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Research Article

Understanding Gut Health: Probiotics, Dysbiosis, and their Connection to Type 2 Diabetes - A Review

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Abstract:

Type 2 diabetes mellitus (T2DM) is a complex metabolic disorder characterized by hyperglycaemia resulting from defects in insulin secretion, insulin action, or both. The pathophysiology of T2DM involves a multifaceted interplay of genetic, behavioural, and environmental factors. Beta cells play a central role in regulating blood glucose levels through intricate mechanisms involving insulin secretion triggered by elevated glucose concentrations and other factors. Dysfunction of beta cells in T2DM encompasses various molecular pathways influenced by factors such as hyperglycaemia, hyperlipidaemia, chronic inflammation, and genetic susceptibility, leading to impaired insulin secretion and insulin resistance.

Recent research has highlighted the role of gut dysbiosis in the pathogenesis of T2DM, with alterations in gut microbiome composition impacting glucose metabolism. Dysbiosis-induced intestinal permeability can lead to systemic inflammation, contributing to insulin resistance and diabetes progression. Conversely, a diverse and rich gut microbiome has been associated with protection against obesity, diabetes, and metabolic syndrome.

Probiotics, defined as live bacteria conferring health benefits when administered in adequate amounts, hold promise in mitigating T2DM-related metabolic derangements through various mechanisms, including modulation of gut microbiota, regulation of the gut-brain axis, and reduction of chronic low-grade inflammation. This provides a comprehensive overview of the mechanisms through which probiotics may positively impact glucose metabolism and discusses current evidence on the efficacy of probiotic supplementation in improving glycemic parameters and highlights the need for further research to elucidate strain-specific effects, optimal dosages, and long-term outcomes. Additionally, the translation of research findings into clinical practice and the potential of microbiome-targeted therapies for precision management of T2DM are explored, underscoring the importance of evidence-based guidelines for healthcare practitioners.

Key words: probiotics; type 2 diabetes; dysbiosis; insulin resistance

Introduction

Type 2 diabetes mellitus (T2DM) represents a significant global health burden, characterized by insulin resistance, β-cell dysfunction, and hyperglycaemia. The aetiology of T2DM is multifaceted, involving complex interactions between genetic predisposition, lifestyle factors, and environmental influences. Dysbiosis of the gut microbiome, marked by alterations in microbial composition and function, has emerged as a compelling factor contributing to T2DM pathogenesis. In individuals with T2DM, dysbiosis disrupts intestinal barrier integrity, leading to the translocation of bacteria and their metabolites into systemic circulation,

thereby triggering a pro-inflammatory state and exacerbating insulin resistance.

Probiotics, comprising live beneficial bacteria, offer a promising avenue for mitigating T2DM-related metabolic disturbances. Through modulation of gut microbiota composition and function, probiotics exert beneficial effects on glucose homeostasis. Studies have demonstrated that probiotic supplementation improves glycaemic parameters, including fasting blood glucose, insulin sensitivity, and HbA1c levels, in individuals with T2DM. Mechanisms underlying these effects involve the production of short-chain fatty acids (SCFAs), modulation of the gut-brain axis, and reduction of chronic low-grade inflammation.

Despite promising findings, challenges remain in translating research outcomes into clinical practice. Strain-specific effects, optimal dosages, and long-term safety considerations warrant further investigation. Moreover, the development of microbiome-targeted therapies holds potential for personalized management strategies tailored to individual microbial profiles. By bridging the gap between experimental evidence and clinical application, probiotics offer a promising therapeutic avenue for precision management of T2DM, emphasizing the need for evidence-based guidelines to guide healthcare practitioners in optimizing patient care.

Methods

PRISMA guidelines have been followed for conducting the review.

Search Strategy:

Two researchers have conducted an independent literature search on the **PubMed** and **Google Scholar** for the Randomised controlled trials published since the inception of the databases using the keywords "PROBIOTICS ", "TYPE 2 DIABETES", and "GLYCEMIC CONTROL "and the results were matched to ensure that they were correct.

Study Selection:

All the retrieved articles were initially screened for the Title and Abstract.

Inclusion and Exclusion Criteria:

All Randomized control trials published in English with no restriction on publication date to ensure comprehensive were selected with the following PICO characteristics

1. Population:
    - Participants with diagnosed type 2 diabetes.
2. Intervention:
    - Studies focusing on the administration of probiotics as an intervention in the treatment or management of type 2 diabetes.
    - Probiotic interventions could include single strains, multiple strains, combinations with prebiotics, Synbiotics, or fermented foods.
3. Comparison:
    - Studies with a control group receiving a placebo, standard care, or an alternative intervention (excluding probiotics) for comparison.
4. Outcome Measures:
    - Studies reporting outcomes related to glycemic control in participants with type 2 diabetes.
    - Primary outcome measures can include glycated hemoglobin (HbA1c), fasting blood glucose levels, postprandial glucose levels, or measures of insulin sensitivity.
5. Exclusion criteria:
6. Studies assessing the role of interventions other than probiotics compared to the control group.

Discussion

Type 2 Diabetes - Background and pathophysiology

Diabetes is defined by the American Diabetes Association as a group of metabolic diseases characterized by hyperglycaemia resulting from defects in either insulin secretion, insulin action, or both **[1].** It occurs because of a very complex interplay between Genetic, Behavioural, and environmental factors. Type 1 Diabetes is characterized by absolute or near absolute insulin deficiency whereas type 2 diabetes also has a component of Insulin Resistance where insulin cannot act on the peripheral tissues to exert its effect.

Beta cells orchestrate an intricate and precisely synchronized response to increasing blood glucose levels. Insulin release from β-cells is primarily triggered by high glucose concentrations. When glucose levels rise, β-cells take in glucose via GLUT2 transporters, increasing the intracellular ATP/ADP ratio **[2].** This leads to the closure of ATP-dependent potassium channels and rise in intracellular potassium levels leading to membrane depolarization, and opening of voltage-dependent Ca2+ channels **[3]**. Ca ^{2}+ influx induces fusion of insulin-containing granules with the plasma membrane, facilitating insulin exocytosis as described in **figure 1**

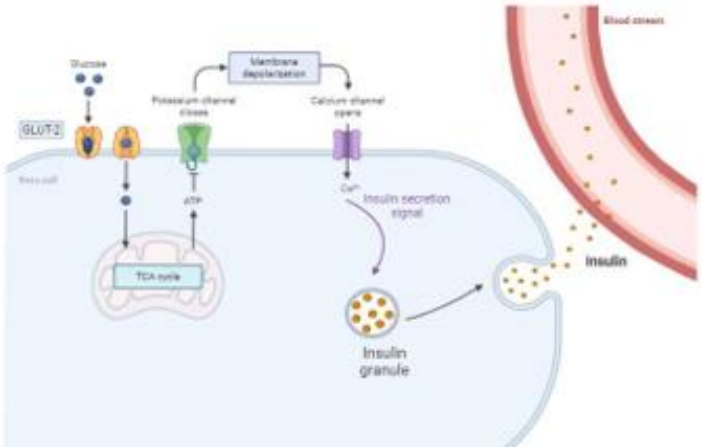

Figure 1: Insulin release from Beta cells

The insulin thus released acts on the tyrosine kinase Insulin receptors which on Stimulation activate further downstream signalling pathways as described in **FIGURE 2** to exert its effects.

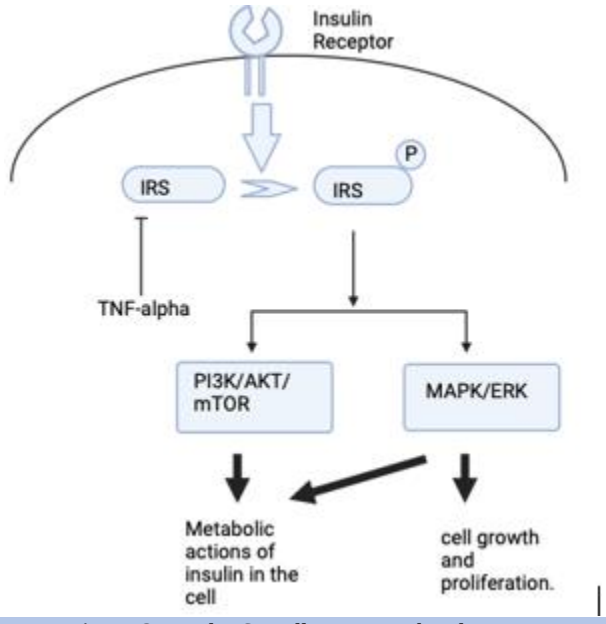

Figure 2: Insulin Signalling at peripheral tissues.

Type 2 diabetes may arise from impairments occurring at any of the aforementioned stages. Insulin resistance denotes a condition characterized by diminished responsiveness of typically insulin-sensitive tissues.[4] This phenomenon typically serves as the primary catalyst for the onset and advancement of type 2 diabetes. [5] Insulin resistance is multifaceted, influenced by various underlying risk factors, and can manifest at different junctures within the intricate pathways of insulin signalling. These include Splicing mutations of the insulin gene or the presence of autoantibodies which target the insulin receptor leading to conditions like Type A and type B IR syndrome respectively [6].

A Proinflammatory state induces insulin resistance by phosphorylating insulin receptor and its substrates via communication through receptors such as tumour necrosis factor receptor 1 (TNFR1) thereby worsening the insulin resistance [7].

These factors collectively disrupt insulin signalling pathways, particularly the MAPK/ERK and PI3K/AKT/mTOR pathways, contributing to insulin resistance.

As the insulin resistance worsens Beta cells compensate by increasing the production of insulin creating a state of hyperinsulinemia [8]. which contributes to the development of cardiovascular disease by various mechanisms most notably endothelial dysfunction and subsequent atheroma plaque progression and ventricular hypertrophy and diastolic dysfunction [9].

β-cell dysfunction in type 2 diabetes mellitus (T2DM) is a complex phenomenon influenced by various factors, and several concepts have been proposed to explain its mechanisms. While these concepts are not mutually exclusive and often interact with each other, they provide valuable insights into understanding the pathophysiology of T2DM. Here are three key concepts:

1. **Glucotoxicity:** Glucotoxicity refers to the harmful effects of chronically elevated blood glucose levels on pancreatic β-cells.[10] Prolonged exposure to high glucose levels induces oxidative stress, endoplasmic reticulum (ER) stress, and mitochondrial dysfunction in β-cells, ultimately impairing their function and survival [11]. contributing to β-cell apoptosis and decreasing β-cell mass, thereby exacerbating insulin deficiency in T2DM.

2. **Lipotoxicity:** Lipotoxicity refers to the harmful effects of elevated levels of free fatty acids (FFAs) and lipid metabolites on pancreatic β-cells [12]. insulin-resistant states like T2DM creates a state of dysregulated lipolysis resulting in excessive Free fatty acid production (FFAs). These FFAs accumulate in pancreatic β-cells and interfere with insulin synthesis, secretion, and signalling pathways. Lipid metabolites such as diacylglycerol (DAG) and ceramides activate protein kinase C (PKC) and c-Jun N-terminal kinase (JNK) pathways, leading to impaired insulin gene expression, insulin exocytosis, and insulin receptor signalling. Furthermore, lipotoxicity induces ER stress, mitochondrial dysfunction, and inflammation in β-cells, contributing to their dysfunction and apoptosis.[13]

3. **Inflammation and immune-mediated dysfunction:** Chronic low-grade inflammation and immune-mediated processes play a significant role in the pathogenesis of T2DM and β-cell dysfunction [14].

Role of Gut Dysbiosis in the Pathogenesis of Type 2 Diabetes

In a healthy individual, the gut microbiome primarily comprises Firmicutes and Bacteroidetes phyla, which collectively constitute 60–80% and 20–30% of the gut microbiota, respectively [15] (FIGURE 3) Within the Firmicutes phylum, dominant genera include Lactobacillus, Bacillus, Clostridium, Enterococcus, and Ruminicoccus, while Bacteroides and Prevotella are prominent genera within the Bacteroidetes phylum. Both Firmicutes and Bacteroidetes are known producers of butyrate,[16] a crucial short-chain fatty acid (SCFA) that serves as a primary energy source for colonic epithelial cells, essential for maintaining their integrity. Insufficient levels of butyrate have been linked to increased gut permeability due to damage to colonic epithelial cells [17].

Increased intestinal permeability leads to the translocation of bacteria, their metabolites, and endotoxins into the bloodstream, resulting in bacteraemia and endotoxemia [18].

Bacteraemia refers to the presence of bacteria in the bloodstream, while endotoxemia involves the circulation of endotoxins, primarily lipopolysaccharides (LPS) from gram-negative bacteria. This systemic dissemination triggers an inflammatory response, characterized by the activation of immune cells and the release of pro-inflammatory cytokines like TNF alpha and interleukins with resultant chronic systemic low-grade inflammation [19].

Systemic inflammation induced by bacteraemia and endotoxemia can contribute to the development of insulin resistance, a key component of diabetes pathogenesis as described before as Chronic inflammation disrupts insulin signalling pathways, impairing glucose uptake by target tissues such as muscle and adipose tissue. Additionally, inflammatory cytokines interfere with pancreatic beta-cell function, further exacerbating insulin resistance. Consequently, sustained systemic inflammation can promote the onset and progression of diabetes by disrupting glucose homeostasis and exacerbating insulin resistance.

Butyrate has been shown in in vitro studies in animal models to improve insulin sensitivity [20], by histone deacetylase (HDAC)-mediated transcription regulation and subsequent activation of mitochondrial fatty-acid oxidation [21].

Phylum	Dominant Genera	Percentage of Gut Microbiota
Firmicutes	Lactobacillus, Bacillus, Clostridium, Enterococcus, Ruminicoccus	60–80%
Bacteroidetes	Bacteroides, Prevotella	20–30%

Figure 3: Predominant Gut Microbiota

Actinobacteria, Proteobacteria, Fusobacteria, and Verrucomicrobia are the other phyla that make up the rest 10% of the gut microbiota [9]. Actinobacter phyla are mainly represented by the Bifidobacterium genus. One study by Jinlan et al found that supplementing with B.animalis 01 1 significantly increased the expression of IRS/PI3K/Akt expression leading to improved insulin sensitivity.[22] Few other probiotics like Bifidobacterium lactis HY8101 or Lactobacillus paracasei TD062, have also been shown to enhance this insulin signalling pathway [23,24].

A Rich microbiome in the gut with various species has been shown to be protective against the development of various chronic diseases like obesity, Diabetes, and metabolic syndrome [25].

People with diabetes have been shown to have a different composition of gut microbiome. A systematic review conducted by Umirah et al has shown that Butyrate-producing bacteria are significantly lower in patients with type 2 diabetes and that treatment with metformin actually altered the situation.(7)[26] Butyrate producing bacteria specifically decreased in T2DM include Clostridiales order, including the genera Ruminococcus and Subdoligranulum, and the species Eubacterium rectale, Faecali prausnitzii, Roseburia intestinalis and Roseburia inulinivorans [27], as summarised in Table 1

DECREASED IN T2DM	INCREASED IN T2DM
Bacteroides	Clostridium hathewayi
Prevotella	Clostridium symbiosum
Bifidobacterium	Eggerthella
Akkermanisa muciniphila	Lenta Clostridium ramosum
Faecali prausnitzii	Escherichia coli
Roseburia intestinalis Roseburia inulinivorus	

Table 1: Gut microbiome in Type 2 Diabetes

Altered Gut Microbiome in Diabetes

The genera Bacteroides, Prevotella and Bifidobacterium are found in significantly less numbers in T2DM patients. This microbiota, improve the intestinal integrity and reduce the translocation of endotoxins and thereby systemic inflammation.

Other microbiota that are significantly reduced in T2DM are of the species Akkermansia muciniphila and Faecali prausnitzii [27].

There is also significant evidence that, there are increased opportunistic pathogens such as Bacteroides caccae, Clostridium hathewayi, Clostridium symbiosum, Eggerthella, lenta Clostridium ramosum, and Escherichia coli [28].

The enumerated examples presented herein represent only a subset of the microbiota implicated in the gut dysbiosis associated with Type 2 Diabetes Mellitus (T2DM). Nevertheless, it is imperative to underscore the need for additional research and comprehensive clinical studies to elucidate the intricate relationship between the gut microbiome and T2DM. Further investigations will contribute invaluable insights into the nuanced dynamics and potential therapeutic implications of these interactions.

Probiotics and type 2 diabetes

Probiotics are defined by FA0/WHO as living bacteria which, when administered in adequate amounts, confer a health benefit on the host [29],

and are currently being widely studied for their ability to alter glucose homeostasis. Numerous trials have been done showing the role of probiotic supplementation in improving the glycaemic parameters in diabetes. A systematic review of over 30 RCTs by —- has shown that probiotic supplementation was associated with a significant decline in glycaemic parameters including FBG (SMD = - 0.331, 95% CI - 0.424 to - 0.238, P-effect < 0.001), insulin (SMD = - 0.185, 95% CI - 0.313 to - 0.056, P-effect = 0.005), HbA1c (SMD = - 0.421, 95% CI - 0.584 to - 0.258, P-effect < 0.001), and HOMA-IR (SMD = - 0.224, 95% CI - 0.342 to - 0.105, P-effect < 0.001).[30]

Various mechanisms have been proposed to understand how probiotics improve glucose metabolism and help achieve good glycaemic control. This understanding of the mechanisms is very helpful in directing future studies and making way for novel therapeutic methods to treat Type 2 Diabetes Mellitus.

One of the mechanisms that has been described is via the Modulation of Gut Microbiota. As discussed earlier, Studies reveal a correlation between dysbiosis, characterized by altered gut microbiome composition, and impaired glucose metabolism in individuals with T2DM. Probiotics have demonstrated the ability to restore this dysbiosis by increasing the abundance of beneficial bacteria, such as Lactobacillus and Bifidobacterium. These alterations in gut microbiota contribute to improved glucose homeostasis by enhancing dietary fiber fermentation and subsequent short-chain fatty acids (SCFAs) production, notably butyrate, a prominent SCFA, as described before whs been shown to enhance glucose uptake in peripheral tissues by improving insulin sensitivity [20]. SCFAs also stimulate G protein-coupled receptors (GPCR) on L cells which are neuroendocrine cells present in the ileum that lead to the release of and stimulates the production of Glucagon-like Peptide-1 (GLP-1) which is an incretin meaning that it will stimulate Insulin secretion from the pancreas and promote gastric emptying thus helping with satiety [31].

Another mechanism that has been postulated is via the Modulation of the Gut-Brain Axis. Probiotics exert their influence on the gut-brain axis, a bidirectional communication system linking the gastrointestinal tract to the central nervous system. This axis plays a pivotal role in regulating glucose metabolism and insulin secretion. Probiotics have been found to regulate the release of gut hormones, including glucagon-like peptide-1 (GLP-1) and peptide YY, both crucial in glucose homeostasis. The stimulation of GLP-1 enhances insulin secretion, improves insulin sensitivity, and reduces glucagon secretion, while peptide YY regulates food intake and promotes satiety. Probiotic use may enhance the secretion of these hormones, contributing to improved glycemic control. Reduction of Chronic Low-Grade Inflammation is another potential mechanism linking the use of probiotics in type 2 diabetes. Chronic low-grade inflammation, closely linked to impaired glucose homeostasis and insulin resistance, is mitigated by probiotics through the suppression of pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6). Concurrently, there is an increase in the secretion of anti-inflammatory cytokines, such as interleukin-10 (IL-10). This anti-inflammatory action of probiotics holds promise for attenuating the development of T2DM by improving glucose metabolism and insulin sensitivity.

Type of Probiotic	Altered Glycaemic parameters	Duration of intervention	Reference
Lactobacillus acidophilus La-5 and Bifidobacterium animalis subsp. lactis BB-12	FFG - Mean difference of 12.6mg/dl (p= 0.009) HbA1C- Mean difference of 0.12%(p=0.019)	6 weeks	[32]
Bifidobacterium longum APC1472	FPG- Mean difference of 4.788 (95% CI [7.92-1.62])	12 weeks	[33]
Ecologic® Barrier (multi-strain probiotics) Bifidobacterium Lactis, Lactobacillus Acidophilus, Lactobacillus Salivarius, Lactobacillus Casei, Bifidobacterium Bifidum,	Decrease in HOMA IR- by 64% Insulin by 38% Glucose by 38%	6 months	[34]
Lactobacillus casei 01	Fasting blood sugar -28.32 [-50.23 to -6.41], 0.013 insulin concentration -3.12 [-5.90 to -0.35], 0.028 insulin resistance -32.31 [-55.09 to -9.54], 0.007	8 weeks	[35]
"Symbiter" (multi-strain)	HOMA-IR decreased from 6.85 ± 0.76 to 5.13 ± 0.49 (p = 0.047) HbA1C decreased by 0.24% (p = 0.068)	8 weeks	[36]

Table 2: Comparison of various probiotics in their efficacy in reducing glycaemic parameters.

Results:

The comprehensive review of the various RCTs and Meta-analysis updated to the latest article, clearly signifies the positive impact of Probiotics in the gradual reversal of insulin resistance, glycaemic control

and increased glucose uptake and the glycaemic efficacy of various probiotics have been summarised in table 2. The various mechanisms substantiating this result as mentioned in the above section strengthens the need to imply this importance in addressing the type 2 diabetic patients in clinical healthcare settings.

Conclusion:

In summary, the multifaceted effects of probiotics on glucose homeostasis encompass the modulation of gut microbiota, the regulation of the gut-brain axis, and the reduction of chronic low-grade inflammation. While these mechanisms provide valuable insights, ongoing research is essential to fully elucidate the complex interplay and identify specific strains, doses, and durations of probiotic supplementation required for optimal glycaemic control in T2DM.

Future perspectives

Microbiome-Targeted Therapies:

As our understanding deepens, there is a growing interest in microbiome-targeted therapies for T2DM. Precision medicine approaches may involve identifying and utilizing specific probiotic strains that exhibit superior efficacy in modulating gut microbiota and influencing the gut-brain axis. Customized interventions based on an individual's microbiome profile could pave the way for personalized probiotic regimens tailored to address the unique microbial composition and metabolic needs of each patient.

Unexplored Pathways and Future Research Directions:

While the mechanisms discussed provide valuable insights, it is crucial to acknowledge the vastness of unexplored pathways that may contribute to the effects of probiotics on glucose homeostasis. Future research endeavours should focus on unveiling these hidden pathways, possibly involving intricate interactions between the immune system, metabolic organs, and the gut. Cutting-edge technologies, such as metagenomics and advanced imaging, hold promise in unravelling the complexities of the gut microbiome and its role in metabolic health.

Strain-Specific Effects and Optimal Dosages:

The identification of strain-specific effects remains a priority in shaping the future of probiotic research for T2DM. Different strains may exhibit varying abilities to modulate gut microbiota and influence metabolic pathways. Thus, delineating the specific strains responsible for the observed benefits is crucial for designing targeted interventions. Moreover, optimizing probiotic doses and duration of supplementation is essential, as these factors may significantly impact the efficacy of probiotics in improving glycemic control.

Clinical Translation and Therapeutic Potential:

As the scientific community continues to unravel the intricacies of probiotic mechanisms, the translation of research findings into clinical practice becomes paramount. Establishing robust clinical trials, exploring long-term effects, and addressing safety considerations will be critical steps in validating the therapeutic potential of probiotics in the management of T2DM. This translational approach will bridge the gap between experimental evidence and real-world applications, ultimately shaping evidence-based guidelines for healthcare practitioners.

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