JMH
Jurnal Medika Hutama
Vol 07 No 01, Oktober 2025
http://jurnalmedikahutama.com

e-ISSN. 2715-9728
p-ISSN. 2715-8039

Open Acces

The Potential of Precision Therapy Based on Shotgun Metagenomic Sequencing for Gut Microbiota Modulation through Synbiotics and Dietary Regulation as a New Strategy in the Management of Type 2 Diabetes Mellitus : A Literature Review

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Received 10 Agustus, 2025; **Accepted** 28 September 2025; **Online Published** 28 Oktober 2025

Abstrak

Type 2 Diabetes Mellitus (T2DM) is a chronic metabolic disorder characterized by insulin resistance and impaired insulin secretion, commonly driven by sedentary lifestyles and unhealthy dietary habits. While conventional antidiabetic therapies are effective, they often cause adverse effects such as hypoglycemia and gastrointestinal disturbances. This review explores the potential of precision therapy via gut microbiota modulation as an innovative strategy in T2DM management. Shotgun metagenomic sequencing provides high-resolution insights into individual gut microbiome compositions, enabling tailored interventions. T2DM is frequently associated with gut dysbiosis, marked by reduced populations of *Bifidobacteria* and *Akkermansia*, which contributes to metabolic inflammation and insulin resistance. Synbiotics, a combination of prebiotics and probiotics, have shown efficacy in restoring microbial balance, enhancing short-chain fatty acid (SCFA) production, reinforcing intestinal barriers, and reducing systemic inflammation. Additionally, dietary regulation—particularly increased fiber intake and caloric restriction—supports microbiome diversity and glycemic control. A total of 156 articles were initially identified, and 7 studies meeting the inclusion criteria were selected and reviewed in detail. These studies collectively demonstrate the potential of synbiotic-based precision therapy supported by shotgun metagenomic profiling in improving metabolic outcomes among T2DM patients. This review advocates for the integration of microbiome profiling and personalized nutritional therapy as a promising avenue in T2DM treatment, with recommendations for future large-scale clinical validation.

Keywords: Precision Therapy, Shotgun Metagenomic Sequencing, Gut Microbiota, Synbiotics, Type 2 Diabetes Mellitus, Dietary Intervention

INTRODUCTION

The shift in societal structure from an agrarian pattern to an industrial society has significantly contributed to lifestyle changes, which potentially increase the prevalence of Non-Communicable Diseases (NCDs), including diabetes mellitus. The industrial revolution also altered the nature and volume of work performed by individuals. Prior to this, most people engaged in physically demanding labor. However, with the advancement of machinery, the need for manual labor has steadily declined. As a result, fewer people are involved in physical work, while more are engaged in desk jobs or sedentary occupations.[1]

Lifestyle factors that influence diabetes mainly include dietary habits and physical activity. Research shows that lifestyle plays a crucial role in preventing type 2 diabetes mellitus by reducing disease risk through healthy eating habits and regular physical exercise. A healthy diet emphasizes the 3 principle: the right portion, type, and timing of meals. However, modern society has shifted toward more instant and convenient food patterns, which are often associated with the emergence of various diseases, including diabetes mellitus.[2]

Diabetes Mellitus (DM), commonly known as diabetes, is a chronic metabolic disorder caused by the body's inability to use insulin effectively to regulate blood sugar levels, resulting in increased blood glucose concentrations, also known as hyperglycemia.[3] The prevalence of diabetes is projected to rise with increasing age, reaching 19.9% or approximately 111.2 million people aged 65–79 years by 2020. According to the International Diabetes Federation (IDF) in its 10th edition atlas published in late 2021, around 537 million people were living with diabetes worldwide. This number is projected to continue increasing, with estimates reaching 643 million by 2030 and approximately 783 million by 2045.[4] [5]

The International Diabetes Federation (IDF) in 2022 stated that the cost of diabetes treatment in Indonesia will continue to rise, reaching a 33% increase by 2045. Meanwhile, the average cost of diabetes care per person was US$323.8 in 2021. The cost of diabetes treatment has increased by 305% compared to US$80 per person ten years ago. Based on IDF data, diabetes-related healthcare costs in Indonesia could increase by 14% to US$370.6 by 2030.[6] This indicates that diabetes poses a significant economic threat to Indonesia, with a continually rising number of cases each year. Diabetes Mellitus is a disease that can drastically reduce a person's health status because it affects multiple organs and can cause a wide range of symptoms. Over time, diabetes may lead to complications that affect various organ systems.[7]

Complications of diabetes can be classified as microvascular and macrovascular. Microvascular complications include nerve damage (neuropathy), kidney damage (nephropathy), and eye damage (retinopathy). Meanwhile, macrovascular complications include heart disease and peripheral vascular disease, which can result in bruising or non-healing wounds, gangrene, and even lead to amputation.[8]

In medical practice, antidiabetic drugs are indeed effective, but many of them come with serious side effects. These are compounded by lifestyle factors, patient non-compliance, and

concerns regarding treatment costs not covered by insurance (out-of-pocket costs).[9] Unfortunately, several antidiabetic medications are known to cause side effects—for example, sulfonylureas may increase the risk of acute hypoglycemia, biguanides can lead to lactic acidosis, and gastrointestinal side effects are common with metformin. As an alternative, diabetes can be effectively minimized and managed through synbiotic activity (a combination of prebiotics and probiotics). Clinical evidence has shown that gut microbiota modulation by synbiotics does not cause adverse effects, and thus, this approach can be considered as a promising therapeutic option for diabetes mellitus.[10] [11]

MATERIAL AND METHOD

This study employed a literature review approach. The research was conducted by searching various reputable journal databases, including PubMed, ScienceDirect, and Google Scholar. The search was carried out using the following keywords: *Precision Therapy*, *Shotgun Metagenomic Sequencing*, *Gut Microbiota Modulation*, *Synbiotics*, *Dietary Intervention*, and *Type 2 Diabetes Mellitus*.

Several inclusion criteria were applied to select relevant literature. These criteria included articles published within the last ten years, written in either English or Indonesian, available in full text, and specifically discussing the application of shotgun metagenomic sequencing for gut microbiota modulation, the use of synbiotics, and dietary interventions in the management of Type 2 Diabetes Mellitus.

The journal selection process involved multiple stages, including identification, screening based on the inclusion criteria, and exclusion of articles that did not meet the requirements. After this process, seven articles were identified as relevant and appropriate for inclusion in this study.

Data analysis was performed using a descriptive approach by compiling and summarizing the key findings from the selected articles. This enabled a comprehensive understanding of the potential of precision therapy based on shotgun metagenomic sequencing for modulating gut microbiota through synbiotics and dietary regulation as a novel strategy in managing Type 2 Diabetes Mellitus.

RESULT

The literature search retrieved 96 articles from Google Scholar, 26 articles from ScienceDirect, and 34 articles from PubMed, totaling 156 articles. After removing duplicates and screening titles and abstracts, seven articles were selected as relevant to the research topic and met the established inclusion criteria. A summary of these seven articles is presented in Table 1.

No.	Author	Year	Methods	Result and Discussion
1	Hamasaki-Matos et al.[57]	2021	A cross-sectional observational study involving PCR analysis of 13 gut bacterial genera in patients with controlled and uncontrolled type 2 diabetes mellitus (n=26), along with an assessment of dietary fiber intake.	Firmicutes, Prevotella, Proteobacteria, and Bacteroidetes were more frequently detected in controlled T2DM patients compared to those with uncontrolled T2DM. Fusobacterium and Actinobacteria were not detected in any samples. Dietary fiber intake was found to influence gut microbiota composition.
2	Fu et al.[58]	2025	Mendelian Randomization (MR) analysis was conducted using genome-wide association study (GWAS) data from over 1 million individuals to evaluate the causal relationships between gut microbiota (GM), body mass index (BMI), and type 2 diabetes mellitus (T2DM).	The analysis reveals bidirectional causal links between gut microbiota (GM) and both obesity and type 2 diabetes (T2D), highlighting the mediating role of GM in the obesity–T2D pathway. Maintaining a balanced GM may be critical for the prevention and management of both conditions. These findings suggest that alterations in GM may serve as a potential target for personalized therapeutic interventions.
3	Yassour et al.[59]	2016	Shotgun metagenomic sequencing was performed on 36 fecal samples from 20 Korean monozygotic twin pairs in a longitudinal study. The analysis focused on the composition and functional profiles of the gut microbiota and their associations with clinical parameters.	Alterations in microbial function were observed, including an increased response to oxidative stress, which mirrors patterns seen in type 2 diabetes mellitus (T2DM) and inflammatory bowel disease (IBD). Akkermansia muciniphila levels were decreased, while Roseburia abundance was increased in individuals with higher BMI. These findings suggest the potential of specific gut microbes as early biomarkers and targets for the prevention of T2DM.
4	Navab-Moghadam et al.[60]	2017	A case-control study was conducted using real-time quantitative PCR (qPCR) to detect three microbial species (*Faecalibacterium prausnitzii*, *Bacteroides fragilis*, and *Bifidobacterium longum)* in 18 patients with type 2 diabetes mellitus (T2DM) and 18 healthy controls.	Real-time PCR analysis demonstrated that, although there were no significant differences in *Bacteroides fragilis* and *Bifidobacterium longum* levels, the fecal concentration of *Faecalibacterium prausnitzii* was significantly lower in patients with type 2 diabetes compared to the healthy control group. These findings suggest that type 2 diabetes is associated with alterations in the composition of the intestinal bacterial flora.

5	Aljuraiban et al.[61]	2023	An observational study involving 92 young Saudi women utilized whole-genome sequencing (WGS) of the gut microbiota to investigate its association with body composition and insulin resistance.	A negative correlation was found between Actinobacteria abundance and HOMA-IR, with several *Bifidobacterium* species negatively correlated with glucose and insulin levels. Both alpha and beta diversity were lower in the group with high insulin resistance. Whole-genome sequencing (WGS) provided high-resolution detection of specific gut microbiota biomarkers.
6	Kanazawa et al.[62]	2021	A 24-week randomized controlled trial (RCT) was conducted involving 88 obese patients with type 2 diabetes mellitus (T2DM), who received either a synbiotic supplement (LcS, *Bifidobacterium breve*, and galacto-oligosaccharides [GOS]) or a control treatment. Gut microbiota composition and inflammatory markers were evaluated.	The synbiotic intervention did not significantly reduce IL-6 levels; however, it improved the gut microbiota profile and increased the production of short-chain fatty acids (acetate and butyrate). Additionally, it enhanced the abundance of *Bifidobacterium adolescentis*, *Bifidobacterium pseudocatenulatum*, and total *Lactobacilli*.
7	Carrizales-Sánchez et al.[63]	2023	Shotgun metagenomic sequencing was performed on fecal samples from 30 school-aged children (10 healthy, 10 with metabolic syndrome, and 10 with type 2 diabetes mellitus) to analyze correlations between gut microbiota composition and metabolic function.	Children with metabolic syndrome (MetS) and type 2 diabetes mellitus (T2DM) exhibited gut microbial dysbiosis, indicating the potential of gut microbiota as biomarkers for metabolic diseases. Notable changes included a decrease in *Erysipelatoclostridium* and *Actinomyces*, alongside an increase in lactic acid bacteria. Functional alterations in the microbiota were associated with nitrogen metabolism and inflammation.

DISCUSSION

Gut Microbiota and Diabetes Mellitus

The human gut microbiota is a complex ecosystem of microorganisms comprising bacteria, fungi, archaea, and viruses that plays a vital role in maintaining health. These microorganisms aid in enhancing energy extraction from food, processing nutrients, metabolizing indigestible compounds, and synthesizing vitamins.

Additionally, the gut microbiota acts as a physical barrier that protects the body from pathogenic invaders. The majority of the gut microbiota is composed of two main phyla: Bacteroidetes and Firmicutes, which together account for approximately 90% of the total population. Over half of the Firmicutes belong to the Clostridia class (20.3%), making it the most

abundan group, followed by Bacteriodia (18,5%), Bifidobacteriales (16,6%), Enterobacterales (14%), and Lactobacillales (14%).[12]

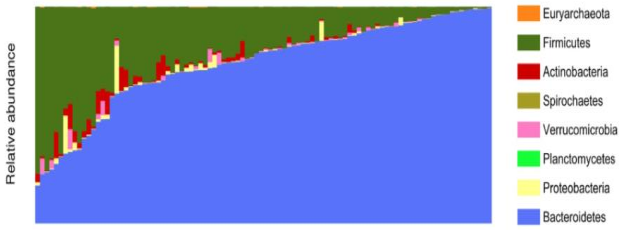

Figure 1. Composition Gut Microbiota in Healthy Person[12]

Type 2 Diabetes Mellitus and Gut Microbiota Dysbiosis

Type 2 diabetes mellitus, previously known as non-insulin-dependent diabetes, is characterized by reduced insulin production and insulin resistance. In individuals with type 2 diabetes, the levels of *Bifidobacteria* and *Akkermansia* in the gut are decreased, whereas the population of *Dallella* is increased.[13]

An imbalance in the gut microbiota that deviates from the normal (eubiosis) state is referred to as dysbiosis, which is marked by changes in the composition or function of the microbial community.[14] [15] *(See Figure 2)*. Dysbiosis can increase intestinal membrane permeability, leading to a compromised gut barrier, a condition known as leaky gut syndrome. This disruption allows bacteria to translocate across the gut wall, triggering metabolic endotoxemia and contributing to low-grade systemic inflammation.[16]

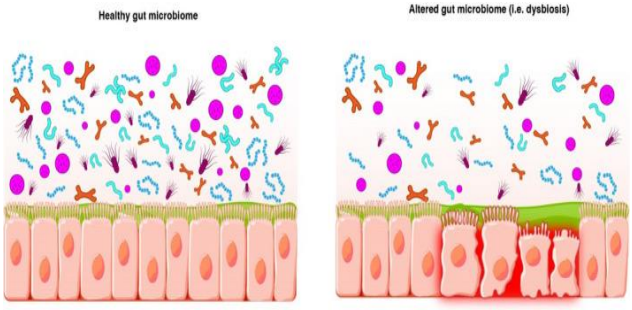

Figure 2. Different Normal Gut Microbiota and Dysbiosis[15]

Leaky gut can also induce low-grade chronic inflammation of a metabolic nature, both at local and systemic levels—a condition known as metainflammation, which has been shown to play a role in the onset of insulin resistance and the progression of type 2 diabetes (T2D). This metainflammation is associated with impaired insulin function and secretion.[17] Gut microbiota has been identified as a key driver of metainflammation observed in obesity and T2D, a state also marked by alterations in gut microbiota composition.[18] [19] [20]

Several proinflammatory cytokines are elevated in the circulation of individuals with metabolic syndrome, exerting negative effects on the metabolism of peripheral tissues. *(See Figure 3)*. T cells, particularly Th1 cells (via IFN-γ) and CD8+ T cells, act as secondary mediators that attract macrophages and promote the secretion of proinflammatory cytokines, thereby exacerbating insulin resistance. Among these, M1 macrophages—also known as classically activated macrophages—are especially implicated in the metainflammatory processes observed in metabolic diseases.[21]

Persistently elevated levels of proinflammatory cytokines lead to the expansion of alpha cells and dysfunction of beta cells in the pancreatic islets, thereby promoting the progression of T2D. Other studies have supported these findings by demonstrating increased cytokine levels in insulin-resistant individuals, with a positive correlation to hyperglycemia.[22]

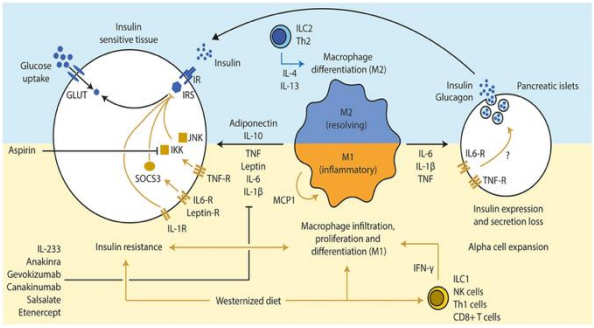

Figure 3. Inflammation affects beta cell function and insulin sensitivity.[22]

Cytokines known as chemokines function to recruit immune cells to metabolically active tissues. One of the key chemokines involved in this process is Monocyte Chemoattractant Protein-1 (MCP-1), which plays a crucial role in monocyte recruitment. Human pancreatic islets also produce MCP-1, and its expression increases upon exposure to pro-inflammatory stimuli such as lipopolysaccharide (LPS). Studies have shown that overexpression of MCP-1 in pancreatic beta cells in mice leads to macrophage infiltration into the islets, eventually triggering the development of spontaneous diabetes. These findings highlight the pivotal role of MCP-1 in the pathogenesis of insulin resistance and beta-cell dysfunction through immune cell infiltration.[23]

In the pancreas, IL-6 receptors are primarily located in the endocrine compartment, with particularly high expression in alpha cells. Increased IL-6 expression in the islets of obese mice is associated with alpha-cell expansion, a phenomenon also observed in individuals with type 2 diabetes (T2D). In IL-6 knockout obese mice, alpha-cell expansion is suppressed, accompanied by a reduction in glucose-stimulated insulin secretion (GSIS).[24]

Tumor Necrosis Factor (TNF), produced by macrophages in adipose tissue, was among the first cytokines identified to be elevated in both adipose tissue and the bloodstream of individuals with T2D.[25] These macrophages are also major contributors to circulating IL-6 levels, accounting for approximately 15–35% of total IL-6. Chronic elevation of IL-6 is known to reduce hepatic insulin sensitivity, induce hyperinsulinemia, and contribute to insulin resistance in skeletal muscle.[26]

Toll-like receptors (TLRs) are essential components of the innate immune system that detect microbial invaders. Among them, TLR2 and TLR4 have been linked to the development of metabolic syndrome. TLR4 specifically recognizes lipopolysaccharide (LPS), a component of Gram-negative bacterial cell walls, which is believed to trigger metabolic inflammation. Elevated levels of LPS have been detected in the bloodstream of diabetic patients. In individuals with T2D, monocytes exhibit upregulated TLR4 expression, along with increased levels of circulating cytokines and LPS.[27]

Precision Therapy

Precision therapy refers to a medical approach tailored to the individual characteristics of each patient, including genetics, environment, and lifestyle. Unlike traditional, generalized treatments, precision therapy aims to identify the

specific factors causing a disease and select the most effective therapy for each individual. This personalized approach enhances treatment accuracy, minimizes adverse effects, and improves overall therapeutic outcomes.[28] Importantly, precision therapy focuses not solely on the disease, but on the patient as a whole.[29]

With the rising global prevalence of diabetes and the limited efficacy of existing treatments, there is an urgent need to develop novel therapeutic strategies that can complement conventional approaches. Ideally, such strategies should be more personalized to enhance both treatment tolerance and effectiveness.[30] This has led to the emergence of precision medicine, powered by advancements in "omics" technologies including genomics, transcriptomics, epigenomics, metabolomics, proteomics, and microbiomics which collectively shape the future of individualized therapy.[31]

These omics-based technologies utilize advanced big data analytics to generate comprehensive molecular, biological, and clinical phenotyping. This enables early diagnosis, improved risk stratification, and a more integrated healthcare delivery system with superior disease management capabilities at an individualized level.[32]

One of the most innovative strategies in precision therapy is the modulation of the gut microbiota. The gut microbiota—a complex community of microorganisms residing in the human gastrointestinal tract—plays a critical role in various physiological processes, including metabolism, immune regulation, fluid balance, and pathogen resistance. Dysbiosis, or an imbalance in the composition of the gut microbiota, has been linked to numerous chronic diseases such as hypertension, obesity, diabetes, and inflammatory disorders.[33]

As such, gut microbiota modulation presents a promising approach for delivering targeted and personalized therapeutic effects. As part of a precision therapy framework, gut microbiota modulation allows treatment to be adapted to an individual's unique microbial profile.[34] Since each person's microbiome is shaped by a combination of genetic and environmental factors, this strategy supports more effective and personalized interventions.[35] Furthermore, modulating the gut microbiome addresses not only the symptoms of disease but also the underlying mechanisms driving dysbiosis, thereby promoting long-lasting therapeutic effects and reducing disease recurrence.[36]

To effectively implement microbiota-targeted precision therapy, it is essential to first analyze the patient's gut microbial composition. One of the most advanced techniques for this is Shotgun Metagenomic Sequencing, which allows for the comprehensive analysis of the total genetic material within a microbial community from an environmental sample—such as the human gut. Unlike marker-based approaches such as 16S rRNA sequencing, shotgun metagenomics enables species-level identification of microorganisms and provides functional insights into their gene expression profiles.[37]

This technology provides researchers and clinicians with a comprehensive overview of the gut microbiome's composition and metabolic potential, offering a critical foundation for understanding the role of gut microbiota in health and disease, and for designing effective microbiome-targeted interventions.[38]

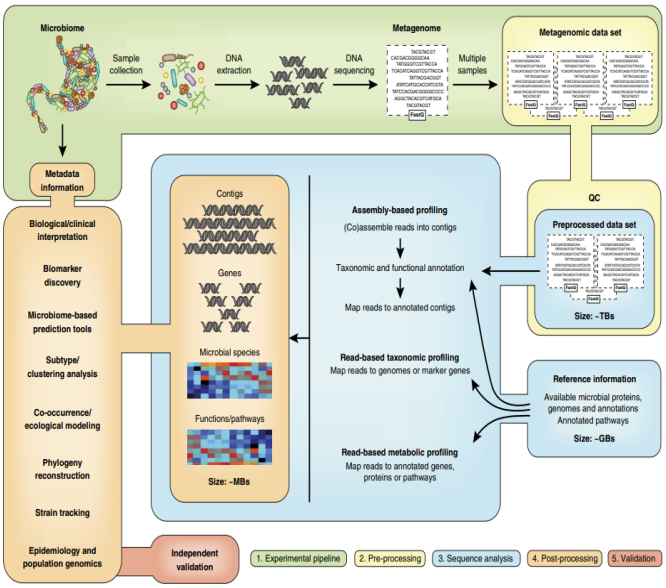

Figure 4. How Shotgun metagenomic sequencing works[38]

Shotgun metagenomic sequencing plays a pivotal role in the development of microbiota-based therapeutic strategies. This advanced technology enables high-resolution analysis of an individual's microbial composition, facilitating personalized therapeutic approaches. For instance, when gut dysbiosis contributes to a disease, shotgun sequencing can identify specific pathogenic microorganisms or the absence of beneficial microbes within a patient's microbiota.[39] This allows gut microbiota modulation strategies to be tailored to individual microbial profiles, thereby enhancing treatment effectiveness.[40]

In addition to compositional insights, shotgun metagenomics provides functional data on the gut microbiome. For example, certain microbiota have the ability to produce key metabolites, such as short-chain fatty acids (SCFAs), which exert anti-inflammatory effects and may aid in the prevention and management of chronic diseases including diabetes and cardiovascular conditions.[41]

Once the composition and function of the gut microbiome have been analyzed, intervention strategies can be designed to modulate the microbiota for disease management. Among the most effective and practical strategies for type 2 diabetes (T2D) are synbiotic supplementation and dietary modification. Gut dysbiosis is commonly observed in T2D patients. The administration of probiotics (e.g., *Bifidobacteria*, *Lactobacillus*), prebiotics (e.g., oligofructose, inulin), and their combination as synbiotics plays a significant role in modulating gut microbiota and improving metabolic outcomes.

Clinical studies have shown that probiotic intake can significantly reduce fasting blood glucose and hemoglobin A1clevels in T2D patients. Probiotics confer health benefits by mechanisms such as lowering intestinal pH, enhancing antimicrobial peptide secretion, inhibiting bacterial adhesion and invasion, reinforcing the gut barrier, and modulating immune responses.[42]

Several specific strains have demonstrated efficacy in T2D models. The combination of *Bifidobacterium lactis* LMG P-28149 and *Lactobacillus rhamnosus* LMG S-28148 upregulates PPARγ expression and improves insulin sensitivity in high-fat diet (HFD)-

induced obese mice.[43] *Bifidobacterium longum* and *Lactobacillus* strains have also been shown to increase GLP-1 and IL-10 expression, thereby reducing lipid accumulation in adipocytes.[44] Moreover, *Lactobacillus fermentum* MCC2760 enhances GLUT4, GLP-1, and ZO-1 expression, thereby improving glucose tolerance in HFD-fed mice.[45]

Inulin, a prebiotic dietary fiber indigestible by the human body, is fermented by gut microbes to produce SCFAs in the colon.[46] In a clinical trial (NCT02009670), inulin supplementation enhanced SCFA production and lipid oxidation, resulting in significant improvements in glycemic control.[47] Another study (NCT00750438) found that inulin-propionate ester supplementation significantly increased colonic propionate and prevented weight gain by boosting GLP-1 secretion.[48]

When synbiotics combinations of probiotics and prebiotics—are used, they may produce greater benefits than either component alone. For example, *Lactobacillus paracasei* N1115 combined with oligofructose downregulates TLR4 and NF-κB expression while enhancing p38 MAPK signaling, thereby improving anti-inflammatory responses.[49]

In addition to synbiotics, a healthy dietary pattern plays a key role in T2D management. Clinical evidence shows that caloric restriction leading to a weight loss of ~15 kg can induce remission in ~80% of obese patients with T2DM.[50] High-fat diets (HFD) are associated with increased levels of lipopolysaccharide (LPS) and trimethylamine-N-oxide (TMAO), and decreased SCFA production, all of which affect host metabolism and immunity. HFD has been linked to increased abundance of potentially pathogenic genera like *Escherichia coli*, *Klebsiella*, and *Shigella*, and a decrease in beneficial *Lactobacillus* spp.—providing potential early indicators of T2D progression. Interestingly, HFD may also transiently increase β-cell mass and reduce islet infiltration, which could protect against diabetes development through mechanisms such as immune checkpoint dysregulation and reduced T cell-mediated β-cell attack a phenomenon warranting further investigation.[51−52]

Other interventions such as caloric restriction (CR), very low-calorie ketogenic diets (VLCKD), and fasting-mimicking diets (FMD) have shown efficacy in combating metabolic diseases. CR is known to alter gut microbiota and reprogram metabolism, characterized by distinct bile acid profiles and elevated non-12α-hydroxylated bile acids.[53] These changes may stimulate GLP-1 secretion via TGR5/CAM signaling, contributing to glucose homeostasis.[54] Additionally, CR can reshape the gut microbiome and boost SCFA production, reinforcing its anti-inflammatory potential. Ketogenic diets can also elevate circulating acetoacetate and **β**-hydroxybutyrate (β-OHB), promoting lipolysis in white adipose tissue.[55] Moreover, such diets remodel the gut microbiome and reduce pro-inflammatory Th17 cells, highlighting their systemic immunometabolic effects.[56]

CONCLUSION

The shift in societal structure from an agrarian to an industrial society has significantly contributed to lifestyle changes that potentially increase the prevalence of type 2 diabetes mellitus. The use of various diabetes medications can trigger side effects, including the risk of acute hypoglycemia, lactic acidosis, and gastrointestinal issues. Therefore, innovative alternative therapies are needed for the management of type 2 diabetes mellitus.

One promising approach in precision therapy is the modulation of the gut microbiome. To implement precision therapy by modulating the gut microbiota, it is essential to first analyze the composition of the patient's gut microbiota. One technique that can be used is Shotgun Metagenomic Sequencing. Shotgun Metagenomic Sequencing is a sequencing technique used to analyze the entire genetic material of microbial communities in environmental samples, including the human gut microbiome. Following this, an effective and efficient strategy that can be applied for modulation involves the use of synbiotics and dietary management. Therefore, we hope this research can become an innovative therapy for type 2 diabetes mellitus that is more effective and reduces treatment side effects.

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