thematically to identify key patterns related to dysbiosis, metabolic disorders, inflammation, and potential therapeutic interventions. Data validity was maintained through source triangulation, comparison of findings between studies, and critical evaluation of the quality of research methods. Through this approach, research produces a comprehensive understanding of the role of microbiota dysbiosis in the pathogenesis of T2DM as well as the opportunities for microbiota modulation as a therapeutic strategy.

RESULT DAN DISCUSSION

Gut Microbiota and Type 2 Diabetes Mellitus

The balance of gut microbiota is a critical factor in maintaining metabolic health, particularly in the context of type 2 Diabetes Mellitus. An imbalance, characterized by an increased ratio of Firmicutes to Bacteroidetes, is commonly observed in individuals with diabetes. This skewed microbial composition is linked to disruptions in glucose metabolism and increased insulin resistance, both of which are critical in the pathogenesis of diabetes (Ohtani, 2019). According to Zhu et al., altered gut flora can precipitate metabolic disorders by impacting the body's ability to process glucose effectively (Zhu et al., 2017). Therefore, maintaining an optimal gut microbiota may help alleviate some of metabolic disturbances associated with diabetes, offering potential avenues for therapeutic interventions aimed at restoring microbial balance to support metabolic health.

The gut microbiota significantly influences type 2 diabetes mellitus (T2DM) through its impact on body composition. Specific beneficial bacteria, such as Bacteroides and Bifidobacterium, are associated with improved metabolic profiles, potentially counteracting diabetes-related effects by regulating fat storage and energy metabolism (Pintarič et al., 2022; Liu et al., 2022). These microbes produce short-chain fatty acids (SCFAs), particularly butyrate, which serve as energy substrates for colonocytes and exhibit anti-inflammatory effects, thereby reducing systemic inflammation—a key contributor to insulin resistance (Canfora et al., 2015). Additionally, these bacterial communities help maintain gut barrier integrity; their disruption can lead to increased intestinal permeability ("leaky gut"), endotoxinemia, and worsened metabolic dysfunction (Agus et al., 2021). Targeted modulation of the gut microbiota, through probiotics, prebiotics, or dietary interventions, may therefore offer a promising therapeutic approach to enhance metabolic health in T2DM (Depommier et al., 2019).

Alterations in Gut Microbiota Composition

In individuals with type 2 diabetes mellitus, a notable alteration in gut microbiota composition is the relative increase in Firmicutes acoompanied by a decrease in Bacteroidetes. This imbalance is significant due to its role in exacerbating insulin resistance and compromising glucose metabolism. The skewed Firmicutes to Bacteroidetes ration has been linked to an increase in calorie extraction from food, potentially leading to obesity and subsequent metabolic issues (Ohtani, 2019). According to Li et al., this microbial dysbiosisis observed consistently among diabetic patient populations, further emphasizing its importance in the disease's pathology (Li et al., 2019). Consequently, understanding and addressing these microbial shift could represent a key approach in mitigating the progression of type 2 diabetes mellitus and improving health outcomes.

Furthermore, the alteration in gut microbiota, specifically the increased Firmicutes to Bacteroidetes ratio, affect metabolic process that are integral to diabetes progression. This change has been suggested to enhance the ability to extract energy from consumed food, potentially leading to increased calorie intake and obesity, both of which are precursors to type 2 diabetes mellitus (Ohtani, 2019). The microbial population shifts also have implications for the regulation of insulin sensitivity and glucose absorption, as they can promote inflammatory pathways, which in turn exacerbate insulin resistance (Zhu et al., 2017). Studies indicate that these microbial imbalances interfere with the secretion and signalling of insulin, crucial for glucose homeostasis, thereby contributing to the metabolic dysfunctions observed in diabetic patients (Li et al., 2019). Therefore, targeting these specific microbial differences presents an opportunity for novel therapeutic approaches aimed at ameliorating metabolic disturbances and improving glucose regulation in individuals with type 2 diabetes mellitus.

Additionally, numerous studies have observed consistent patterns in the gut microbiota alterations among patients with type 2 diabetes mellitus. Specifically, the rise in the Firmicutes to Bacteroidetes ratio has been a recurring finding, suggesting a foundational link between these bacterial shifts and metabolic disorder (Ohtani, 2019). Li et al. noted that such microbial changes are prevalent among diabetic populations, demonstrating a strong association across diverse patient groups (Li et al., 2019). Variations do exist, however, as Zhu's research highlighted the role of dietary interventions, which can modulate these microbial communities, potentially offering new avenues for managing insulin resistance (Zhu el al., 2021). Thus, while the overarching trend of altered gut microbiota is evident, variations stemming from lifestyle factors reinforce the need for personalized approaches in therapeutic strategies.

Impact on Insulin Resistance and Glucose Metabolism

Understanding the impact of gut microbiota composition on insulin resistance and glucose metabolism is central to addressing type 2 diabetes mellitus. The altered ratio of Firmicutes to Bacteroidetes is closely associated with changes in the host's metabolic processes, which affect insulin sensitivity. As indicated by Zhu et al., this microbial dysbiosis can disrupt glucose processing pathways, leading to heightened insulin resistance and impaired metabolic function (Zhu et al., 2017). Additionally, Ahmed's research suggest that the microbiota imbalance influences oxidative stress, contributing further to insulin resistance (Ohtani, 2019). Therefore, interventions aimed at modulating gut microbiota could

potentially enhance glucose metabolism and insulin sensitivity, offering a strategic avenue to mitigate the risks ot type 2 diabetes mellitus and improve patient outcomes.

Moreover, altered gut microbiota can interfere with insulin signalling pathways, thereby disturbing glucose homeostasis. The increase in Firmicutes and decrease in Bacteroidetes affects the phosphatidylinositol-3-kinase (PI3K) Akt signalling pathways, both of which are vital for insulin mediated glucose uptake (Zhu et al., 2017). Zhu et al. have shown that disruptions in these pathways due to microbial imbalances can lead to heightened insulin resistance and impaired glucose processing. Furthermore, Ahmed highlight that increased oxidative stress resulting from microbiota dysbiosis exacerbates these signalling disruptions, compounding metabolic disturbances (Ahmed et al, 2019). Hence, understanding these specific pathways through which gut microbiota alteration effect insulin signalling offers valuable insights into potential therapeutic interventions that aim to restore insulin sensitivity and ensure effective glucose regulation in type 2 diabetes mellitus.

Similarly, research has highlighted the link between alterations in gut microbiota and components of metabolic syndrome, including obesity and insulin resistance. The increased Firmicutes to Bacteroidetes ratio has been identified as a crucial factor influencing these metabolic disorders, due to its role in enhancing energy harvest from diet, thereby contributing to weight gain and subsequent obesity (Li et al., 2019). Zhu et al.'s research underscores how this microbial shift correlates with heightened insulin resistance, further exacerbating metabolic imbalances characteristic of type 2 diabetes mellitus (Zhu et al., 2017). Additionally, the presence of dysbiotic gut microbiota has been linked to an increased inflammatory state, which is significant in the development and progression of insulin resistance (Ohtani, 2019). Therefore, restoring the natural balance of gut bacteria could be pivotal in managing obesity and insulin resistance, potentially serving as a therapeutic target for mitigating the metabolic complications associated with diabetes.

Role of Short-Chain Fatty Acids

Short chain fatty acids (SCFA), produced by gut bacteria, play a vital role in maintaining metabolic health, particularly in the context of type 2 diabetes mellitus. These metabolic influence insulin sensitivity and regulate energy metabolism, offering potential in the management of diabetes. According to Tang and Li, SCFAs modulate glucose and energy homeostasis through various biochemical pathways, making them promising targets for therapeutic interventions in type 2 diabetes mellitus (Tang & Hazen, 2017). Furthermore, Yang et al. highlight that SCFAs exert anti-inflammatory effects, which could mitigate the inflammatory responses that contribute to diabetes progression (Yang et al., 2020). Therefore, enhancing the production of SCFAs within the gut microbiota could be an effective strategy for modulating metabolic and inflammatory outcomes associated with diabetes, thus paving the way for novel treatment approaches.

Influence on Inflammatory Responses

Short-chain fatty acids (SCFAs) play an essential role in modulating inflammatory responses, which are critical in the development and progression of type 2 diabetes mellitus. These metabolites, by interacting with immune cells, can influence the secretion of inflammatory mediators, thereby affecting the inflammatory environment within the host. According to Yang et al., SCFAs such as butyrate exhibit anti-inflammatory properties by inhibiting the activation of nuclear factor kappa B, a key transcription factor in inflammation pathways (Yang et al., 2020). Moreover, the ability of SCFAs to promote the production of regulatory T cells further underscores their role in maintaining immune homeostasis and mitigating chronic inflammation associated with diabetes (Cherta-Murillo et al., 2022). Therefore, enhancing SCFA production through dietary interventions or supplementation could present an effective strategy in combating the inflammatory aspects of type 2 diabetes mellitus, offering a promising therapeutic avenue.

Consequently, the modulation of SCFAs presents a promising therapeutic avenue for managing pr potentially preventing type 2 diabetes meliitus. Given their role in regulating glucose and energy homeostasis. Targeted increases in SCFA production could enhance insulin sensitivity and mitigate metabolic disorders characteristic of diabetes (Tang & Hazen, 2017). Furthermore, dietary strategies or supplementation aimed at boosting SCFA levels might attenuate the inflammatory responses that exacerbate insulin

resistance and contribute to the disease's progression (Yang et al., 2020). By enhancing the beneficial effects of SCFAs, intervention could not only improve glycemic control but alse support overall metabolic health in diabetic individuals (Cherta-Murillo et al., 2022). Therefore, ongoing research into SCFA modulation holds significant potential for developing nove therapeutic strategies tailored to the complex metabolic needs of type 2 diabetes mellitus patients.

Contribution to Diabetes Development

SCFAs contribute to the development of type 2 diabetes mellitus through both direct and indirect effects on key metabolic pathways. These metabolites enhance insulin sensitivity by engaging with receptors such as G-protein-coupled receptors, which play pivotal roles in glucose homeostasis. Moreover, SCFAs have been linked to the modulation of adipose tissue distribution, which directly impacts insulin resistance and energy metabolism, critical factors in diabetes progression. Indirectly, SCFAs mitigate inflammation, a significant contributor to diabetes, by promoting the growth of beneficial gut bacteria and inhibiting pro inflammatory cytokines (Yang et al., 2020). Consequently, the comprehemsive impact of SCFAs on metabolic health highlights their potential as therapeutic agents, offering promising pathways for innovative diabetes treatments that address both the metabolic and inflammatory dimensions of the diasease.

In fact, the exploration of SCFAs as biomarkers or therapeutic targets for diabetes treatment has garnered significan attention in current research. SCFAs, through their interaction with G-protein cupled receptors, are thought to influence metabolic processes, such as glucose homeostasis and energy balance, delineating their potential as markers of metabolic health. Rekha et al. underscore the necessity of understanding SCFAs' roles within these pathways to delineate their applicability as biomarkers (Rekha et al., 2024). Meanwhile, studies by Tang and Li emphasize the therapeutic promise of modulating SCFA levels to enhance insulin sensitivity and provide novel pathways for controlling type 2 diabetes mellitus. Consequently, as research progresses, SCFAs may serve as both indicators of disease progression and key targets for therapeutic intervention, offering a dual approach to diabetes management that could significantly improve patient outcomes.

Furthermore, re-establishing the balance between Firmicutes and Bacteroidetes may play a critical in mitigating diabetic symptoms by reducing oxidative stress and improving metabolic health. According to Ahmed et al., manipulating the F:B ratio can lessen oxidative stress, a known contributor to the pathogenesis of diabetes, by enhancing the body's antioxidant defences and supressing chronic inflammation (Ohtani, 2019; Qin et al., 2012). This adjustment not only aids in insulin sensitivity but also offers a preventative strategy that could contribute to halting the progression of type 2 diabetes mellitus. Evaluating and modifying the gut microbiota composition offers a novel, natural approach to disease management. By shifting toward a healthier microbial balance, it may be possible to develop interventions that synergize with existing treatments, promoting a more comprehensive approach to diabetes care.

CONCLUSION

In conclusion, the exploration of gut microbiota composition changes and their link to type 2 diabetes mellitus highlights significant pathways through which microbial balance affects metabolic health. The increase in Firmicutes coupled with a decrease in Bacteroidetes has been associated with insulin resistance and glucose metabolism disruptions. Suggesting this imbalance plays a crucial role in diabetes development. Furthermore, the role of SCFAs extend beyond metabolic processes; they modulate inflammatory responses, providing insights into therapeutic strategies that can mitigate diabetes progression. Although these findings offer promising directions, they underline the need for further research to refine our understanding and develop effective therapeutic interventions. Ultimately, focusing on gut microbiota and SCFAs may open new avenues for personalized medicine approaches, offering potential for more effective management of diabetes through tailored microbial modulation strategies.

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