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The Gut-Glycemic Axis in the Indian Geriatric Population: Evaluating Pre and Probiotic Interventions as Adjuncts to Metformin in Type 2 Diabetes Management

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ABSTRACT

Type 2 diabetes mellitus (T2DM) is highly prevalent among the geriatric population in India, driven by aging-related metabolic changes and lifestyle factors. The gut–glycemic axis has emerged as a key regulator linking intestinal microbiota with glucose metabolism. Dysbiosis contributes to insulin resistance, inflammation, and poor glycemic control in T2DM. Metformin, the first-line therapy, exerts part of its effects through modulation of gut microbiota. Prebiotics and probiotics have shown potential in improving metabolic outcomes by enhancing beneficial bacteria and short-chain fatty acid production. Their use alongside metformin may provide synergistic benefits and improve treatment tolerance. However, evidence in the Indian elderly population remains limited despite distinct dietary and microbiome patterns. Understanding these interactions may enable development of targeted, microbiome-based strategies for better diabetes management.

KEYWORDS:

• Gut–Glycemic Axis • Type 2 Diabetes Mellitus • Prebiotics • Probiotics • Metformin • Geriatric Population

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from insulin resistance and impaired insulin secretion.[1] The prevalence of T2DM has increased dramatically over the past few decades, particularly among older adults, making it a major global public health concern.[2] Population aging has further intensified this burden because elderly individuals experience age-related metabolic changes such as reduced insulin sensitivity, altered pancreatic β-cell function, and increased systemic inflammation.[3] In India, the rapid expansion of the geriatric population combined with lifestyle transitions has contributed to a significant rise in diabetes prevalence among older adults.[4] Consequently, there is an urgent need for innovative therapeutic strategies that address not only glycemic control but also the underlying metabolic and physiological factors contributing to diabetes progression.[5]

Recent research has highlighted the importance of the gut–glycemic axis, which describes the interaction between the intestinal microbiota and host glucose metabolism.[6] The human gastrointestinal tract harbors trillions of microorganisms that play essential roles in digestion, immune modulation, and metabolic regulation.[7] These microorganisms influence host metabolism through the production of bioactive metabolites such as short-chain fatty acids (SCFAs), modulation of bile acid metabolism, and regulation of inflammatory pathways.[8] Accumulating evidence indicates that alterations in gut microbiota composition, known as dysbiosis, are associated with metabolic disorders including obesity and T2DM.[9] Patients with T2DM frequently exhibit reduced microbial diversity and decreased abundance of beneficial butyrate-producing bacteria, which may impair glucose homeostasis and promote metabolic inflammation.[10]

Metformin is widely recognized as the first-line pharmacological therapy for T2DM due to its ability to reduce hepatic glucose production and improve insulin sensitivity.[11] Interestingly, recent studies suggest that part of metformin's glucose-lowering effect may be mediated through modifications of the gut microbiota.[12]

Metformin has been shown to increase the abundance of beneficial bacterial genera such as *Bifidobacterium* and *Lactobacillus*, which are associated with improved metabolic outcomes.[13] These microbial changes may enhance the production of SCFAs and improve intestinal barrier function, thereby contributing to better glycemic regulation.[14] In this context, microbiota-targeted dietary interventions such as prebiotics and probiotics have gained increasing attention as complementary approaches in diabetes management.[15] Furthermore, metformin-induced alterations in gut microbiota may influence bile acid metabolism and activate intestinal signalling pathways involved in glucose regulation.[14] For instance, interactions between gut microbes and bile acids can modulate receptors such as the farnesoid X receptor (FXR), which contributes to improved glucose and lipid metabolism.[14] In addition, microbiota changes induced by metformin may strengthen the intestinal barrier and reduce systemic inflammation associated with metabolic disorders.[16] These findings suggest that part of metformin's glucose-lowering effect may be mediated through its ability to modulate gut microbial composition and metabolic activity. Understanding the interaction between metformin and the gut microbiome provides new insights into the mechanisms underlying its therapeutic efficacy and highlights the potential for microbiota-targeted interventions, such as probiotics and prebiotics, as complementary strategies in diabetes management. Several clinical trials and meta-analyses have demonstrated that probiotic supplementation can improve fasting blood glucose, insulin sensitivity, and glycated hemoglobin (HbA1c) levels in individuals with T2DM.[17] Similarly, prebiotic intake has been shown to enhance SCFA production and modulate inflammatory responses associated with metabolic disorders.[8]

Emerging evidence also suggests that combining probiotics or prebiotics with metformin therapy may produce synergistic benefits in glycemic control and metabolic regulation.[18] Such combination approaches may improve treatment efficacy while potentially reducing gastrointestinal side effects commonly associated with metformin therapy.[14] However, the role of microbiota-targeted interventions in the Indian geriatric population remains insufficiently explored. Dietary habits, genetic background, and environmental factors unique to the Indian population may significantly influence gut microbiota composition and metabolic responses.[19] Therefore, understanding the gut–glycemic axis in this demographic context is essential for developing personalized and effective diabetes management strategies. This review aims to evaluate the current evidence regarding the gut–glycemic axis and to explore the potential role of prebiotic and probiotic interventions as adjuncts to metformin therapy in the management of type 2 diabetes among the Indian geriatric population.

THE GUT–GLYCEMIC AXIS: CONCEPT AND MECHANISMS

The gut–glycemic axis refers to the bidirectional relationship between the intestinal microbiota and host glucose metabolism, highlighting the role of the gut in regulating systemic metabolic homeostasis.[6] The human gastrointestinal tract contains a highly diverse microbial ecosystem composed of trillions of microorganisms, including bacteria, archaea, fungi, and viruses, which collectively contribute to metabolic, immunological, and endocrine functions.[7] Increasing evidence suggests that these microbial communities influence glucose metabolism through complex signalling pathways involving microbial metabolites, host immune responses, and hormonal regulation.[8]

One of the primary mechanisms through which the gut microbiota regulates glycemic control is the production of short-chain fatty acids (SCFAs) such as acetate, propionate, and butyrate during the fermentation of dietary fibres. These metabolites play a key role in improving insulin sensitivity, enhancing energy metabolism, and regulating appetite by stimulating the release of gut hormones such as glucagon-like peptide-1 (GLP-1) and peptide YY (PYY).[8] SCFAs also strengthen intestinal barrier integrity and reduce systemic inflammation, which is closely associated with insulin resistance and metabolic disorders.[9] Another important pathway in the gut–glycemic axis involves the modulation of bile acid metabolism by intestinal microbes. Gut bacteria can transform primary bile acids into secondary bile acids, which interact with host receptors such as the farnesoid X receptor (FXR) and Takeda G-protein receptor 5 (TGR5). Activation of these receptors influences glucose and lipid metabolism, improves insulin sensitivity, and regulates energy expenditure.[14]

Gut microbiota also plays a role in maintaining intestinal barrier function. Dysbiosis can increase intestinal permeability, allowing the translocation of microbial components such as lipopolysaccharides (LPS) into the bloodstream. This condition, often referred to as metabolic endotoxemia, triggers low-grade chronic inflammation that contributes to insulin resistance and the development of type 2 diabetes mellitus.[20] Furthermore, gut microbes interact with dietary components and pharmacological agents such as metformin, thereby influencing therapeutic responses in diabetes management.[12] Through these interconnected mechanisms, the gut–glycemic axis represents a crucial regulatory system linking diet, microbiota composition, and host metabolic health. Understanding these interactions provides a foundation for microbiota-targeted interventions, including prebiotics and probiotics, as potential strategies for improving glycemic control.

METFORMIN AND THE GUT MICROBIOME

Metformin is the most widely prescribed first-line pharmacological therapy for the management of type 2 diabetes mellitus (T2DM) due to its ability to effectively reduce blood glucose levels and improve insulin sensitivity.[11] Traditionally, the primary mechanism of metformin has been attributed to the inhibition of hepatic gluconeogenesis, leading to decreased glucose production by the liver.[11] Metformin also enhances peripheral glucose uptake, particularly in skeletal muscle, thereby improving insulin sensitivity and reducing circulating glucose levels.[21] In addition, the drug activates AMP-activated protein kinase (AMPK), a key cellular energy sensor that regulates glucose and lipid metabolism.[21] Activation of AMPK suppresses hepatic glucose production, promotes fatty acid oxidation, and improves metabolic homeostasis in individuals with T2DM.[11] Recent studies have suggested that the gastrointestinal tract plays a central role in mediating the therapeutic effects of metformin.[22] A significant proportion of orally administered metformin accumulates in the intestine, where it interacts directly with gut epithelial cells and the intestinal microbiota[22] This observation has led to an increasing interest in the role of the gut microbiome as an important mediator of metformin's metabolic effects.

PREBIOTICSINDIABETESMANAGEMENT

Prebiotics are non-digestible dietary components that selectively stimulate the growth and activity of beneficial microorganisms in the gastrointestinal tract, thereby conferring health benefits to the host.[15] Unlike probiotics, which involve the administration of live microorganisms, prebiotics function by providing substrates that promote the proliferation of beneficial gut bacteria. Increasing evidence suggests that prebiotics play an important role in improving metabolic health by modulating the gut microbiota and enhancing host metabolic functions. In individuals with type 2 diabetes mellitus (T2DM), dietary prebiotics have been shown to improve glycemic control, reduce inflammation, and enhance insulin sensitivity.[8] These beneficial effects are largely mediated through alterations in gut microbial composition and the production of bioactive metabolites that influence glucose metabolism.

Types of Prebiotics

Several types of prebiotic compounds have been identified and studied for their potential metabolic benefits. Among the most widely investigated are fructo-oligosaccharides (FOS) and inulin, which are naturally occurring fibers found in foods such as chicory root, garlic, onions, and bananas.[15] Another important class includes galacto-oligosaccharides (GOS), which are derived from lactose and have been shown to promote the growth of beneficial bacteria such as *Bifidobacterium and Lactobacillus species*. Additional prebiotics such as resistant starch, xylo-oligosaccharides (XOS), and arabinoxylans have also been studied for their ability to influence gut microbial composition and metabolic health.[8] These compounds are resistant to digestion in the upper gastrointestinal tract and reach the colon intact, where they are fermented by gut microbiota.

Mechanisms of Action

In addition to production of short-chain fatty acids (SCFAs) and secretion of gut hormones such as glucagon-like peptide-1 (GLP-1) and peptide YY (PYY), which help regulate appetite, insulin secretion, and glucose homeostasis, prebiotics enhance intestinal barrier function and reduce gut permeability, thereby preventing the translocation of pro-inflammatory microbial components such as lipopolysaccharides into the bloodstream.[20] This reduction in metabolic endotoxemia helps decrease systemic inflammation, which is a key contributor to insulin resistance and the progression of T2DM. Furthermore, prebiotics promote the proliferation of beneficial microbial taxa, leading to improved microbial diversity and metabolic stability within the gut ecosystem. Through these interconnected mechanisms, prebiotic supplementation represents a promising dietary strategy for supporting glycemic control and metabolic health in individuals with type 2 diabetes.

PROBIOTICS AND SYNBIOTICS IN GLYCEMIC CONTROL

Probiotics are live microorganisms that provide health benefits to the host when administered in adequate amounts, particularly by improving the balance of intestinal microbiota.[23] In recent years, probiotics have attracted considerable interest as potential adjunct therapies in the management of metabolic disorders, including type 2 diabetes mellitus (T2DM). The beneficial effects of probiotics are primarily associated with their ability to modulate gut microbial composition, enhance intestinal barrier function, and influence host metabolic pathways. Studies suggest that probiotic supplementation may improve glucose metabolism by reducing systemic inflammation and enhancing insulin sensitivity.[24] Several probiotic strains belonging to the genera *Lactobacillus* and *Bifidobacterium* have been extensively investigated for their metabolic benefits. These microorganisms can regulate gut microbiota composition and suppress the proliferation of pathogenic bacteria that contribute to metabolic disturbances. Additionally, probiotics can enhance the fermentation of dietary fibers, leading to increased production of beneficial metabolites such as short-chain fatty acids (SCFAs), which play an important role in regulating glucose metabolism and improving insulin sensitivity (Holscher, 2017).

Clinical evidence supports the beneficial role of probiotics in improving glycemic parameters in individuals with T2DM. Randomized controlled trials and systematic reviews have reported that probiotic supplementation can lead to significant reductions in fasting blood glucose, glycated hemoglobin (HbA1c), and insulin resistance markers.[26] These improvements may result from the combined effects of reduced metabolic inflammation, improved gut barrier integrity, and enhanced metabolic signaling pathways mediated by gut microbiota. Synbiotics, which combine probiotics with prebiotics, have also emerged as promising therapeutic strategies for improving metabolic health. The inclusion of prebiotics provides a suitable substrate that supports the survival and activity of probiotic microorganisms in the gut environment. This synergistic interaction enhances microbial colonization and promotes the production of beneficial metabolites that contribute to improved metabolic outcomes.[27] Furthermore, synbiotic supplementation has been shown to positively influence gut microbiota diversity and reduce inflammatory responses associated with metabolic disorders.[28] Overall, prebiotics and probiotics represent promising microbiota-based interventions that may improve glycemic control in individuals with T2DM. By modulating gut microbial composition, enhancing beneficial metabolite production, and improving intestinal barrier integrity, these interventions may complement conventional antidiabetic therapies. However, further large-scale clinical trials are required to determine the optimal strains, dosages, and duration of probiotic or synbiotic supplementation for effective diabetes management.

Clinical Evidence in Geriatric Population

The prevalence of type 2 diabetes mellitus (T2DM) increases significantly with age, making glycemic control an important health concern in the elderly population. Aging is associated with physiological changes such as reduced insulin sensitivity, impaired pancreatic β-cell function, and chronic low-grade inflammation, which collectively increase the risk of metabolic disorders.[29] In addition, aging influences the composition of the gut microbiota, often resulting in reduced microbial diversity and a decline in beneficial bacterial populations. These alterations may contribute to metabolic dysregulation and the development of T2DM in older adults.[30]

Recent research suggests that microbiota-targeted interventions, including probiotics, prebiotics, and synbiotics, may help improve metabolic health in elderly individuals. Probiotic supplementation has been reported to modulate gut microbial composition, strengthen intestinal barrier function, and reduce systemic inflammation, thereby supporting improved glycemic control.[31] Some clinical studies have shown that probiotic intake can lead to modest improvements in fasting blood glucose levels and insulin sensitivity in individuals with metabolic disorders.[24] Prebiotic interventions have also demonstrated potential benefits in the elderly population.[15] Similarly, synbiotic supplementation has shown promising outcomes in improving metabolic parameters, including glycemic control and inflammatory markers, in individuals with metabolic syndrome.[27] Although these findings are encouraging, clinical evidence specifically focusing on geriatric populations remains limited. Further well-designed clinical trials are needed to better understand the effectiveness of microbiota-based interventions in improving glycemic control among elderly patients with T2DM.

Impact of Polypharmacy in Geriatric Diabetes

Elderly patients with T2DM often experience polypharmacy due to multiple comorbidities, which can influence gut microbiota composition and drug-microbe interactions. Certain medications, including antibiotics and proton pump inhibitors, can disrupt microbial diversity, potentially reducing the efficacy of microbiota-targeted interventions.[32] Understanding these interactions is essential when designing adjunct probiotic or prebiotic therapies in geriatric populations. While probiotics are generally considered safe, their use in the elderly population requires careful evaluation due to age-related immune changes. Immunocompromised individuals may be at risk of rare adverse events such as bacteremia or sepsis. However, most clinical trials report good tolerability and minimal side effects, supporting their use as adjunct therapies in diabetes management.[7]

Mechanistic Insights into Incretin Modulation

Recent studies have demonstrated that gut microbiota plays a significant role in modulating incretin hormones such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), both of which are critical regulators of postprandial glucose metabolism. Short-chain fatty acids (SCFAs), particularly butyrate and propionate, have been shown to stimulate enteroendocrine L-cells to secrete GLP-1, thereby enhancing insulin secretion and improving glycemic control.[32,8] Furthermore, microbial metabolites can influence dipeptidyl peptidase-4 (DPP-4) activity, thereby affecting incretin degradation and overall glucose homeostasis. These findings suggest that microbiota-targeted therapies may complement pharmacological incretin-based treatments such as GLP-1 receptor agonists.

Table 1: Evidence Summary of Pre-and Probiotic Interventions as Adjuncts to Metformin in Type 2 Diabetes: Implications for the Gut–Glycemic Axis in the Indian Geriatric Population

Study	Intervention	Study Design/ Population	Key Outcomes	Clinical Relevance to Indian Geriatric T2DM
***Tao et al.*, 2020**	Probiotic supplementation	Meta-analysis of RCTs in adults with T2DM	↓ HbA1c, ↓ FPG; improved glycemic control	Supports probiotics as adjunct therapy; applicable to elderly Indian patients with poor glycemic control
***Zhang et al.*, 2021**	Probiotics	Systematic review & meta-analysis	Improved glycemic indices; heterogeneity across strains/doses	Highlights need for strain-specific evaluation in Indian elderly
***Palacios et al.*, 2020**	Probiotics adjunct therapy	Clinical studies in T2DM	Improved metabolic outcomes, ↓ inflammation	Adjunct potential with metformin in elderly with comorbidities
***Yadav et al.*, 2018**	Probiotic-induced butyrate → GLP-1 secretion	Translational/animal models	↑ GLP-1, improved insulin sensitivity	Mechanistic insight into gut-hormone axis relevant for adjunct therapy
***Gibson et al.*, 2017**	ISAPP consensus on prebiotics	Expert consensus	Defined scope, safety, efficacy of prebiotics	Provides framework for prebiotic interventions in elderly diabetics
***Sanders et al.*, 2016**	Safety assessment of probiotics	Human safety review	Generally safe, rare adverse events	Confirms safety in elderly Indian population
***Sun et al.*, 2018**	Metformin–gut microbiota interaction	Clinical study in T2DM	Metformin benefits mediated via gut microbiota & FXR	Critical for Indian elderly on metformin; probiotics may synergize
***Forslund et al.*, 2015**	Metformin signatures in gut microbiota	Metagenomic analysis	Distinct microbiota changes linked to metformin	Suggests combined probiotic-metformin strategies
***de la Cuesta-Zuluaga et al.*, 2017**	Metformin & *Akkermansia*	Clinical study in T2DM	↑ *Akkermansia* abundance with metformin	Supports microbiota modulation in elderly Indian diabetics

Gut-Brain Axis and Appetite Regulation

The gut–brain axis represents another critical pathway linking intestinal microbiota to metabolic regulation. Microbial metabolites and vagal nerve signaling influence central appetite regulation, satiety, and energy balance. In elderly individuals, dysregulation of this axis may contribute to altered eating patterns and impaired metabolic control. Emerging evidence suggests that probiotics may improve satiety signaling and reduce caloric intake, thereby indirectly improving glycemic outcomes.[36]

RELEVANCE TO THE INDIAN POPULATION

Dietary patterns

India has one of the largest populations of individuals affected by type 2 diabetes mellitus (T2DM), and dietary habits play a crucial role in shaping metabolic health and gut microbiota composition. Traditional Indian diets are often rich in carbohydrates, particularly polished rice and wheat-based foods, which may contribute to higher glycemic load and increased risk of metabolic disorders when consumed in excess.[4] However, traditional diets also include a variety of fiber-rich foods such as whole grains, legumes, vegetables, and fermented products, which can positively influence gut microbiota composition and metabolic regulation.[24] Fermented foods such as curd, buttermilk, and traditional pickles contain beneficial microorganisms that may support gut microbial balance and improve digestive health.

Modern dietary transitions in urban Indian populations have led to increased consumption of processed foods, refined carbohydrates, and high-fat diets. These dietary shifts may negatively affect gut microbiota composition and contribute to the increasing prevalence of metabolic diseases, including T2DM.[5] Therefore, dietary interventions that incorporate prebiotic-rich foods such as dietary fibers and probiotic-containing fermented foods may help restore microbial balance and support better glycemic control in the Indian population.

Microbiome Diversity

The composition of gut microbiota varies significantly across populations due to differences in diet, genetics, environment, and lifestyle factors. Studies have shown that individuals from South Asian populations, including India, often exhibit distinct gut microbiome profiles compared with Western populations.[37] These differences may influence metabolic responses to dietary interventions and pharmacological treatments. Research has also indicated that gut microbiota diversity may be reduced in individuals with metabolic disorders such as T2DM. Alterations in microbial composition, including decreased abundance of beneficial bacteria and increased levels of pro-inflammatory microbial species, may contribute to insulin resistance and chronic inflammation.[16] In the Indian context, understanding these microbial patterns is particularly important because dietary practices and environmental exposures can strongly influence microbiome diversity. Overall, investigating the gut–glycemic axis in the Indian population is essential for developing culturally relevant dietary and microbiota-targeted interventions. Such strategies may help improve metabolic health and enhance the effectiveness of conventional therapies such as metformin in managing T2DM among Indian patients.

CONCLUSION

The gut–glycemic axis has emerged as an important factor influencing glucose metabolism and the development of type 2 diabetes mellitus (T2DM). Alterations in gut microbiota composition can contribute to insulin resistance, inflammation, and impaired metabolic regulation. Recent evidence suggests that the interaction between gut microbiota and antidiabetic therapies, particularly metformin, may play a significant role in improving glycemic control. Dietary interventions involving prebiotics, probiotics, and synbiotics have shown potential in modulating gut microbiota and supporting metabolic health. These approaches may enhance beneficial microbial populations, improve intestinal barrier function, and promote the production of metabolites that contribute to better glucose regulation. In the Indian context, dietary habits, lifestyle factors, and unique microbiome diversity may influence the effectiveness of microbiota-targeted interventions. Therefore, integrating dietary strategies with conventional therapies such as metformin may offer a more comprehensive approach to diabetes management. Further research focusing on elderly populations is necessary to better understand the long-term benefits and clinical applicability of these interventions.

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