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Metformin's Gut Microbial Influence in Type 2 Diabetes: Unraveling a Therapeutic Symphony

Hinduja A[1]*, Chheda N[2] and Pandya A[3]

[1]Aarti Clinic ®, India

[2]Product Lead, Virtus Nutrition Pvt Ltd, India

[3]Lead Customer Success, Virtus Nutrition Pvt Ltd, India

***Corresponding author:** Anand Hinduja, Aarti Clinic ®, Kharghar, Navi Mumbai, Maharashtra, India; Tel no: 7738139998; E-mail: dranand01@gmail.com

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Abstract

This article explores the intricate relationship between metformin, the gut microbiome, and type 2 diabetes (T2DM), highlighting interconnected therapeutic effects while incorporating technological advancements in gut microbiome testing. Recent evidence challenges the conventional perspective on metformin's action, emphasizing the gut, particularly through modulation of the adenosine monophosphate-activated protein kinase (AMPK) pathway. The introduction of delayed-release formulations further underscores the importance of metformin's interactions within the gastrointestinal system. Detailed investigations into metformin's impact on the gut microbiome reveal positive shifts, including increased *Akkermansia muciniphila and Escherichia coli* populations, influencing the production of short-chain fatty acids. Concurrently, studies with probiotics exhibit promising outcomes, showing reductions in fasting glucose and HbA1c levels among individuals with T2DM.

However, metformin therapy comes with challenges, such as a reduction in gut microbiota diversity and the emergence of gastrointestinal symptoms. This article emphasizes the need for a holistic and personalized approach to T2DM management, incorporating technological advancements in gut microbiome testing. In this context, emerging technologies in gut microbiome testing offer a transformative approach, allowing for precise monitoring and individualized interventions. Integrating advanced diagnostics enables a more nuanced understanding of the dynamic interplay between metformin, the gut microbiota, and T2DM. Strategic interventions involving dietary modifications, prebiotics, probiotics, and vigilant monitoring using cutting-edge technology form a sophisticated and personalized approach to diabetes management. In summary, this exploration not only sheds light on the metformin-microbiome interplay but also underscores the potential of technology in refining health strategies for the tailored management of T2DM.

Keywords: Metformin; Gut Microbiome; Type 2 Diabetes; Probiotics; Gut Management; SCFA

Abbreviations: AMPK: Adenosine Monophosphate-activated Protein Kinase; T2DM: Type 2 Diabetes Mellitus; SCFA: Short-Chain Fatty Acid; FXR: Farnesoid X Receptor.

Introduction

Type 2 diabetes mellitus (T2DM) represents a pervasive chronic metabolic disorder characterized by hyperglycemia, stemming from the interplay of insulin resistance and inadequate insulin secretion. Over recent decades, the prevalence of T2DM has surged substantially. Metformin, a member of the biguanide class, is a widely endorsed first-line therapy for T2DM by both the American Diabetes Association and the European Association for the Study of Diabetes. Historically derived from galegine in *Galega officinalis*, metformin has traditional roots in lowering blood

sugar and alleviating diabetes symptoms [1,2].

Metformin, a widely prescribed first-line therapy for T2DM, while traditionally acknowledged for its hepatic actions, recent evidence elevates the gut to a pivotal site of metformin activity. The drug exerts influence on various aspects of intestinal function, including glucose uptake, lactate production, GLP-1 concentrations, bile acid pool, and microbiome composition. The introduction of a novel delayed-release metformin formulation presents a promising advancement, demonstrating comparable efficacy with reduced systemic exposure. Metformin's effects on the gut, encompassing shifts in microbiome dynamics and bile acid exposure, contribute significantly to both its therapeutic benefits and observed intolerances [3,4].

While metformin has been conventionally perceived to primarily target the liver, recent investigations challenge this perspective, proposing that the gut plays a pivotal role in metformin's therapeutic actions. This shift in focus stems from emerging evidence indicating that metformin, lacking specificity in targeting particular pathways or disease mechanisms, may exert its effects, particularly in glucose tolerance modulation, through the adenosine monophosphate-activated protein kinase (AMPK) activity in the gut. Thus, the gut microbiome gains attention as a crucial factor in T2DM treatment, with the hypothesis that the human gastrointestinal tract is metformin's primary site of action.

This article explores the intricate relationship between the gut microbiome and the anti-diabetic effects of metformin. Numerous studies have revealed metformin's impact on inflammation, gut permeability, glucose homeostasis, and the abundance of short-chain fatty acid (SCFA)-producing bacteria. Medications like metformin play a pivotal role in comprehensively addressing insulin resistance and achieving blood glucose control. Metformin's multifaceted activities include cellular pathway activation, insulin sensitivity enhancement, glucose uptake facilitation in the intestines, SCFA production promotion, intestinal barrier protection, and gut peptide secretion regulation. Additionally, the complex interplay between metformin and the gut microbiota adds a layer of complexity, as gut microbes participate in drug metabolism, influencing metformin's overall efficacy. In this exploration of the symbiotic relationship between metformin, the gut microbiome, and T2DM, we unravel the intriguing mechanisms underpinning their interconnected therapeutic effects.

Research

Recent studies have delved into the intricate relationship between metformin, a widely used medication for T2DM, and the gut microbiota. The following summaries provide a comprehensive overview of the diverse findings, shedding light on the multifaceted effects of metformin on gut microbial composition and its potential implications for T2D treatment.

Akkermansia muciniphila, a pivotal species affected by metformin, plays a role in maintaining mucosal integrity and is linked to glucose regulation. In patients with prediabetes and newly diagnosed T2DM, its reduced abundance may serve as a biomarker of glucose intolerance. Metformin-treated patients with T2DM show an elevated proportion of *Akkermansia muciniphila*, implying a positive impact on gut health. Furthermore, these patients demonstrate gut microbiome richness similar to that of the control group, hinting at a potential mitigating effect of metformin on microbiome alterations associated with T2DM [5].

A broader examination of metformin's impact on the gut microbiome reveals both positive and negative changes. Positive alterations include increased abundance of beneficial species like *Akkermansia muciniphila* and *Escherichia coli*, crucial for mucosal integrity and implicated in conditions like obesity, diabetes, and cardiovascular disease. Metformin also leads to shifts in gut metabolomics, enhancing the production of butyrate and propionate, vital for glucose homeostasis. The reduction in pathogenic taxa like *Peptostreptococcaceae* and *Clostridiaceae* further signifies the potential benefits of metformin [6,7]. The observed alterations in gut microbiota composition and metabolomics underscore metformin's broader impact on the microbiome.

Further studies delve into the intricate landscape of disease and drug signatures within the human gut microbiome of individuals with T2DM, through an examination of 784 human metagenomes. This research sheds light on the intricate interplay influenced by antidiabetic medication, particularly metformin. While confirming the concept of microbial mediation in metformin's therapeutic effects, notably through the production of short-chain fatty acids (SCFAs), the study uncovers additional facets of potential microbiota-mediated mechanisms, including a noteworthy relative increase in *Escherichia* abundance associated with intestinal adverse effects. By meticulously controlling for metformin treatment, this study elucidates a cohesive signature of gut microbiome shifts in T2D, underscoring the imperative to disentangle disease-specific effects from those attributed to medications in the realm of microbiome research [8].

In another exploration of metformin's anti hyperglycemic effects among individuals newly diagnosed with T2DM, a three-day treatment regimen induced notable shifts in the gut microbiota. Specifically, there was a decrease in

Bacteroides fragilis levels, accompanied by an increase in the bile acid glycoursodeoxycholic acid (GUDCA), and the inhibition of intestinal farnesoid X receptor (FXR) signaling. These alterations were correlated with improvements in metabolic dysfunction, particularly hyperglycemia. The study posits that metformin may, at least partially, act through a *Bacteroides fragilis*-GUDCA-intestinal FXR axis to deliver therapeutic benefits for metabolic health in individuals with T2D [9].

Combining metformin with probiotics emerges as a potential strategy in T2D management, as evidenced by a systematic review and meta-analysis encompassing 14 randomized controlled trials with 1009 patients. The combination results in a significant reduction in fasting glucose and HbA1c levels. Notably, this combined approach was also associated with a lower incidence of gastrointestinal adverse events [10]. Another study, focusing on the impact of a multi-strain probiotic in a 12-week randomized controlled subgroup taking probiotics, suggests a synergistic effect with metformin, particularly in enhancing glucose management through decreased fasting plasma glucose, HbA1c, insulin resistance and zonulin along with increased butyrate production. This suggests that probiotics may act as an adjunct to metformin, enhancing glucose management through increased butyrate production [11].

Building on this exploration, another study focused on the pivotal role of gut microbiota in the prevention and treatment of T2D. This research delved into the impact of environmental factors, such as diet, medication, and surgery, on the gut microbial composition of individuals with T2D. The study revealed altered bacterial profiles, including reduced abundance of butyrate-producing bacteria and *Akkermansia muciniphila*. Notably, metformin, a common T2D medication, was identified as an influencer of gut microbiota, leading to changes in the abundance of specific bacterial species. This study suggested potential personalized interventions, highlighting the importance of a comprehensive approach involving diet, probiotics, and microbiota modulation, along with targeted delivery of short-chain fatty acids [12].

Expanding our understanding of the microbiota-mediated impact on metabolic health, a third study elucidated the role of metformin in influencing glucose metabolism through positive effects on the gut microbiota. This study emphasized that abnormalities in gut microbiota composition, such as reduced microbial diversity, a higher *Firmicutes*/*Bacteroidetes* ratio, and altered metabolites, play a role in obesity and T2D. Metformin was found to promote beneficial changes, including increased *Akkermansia muciniphila* and enhanced production of short-chain fatty acids, suggesting a potential avenue for reshaping the microbial landscape to improve metabolic outcomes in T2D [13].

In a study analyzing metagenomics data from 22 treatment-naïve individuals with T2DM, the impact of metformin on the gut microbiome was investigated. Over a 12-week period, metformin treatment induced significant alterations in microbiome composition, marked by changes in taxonomic abundance and enterotype shifts. Notable increases were observed in beneficial microbes such as *Akkermansia muciniphila* and *Bifidobacterium*, while potentially harmful species like *Intestinibacter bartlettii* decreased. The study utilized systems biology approaches to explore metformin's effects on specific species, metabolic pathways, and metabolites, including short-chain fatty acids and amino acids. Emphasizing the potential interplay between metformin, gut microbiota, and dietary factors, the research aimed to better understand how these interactions modulate metabolic responses and minimize side effects in individuals with T2D [14].

Another investigation focused on newly diagnosed, treatment-naive individuals with T2D and explored the impact of metformin over a 2-month period. Beyond conventional glycemic improvements, this study utilized 16S rRNA sequencing to analyze the gut microbiota. The findings revealed specific microbial changes, with reductions observed in *Megamonas* and *Klebsiella*. Spearman's correlation analysis indicated positive associations between *Megamonas* and various glycemic markers, as well as similar correlations for *Klebsiella* with glycated hemoglobin and alanine aminotransferase. These results suggested that metformin's influence on T2D outcomes might extend beyond glycemic control to encompass the modulation of specific gut bacteria, presenting potential avenues for personalized therapeutic interventions [15].

These studies collectively advance our understanding of the intricate interplay between gut health, medication, and metabolic outcomes, emphasizing the potential benefits of personalized interventions, including combining probiotics with metformin, for individuals with T2DM. This evolving knowledge opens avenues for further research and targeted strategies in T2D management. The studies offer valuable insights into the complex relationship between metformin, the gut microbiome, and T2D outcomes. While one study employed a broader metagenomic analysis, the second, focusing on newly diagnosed individuals, identified specific microbial changes associated with improved glycemic markers. Both studies highlight the importance of comprehending the interplay between metformin and the gut microbiome for a holistic approach to T2D management.

However, the beneficial aspects coexist with negative effects. Metformin treatment is associated with reduced gut microbiota diversity, an increased abundance of opportunistic pathogens like *Escherichia-Shigella* spp., and heightened

abdominal symptoms, including diarrhea, constipation, and gastrointestinal discomfort. Furthermore, increased glucose uptake in the intestine contributes to elevated lactate concentrations, potentially leading to metformin intolerance [16]. Recognizing these side effects becomes imperative in prescribing metformin for the long term.

Conclusion

The bidirectional relationship between the gut microbiome and diabetes highlights the need for a holistic approach to diabetes management. Factors influencing the gut microbiome, such as age, nutrition, lifestyle, sleep cycles, stress, genetic predisposition, and medications, should be considered [17]. Strategies encompassing dietary modifications, prebiotics and probiotics intake, stress management, proper sleep schedules, physical activity, and periodic tests are crucial components of effective diabetes management. Medications, including metformin, should be administered under a physician's guidance, with immediate consultation in case of gastrointestinal side effects.

In conclusion, understanding the intricate interplay between metformin, the gut microbiome, and diabetes is paramount for formulating effective health strategies. Embracing a comprehensive approach that considers recent advancements in metagenomics and addresses both the positive and negative aspects of metformin's impact on the gut microbiome ensures a more nuanced and personalized management of diabetes, promoting overall well-being.

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