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An update and overview of the various health-related benefits of probiotics: A focus on clinical trials demonstrating efficacy, tolerability and use in patients with impaired glucose tolerance and type 2 diabetes

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Abstract

Recently, probiotics have been investigated as potential therapeutic agents for various diseases. Clinical studies using probiotics have been conducted in humans with impaired glucose tolerance and type 2 diabetes mellitus. Chronic inflammation plays a pivotal role in initiating insulin resistance in the pathogenesis of type 2 diabetes, leading to cardiovascular diseases. Intestinal dysfunction and inflammation have been postulated to trigger systemic chronic inflammation, and it is assumed that the suppression of inflammation in the intestine is the point of activity of probiotics. Therefore, in this review, among the randomised controlled trials that evaluated the effects of probiotics in patients with impaired glucose tolerance and type 2 diabetes, we selected trials that evaluated the indices of glycaemic control and inflammation-related markers. Some trials have shown that the probiotics administration improved glycaemic indices, such as HbA1c levels, and reduced C-reactive protein levels and proinflammatory cytokines, such as IL-6, in the blood, suggesting the suppression of inflammation. Two trials showed improvements in glycaemic indices, implying that they were mediated by IL-10, an anti-inflammatory cytokine. Although a correlation between the suppression of inflammation by probiotics and improvement in glycaemic control has not been documented, one trial revealed that glycaemic control worsened, accompanied by a decrease in anti-inflammatory cytokine levels, after probiotics were discontinued. Other studies have shown that probiotics can reduce blood endotoxin levels and increase intestinal mucin production. These findings suggest that probiotic administration has enormous potential to suppress chronic inflammation in metabolic disorders, leading to improved glycaemic control. Suppression of chronic inflammation has been speculated to prevent vascular diseases in type 2 diabetes.

KEYWORDS
clinical trial, inflammation, probiotics, randomised trial, real-world evidence, type 2 diabetes

1 | INTRODUCTION

Probiotics are defined by the International Scientific Association for Probiotics and Prebiotics as microorganisms that provide health benefits. Their clinical application has expanded due to the growing understanding that microorganisms, particularly those in the intestinal tract, play pivotal roles in human health and diseases.[1] Recent clinical studies have revealed that probiotics have beneficial effects on intestinal disorders such as irritable bowel syndrome and enterocolitis, as well as on allergic diseases and metabolic disorders such as type 2 diabetes and obesity.[2–5] Therapeutic strategies for chronic inflammation depend on the immune cells in the intestinal tract.[6–8] Probiotics have recently been reported to enhance the antitumour effects of immune checkpoint inhibitors[9] and are gaining attention as a strategy for moving beyond disease treatment to a healthier and more energetic lifestyle.

However, clinical evidence on the effectiveness of probiotics in the treatment of various diseases is insufficient. For example, probiotics are often administered to treat chronic constipation, and many clinical trials have demonstrated their efficacy against this disorder.[10,11] However, the results of various trials examining the efficacy of probiotics for chronic constipation have been inconsistent, and only a few randomised controlled trials have been made.[11] Similarly, many clinical trials have examined the efficacy of probiotics in obesity, glucose intolerance and type 2 diabetes, and meta-analyses have shown that probiotics have beneficial effects on glucose and energy homeostasis.[3,5,12] However, there have been only a few randomised controlled trials of probiotics in patients with type 2 diabetes, and sufficient research on the mechanism of action of probiotics in glucose regulation has not been conducted in clinical settings. Although certain probiotics have shown significant improvements in glycaemic control in experimental animals, they do not always show beneficial effects in humans, limiting their clinical application in patients with type 2 diabetes.

In this review, we outlined the changes in intestinal function and chronic inflammation in patients with impaired glucose tolerance and type 2 diabetes. Subsequently, we extracted some randomised controlled trials focusing on the effects of probiotics on glycaemic control and chronic inflammation in patients with impaired glucose tolerance and type 2 diabetes, summarised the studies and discussed future perspectives of treatment with probiotics.

2 | IMPAIRED INTESTINAL FUNCTIONS AND SYSTEMIC INFLAMMATION IN GLUCOSE INTOLERANCE AND TYPE 2 DIABETES

Macrophages infiltrate adipose tissue and secrete proinflammatory cytokines, such as TNF-α, causing insulin resistance in patients with obesity and type 2 diabetes.[13] This inflammation is limited to adipose tissue and is thought to occur in the liver and intestine.[14] The epigenomic changes in immune cells caused by metabolic alterations and the molecular mechanisms by which immune cells act on organs that regulate energy homeostasis are elucidated. Inflammation associated with metabolic derangements is termed 'metaflammation'.[15] Besides, this chronic inflammation is thought to play an important role in organ dysfunction with ageing because clinical studies of centenarians reported that serum levels of inflammatory markers such as C-reactive protein (CRP) and IL-6 were associated with ageing and cognitive function, termed 'inflammaging'.[16]

Several clinical studies have investigated the association between intestinal dysfunction and chronic inflammation in patients with metabolic disorders. An essential function of the intestine is to prevent the invasion of bacteria and bacteria-derived components by acting as a barrier. However, one of the bacteria-derived components, lipopolysaccharide (LPS), increases in the blood, even in healthy individuals, after the consumption of a high-fat diet.[17] Another study reported that total energy intake correlated with blood concentration of endotoxins.[18] When bacteria in the mucin layer of colon sections were stained in patients with type 2 diabetes, those with higher HbA1c levels had more bacteria in the mucin layer next to the host intestinal cells.[19] A large amount of bacteria-derived RNA has been detected in the liver and greater omentum of patients who underwent bariatric surgery to manage type 2 diabetes and obesity.[20] These results suggest that patients with type 2 diabetes have an impaired intestinal function that might induce chronic systemic inflammation. In line with these findings, the number of ligands in the faeces of the aryl hydrocarbon receptor, which enhances intestinal barrier function, is low in patients with type 2 diabetes.[21] Overall, intestinal function is impaired in type 2 diabetes, and the disruption causes chronic inflammation.

3 | IMPACT OF PROBIOTICS ON TYPE 2 DIABETES AND CHRONIC INFLAMMATION

Based on impaired intestinal function in type 2 diabetes, many trials have used probiotics to treat or prevent impaired intestinal function in patients with type 2 diabetes. We searched the PubMed and Scopus databases for clinical trials examining the effects of probiotics on glycaemic control and chronic inflammation. We used the following search equations: ((‘diabetes’ [All Fields] OR ‘glucose intolerance’ [All Fields]) AND ‘Probiotics’ [All Fields] AND (‘inflammation’ [All fields] OR ‘inflammatory’ [All fields] OR ‘C-reactive protein’ [All fields])). The PubMed database contained 61 trials after the ‘Randomized Controlled Trials’ filter was applied. The following equations were applied to the Scopus database: TITLE-ABS (‘diabetes’ OR ‘glucose intolerance’) AND TITLE-ABS (‘probiotic*’) AND ALL (‘inflamm*’ OR ‘C reactive protein*’) AND TITLE-ABS-KEY (‘randomized controlled trial’) AND NOT (review) AND ‘meta-analysis’ and 54 trials were observed. Studies that did not address type 2 diabetes or impaired glucose tolerance or incorporate both glycaemic and inflammatory indices into the results were excluded. In addition, those written in languages other than English, protocol articles or reviews, or those that did not assess the impact of probiotics alone were not considered (Tables S1 and S2).

The extracted clinical trials are summarised in Table 1. *Lactobacillus* and *Bifidobacterium* are the most commonly examined probiotics. Four trials investigated the effects of a single probiotic species on glycaemic and inflammatory markers. Sato et al. studied 70 patients with type 2 diabetes who received either *L. casei* Shirota-fermented milk (probiotic group) or milk alone (control group) for 16 weeks. Blood high-sensitivity CRP (hsCRP) levels decreased only in the probiotic group, while other inflammatory markers did not differ between groups. HbA1c levels increased significantly in both groups.[22] Hsieh et al. investigated the effects of live *L. reuteri* strain ADR-1 and heat-treated *L. reuteri* ADR-3. A significant reduction in HbA1c levels was observed in the ADR-1 group. A reduction in HbA1c levels was still observed 3 months after discontinuation of ADR-1. No significant change was observed in the HbA1c level in the heat-treated ADR-3 participants; however, a reduction in serum IL-1β levels was observed after 6 months of intake. No further changes in serum inflammatory cytokine levels were observed in ADR-1-treated participants.[23] Tipici et al. evaluated treatment with *Lactobacillus rhamnosus* GG for 8 weeks. Fasting plasma glucose levels decreased significantly in both the placebo and probiotic groups; however, there was no significant difference between the two groups. The HbA1c, hsCRP and IL-6 levels did not change in either group. However, the expression of genes that are related to mucus production in the intestine increased significantly only in the probiotic group.[24] Toshimitsu et al. reported that patients with impaired glucose tolerance were administered yoghurt with or without heat-treated *L. plantarum* OLL2712 for 12 weeks. Fasting plasma glucose levels did not change in either group; however, the HbA1c levels decreased significantly in both groups. However, this reduction was greater in the probiotic group than in the placebo group. Furthermore, the decrease in HbA1c levels in both groups disappeared 8 weeks after the intervention. The HbA1c level was still lower in the probiotic group than in the placebo yoghurt group 4 weeks after discontinuation of the intervention. A similar trend to HbA1c was observed for serum glycoalbumin levels. After the intervention, IL-6 levels decreased significantly only in the probiotic group. After 8 weeks, IL-10 serum levels increased significantly in the probiotic group and decreased significantly in the placebo group.[25]

Other studies have examined inflammatory markers in patients with type 2 diabetes, including those with multiple strains. Mohamadshahi et al. and Tonucci et al. examined the effects of yoghurt supplemented with or without *L. acidophilus* La-5 and *Bifidobacterium animalis* subsp. *lactis* BB-12 for 6–8 weeks.[26,27] Both studies showed that fasting glucose levels did not change between the probiotic and placebo groups; however, HbA1c levels decreased more in the probiotic group than in the placebo group. The TNF-α level decreased significantly in both studies, but the IL-6 level did not change. The IL-10 serum level was examined only in the study by Tonucci et al., and the level decreased significantly in the placebo group but did not change in the probiotic group. The mixtures were then investigated. Firouzi et al. evaluated the effects of a mixture of six probiotics. Patients in the probiotic group showed a significantly greater reduction in HbA1c and fasting plasma glucose levels than those in the placebo group. However, no significant changes were observed in inflammatory markers.[28] Sabico et al. reported the effects of a mixture of eight probiotic species for 6 months in patients with drug-free, newly diagnosed type 2 diabetes. They revealed that fasting plasma glucose, insulin and HOMA-IR levels decreased significantly in the probiotic group. The CRP, TNF-α, IL-6 and endotoxin levels decreased.[29] Two studies examined the combination of 14 live probiotic strains, and the administration of these strains significantly decreased serum levels of TNF-α and IL-1β.[30,31] The study of the mixture by Savytska et al. showed a significant reduction in fasting plasma glucose and HbA1c levels and a significant increase in HOMA-β levels. Serum IL-6 levels decreased in both the probiotic and placebo groups; however, the magnitude of reduction was greater in the probiotic group.

4 | ADVERSE EVENTS AND SAFETY

Most clinical trials have reported minimal adverse effects of probiotic supplementation. However, clinicians should be aware that certain probiotics pose certain risks. A previous study identified that patients with bacteraemia occurred, and the bacterial strain isolated from the patient's bloodstream matched the probiotic strain they were taking.[32] Although the risk of bacteraemia is low, caution is advised when prescribing probiotics to immunocompromised individuals, including those receiving immunosuppressive therapy or premature infants.[33] Although systemic inflammation may worsen due to the intake of probiotics, no serious concern was reported in the studies included in this review as long as probiotics were administered in the range of approximately 1×10^9/day to 1×10^{11}/day (Table 1).

Another concern is whether the bacterial strains that make up probiotics can colonise the host intestine after ingestion. To address this, it is essential to analyse faecal samples for the absence of bacteria after discontinuation of probiotic administration. However, no such investigations were conducted in these trials. Two studies included follow-up periods after the cessation of probiotic administration, with one study reporting that the improvement in glycaemic control diminished following discontinuation.[25] This observation indicates that probiotics do not induce permanent intestinal colonisation.

5 | DISCUSSION AND FUTURE PERSPECTIVE

Analysis of randomised placebo-controlled clinical trials in this review indicated that probiotics could be a novel treatment for glucose intolerance and type 2 diabetes by suppressing chronic inflammation. Clinical trials have shown that probiotics reduce plasma glucose and HbA1c levels. Decreases in serum CRP and IL-6 levels, which are indicators of inflammation, have been observed in several trials in which probiotics were observed to increase or maintain serum levels of IL-10, an anti-inflammatory cytokine. Although the correlation between the decrease in chronic inflammation and the improvement in glycaemic control is not clear, given that type 2 diabetes is accompanied by

TABLE 1 The summary of randomized controlled trials investigating the impacts of probiotics on glycaemic control and inflammation in IGT and type 2 diabetes.

Authors	Subjects (HbA1c[a])	The duration of IGT or T2DM	Medication	Probiotics/ placebo (*n*)	Intervention	Placebo	Bacterial amount (cfu/day)	Intake period	Effects of probiotics	Comments[b]
Sato et al.[22]	T2DM (6.8%–6.9%)	12–14 years	Yes (including metformin)	34/34	*L. casei* Shirota	Milk	>4 × 10^{10}	16 weeks	FPG → HbA1c↑ hsCRP↓ IL-6 → TNF-α→	HbA1c↑ (pla)
Hsieh et al.[23]	T2DM (7.9%–8.1%)	>6 months	Yes (including metformin)	22/24 (heat-treated)/22	Live *L. reuteri* ADR-1 or Heat-treated *L. reuteri* ADR-3	Capsule	4 × 10^{9}, ADR-1; 2 × 10^{10}, ADR-3	24 weeks	FPG → HbA1c↓ (ADR-1) IL-1β↓ (ADR-3)	HbA1c↓ after the 3-month follow-up period (pro)
Tipici et al.[24]	T2DM (6.4%–6.6%)	5–6 years	Yes (excluding GLP-1RA, insulin)	17/17	*L. rhamnosus* GG ATCC 53103	Corn oil	1 × 10^{10}	8 weeks	FPG↓ HbA1c→ IL-6 → hsCRP→	FPG↓ HbA1c → (pla) faecal mucin gene↑ (pro)
Toshimitsu et al.[25]	IGT (5.8%)	N/A	No	73/72	*L. plantarum* OLL2712 + yoghurt	Yoghurt alone	>5 × 10^{9}	12 weeks	FPG → HbA1c↓ GA↓ IL-6↓ IL-10↑	HbA1c↓ IL-10↓ (pla) HbA1c↑ IL-10↓ after the 8-week follow-up period (pro)
Mohamadshahi et al.[26]	T2DM (8.2%–8.3%)	Not listed	Yes (excluding insulin)	22/22	*L. acidophilus* La5 and *B. animalis* subsp. *lactis* Bb12 + yoghurt	Yoghurt alone	1.1 × 10^{9}, each	8 weeks	FBS → HbA1c↓ TNF-α↓ IL-6 → hsCRP→	
Tonucci et al.[27]	T2DM (5.4%–6.1%)	>1 year	Yes (including metformin)	23/22	*L. acidophilus* La5 and *B. animalis* subsp. *lactis* Bb12 + yoghurt	Yoghurt alone	1 × 10^{9}, each	6 weeks	FPG → HbA1c↓ TNF-α↓ IL-6 → IL-10→	HbA1c → TNF-α↓ IL-10↓ (pla)
Firouzi et al.[28]	T2DM (7.6%–7.7%)	>6 months	Yes (excluding insulin)	68/68	The mixture of 6 strains (*L. acidophilus*, *L. casei*, *L. lactis*, *B. bifidum*, *B. longum*, *B. infantis*)	Powder	6 × 10^{10}, in total	12 weeks	FPG → HbA1c↓ insulin↓ hsCRP→	HbA1c↑ insulin↑ (pla)
Sabico et al.[29]	T2DM (<7%)	<6 months	No	31/30	The mixture of 8 strains (*B. bifidum* W23, *B. lactis* W52, *L. acidophilus* W37, *L. brevis* W63, *L. casei* W56, *L. salivarius* W24, *L. lactis* W19 and W58)	Powder	5 × 10^{9}, in total	24 weeks	FPG↓ insulin↓ HOMA-IR↓ CRP↓ TNF-α↓ IL-6↓ endotoxin↓	
Kobyliak et al.[30]	T2DM (8.3%–8.4%)	>6 months	Yes (including metformin, SUs, insulin)	31/22	The mixture of 14 strains (*Lactobacillus*, *Lactococcus*, *Bifidobacterium*, *Propionibacterium*, *Acetobacter*)	Powder	6 × 10^{10}, *Lactobacillus* + *Lactococcus*; 1 × 10^{10}, 3 × 10^{10}, 1 × 10^{6}, respectively	8 weeks	FPG → HbA1c → HOMA-IR↓ IL-6↓ TNF-α↓ IL-1β↓	FPG → HbA1c→ HOMA-IR → (pla)
Savytska et al.[31]	T2DM (8.9%)	12–14 years	Yes (including metformin)	34/34	The mixture of 14 strains (*Lactobacillus*, *Lactococcus*, *Bifidobacterium*, *Propionibacterium*, *Acetobacter*)	Powder	6 × 10^{10}, *Lactobacillus* + *Lactococcus*; 1 × 10^{10}, 3 × 10^{10}, 1 × 10^{6}, respectively	8 weeks	FPG↓ HbA1c↓ HOMA-β↑ IL-6↓ TNF-α↓ IL-1β↓ IFN-γ↓	HbA1c → IL-6↓ (pla)

[a]Average values at baseline for each group.
[b](pla), changes in the placebo group; (pro), changes in the probiotics group.

chronic inflammation, it can be assumed that the suppression of inflammation contributes to better glycaemic control.[14] A decrease in serum insulin levels and HOMA-IR has been shown in several studies, suggesting an improvement in insulin sensitivity through the suppression of chronic inflammation in type 2 diabetes. An earlier meta-analysis of clinical trials examining the effects of probiotics on patients with diabetes showed that probiotics lowered serum CRP levels, which is consistent with our analysis that examined only randomised trials.[6,34] In contrast, the meta-analysis did not show a consistent trend for serum IL-6 and TNF-α levels; however, our study observed that probiotics lowered serum cytokine levels. This difference may be because the meta-analysis included non-randomised trials.[6] We observed an increase in serum IL-10 levels following probiotic administration in one trial, which remained stable in another trial.[25,27] The HbA1c levels of participants in these two studies were not high. A meta-analysis showed an increase in IL-10 expression in peripheral blood mononuclear cells from healthy participants, although no consistent trend was observed in patients with diabetes. Therefore, probiotics may be more likely to induce IL-10 expression in patients with impaired glucose tolerance whose glycaemic control is relatively favourable.

This review focuses on the role of probiotics in glucose homeostasis and chronic inflammation in the intestine. One study reported a decrease in the level of endotoxins in the blood, and another reported an increase in mucin production in the intestinal tract. Probiotics influence the immune cells in the intestinal tract and regulate cytokine production. Inflammatory cytokines such as IL-6 regulate immune cell proliferation and activation to eradicate intracellular pathogens and induce CRP production, while anti-inflammatory cytokines such as IL-10 suppress inflammation. The reduction in serum CRP levels observed in a few trials indicates the suppression of inflammation by the administration of probiotics. Among the lactic acid bacteria, *L. plantarum* has a particularly high ability to induce IL-10 production compared with other species.[35] Meta-analysis of the effects of various *Lactobacillus* species showed weight gain in humans and animals. The study showed that *Lactobacillus fermentum* and *Lactobacillus ingluviei* were associated with weight gain, whereas *Lactobacillus plantarum* was associated with weight loss.[36] *L. plantarum* strains effectively prevented obesity and improved metabolic disorders by suppressing chronic inflammation, suggesting an improvement in 'metaflammation.' In one study, the ingestion of *L. plantarum* OLL2712 reduced HbA1c levels and increased IL-10 levels in the blood, and an increase in HbA1c levels was accompanied by a decrease in IL-10 levels during the follow-up observational period after the strain was discontinued.[25] These findings support the hypothesis that probiotics ameliorate metabolic abnormalities in metaflammation and inflammaging by producing anti-inflammatory cytokines. In addition to suppressing chronic inflammation, probiotics have been proposed to improve glycaemic control by promoting GLP-1 secretion.[37] Because the clinical trials in this review did not investigate incretin secretion, the contribution of this effect to improvement remains unclear. However, it was challenging to explain the findings of the clinical trials included in this review, which showed an increase in intestinal mucin production and a decrease in blood endotoxin levels by reducing the amount of adipose tissue (Figure 1).

Similar to clinical trials of new drugs, the impact of probiotics on glycaemic control in type 2 diabetes is not always consistent. This may be due to differences in the genetic background, duration of diabetes and the presence of medications for diabetes. Differences exist in the intestinal microbiota of individuals, and a classification of intestinal microbiota patterns by enterotype has been proposed.[38] The following findings regarding the interrelationship between enterotypes and probiotics have been reported. Probiotics, such as *Bifidobacterium breve* CBT BR3 and *Lactobacillus plantarum* CBT LP3 decreased visceral fat more in those with the Prevotella-rich enterotype than in those with the Bacteroide-rich enterotype.[39] Thus, the heterogeneity of enterotypes makes it difficult to determine the effects of probiotics. As for the duration of diabetes, the patients in the studies in this review had a history of diabetes for more than 5 years in which probiotics did not decrease the HbA1c levels. Assuming that probiotics improve glycaemic control primarily through the suppression of chronic inflammation, they may provide little benefit to patients with a long history of diabetes and low insulin secretion. Administration of probiotics to medication-free patients or patients with impaired glucose tolerance is promising. Additionally, the administration of probiotics for several months may be required to demonstrate an improvement in glycaemic control because probiotics do not overpromote insulin secretion as sulfonylureas do. The concomitant use of medication for diabetes is a crucial factor. The patients in six trials were treated with oral hypoglycaemic agents, including metformin (Table 1). Metformin is known to affect microbiota and metabolites in the intestine; therefore, the effects of probiotics could not be determined in these trials.[40] Probiotics should be examined in medication-free patients; only two studies on patients who were free from diabetes medications were included in this review.[25,29] One trial reported an increase in HbA1c levels after discontinuation of probiotics.[25]

In clinical studies, there are several characteristics of probiotics that differ from those in clinical trials of drugs. First, because probiotics are not chemically synthesised, strains of probiotics may differ from facility to facility, even if the names of the bacteria are identical. For instance, strains BB-12 and W52 of the *Bifidobacterium lactis* were used in every study.[27,29] Combining these two studies to evaluate the effects of *Bifidobacterium lactis* might have led to inaccurate conclusions. Second, the probiotic dosage was unclear. The probiotic doses used in this review ranged from 1×10^9 to 1×10^{11}, and a few studies observed it was difficult to identify the exact dose. Probiotics that do not show efficacy may be more effective at higher doses. Third, mixtures of probiotics with different bacterial strains have been used in six clinical trials. In two studies, probiotics were mixed with up to 14 bacterial strains. Considering the potential of bacteria to influence each other in the intestinal tract, it is necessary to proceed from a study with a single bacterial strain to a multi-strain study. Fourth, yoghurt alone improves glycaemic control.[41,42] The Food and Drug Administration recently reviewed the effects of yoghurt consumption on the development of type 2 diabetes, which has become a hot

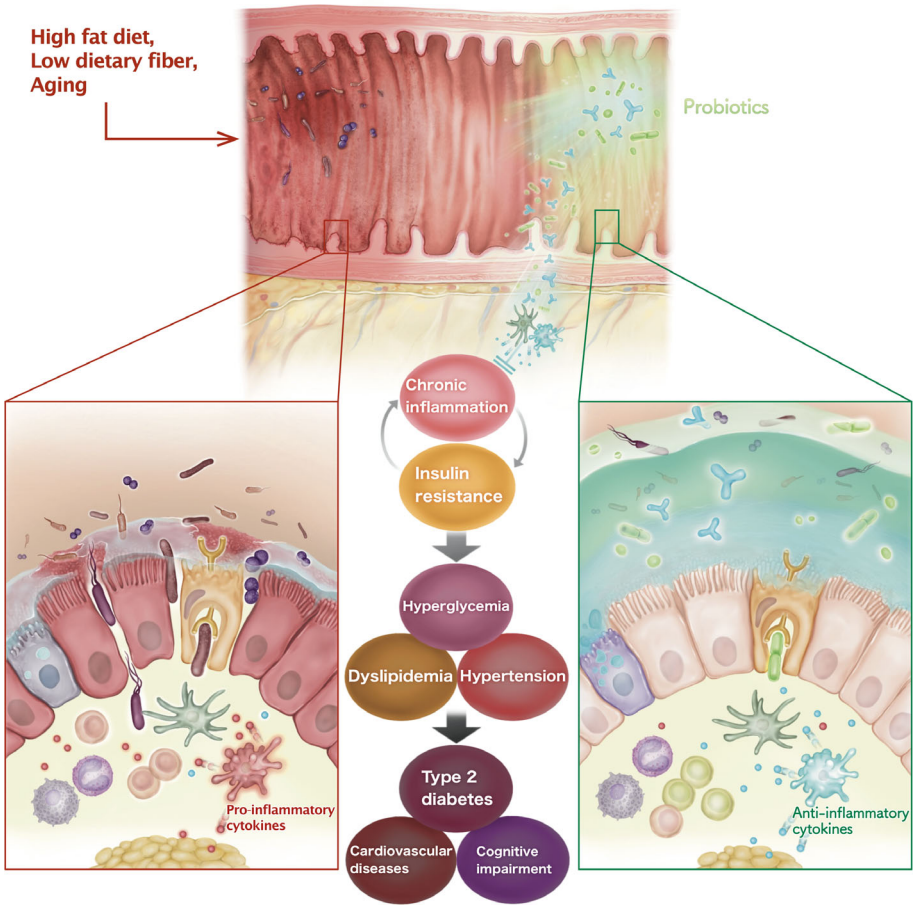

FIGURE 1 Putative mechanism of action of probiotics to prevent type 2 diabetes and its complications. The intestinal microbiota and metabolites are skewed, and intestinal function is impaired due to chronic inflammation with proinflammatory cytokines in patients with impaired glucose tolerance and type 2 diabetes caused by the intake of a high-fat diet, low dietary fibre and ageing. An impaired intestine with a disruption of the intestinal barrier leads to systemic inflammation and organ insulin resistance. Systemic insulin resistance causes hyperglycaemia, hypertension and dyslipidaemia, leading to the development of type 2 diabetes and its complications, such as cardiovascular and cerebrovascular diseases, leading to cognitive impairment. Certain probiotics act on immune cells in the intestine, induce the production of anti-inflammatory cytokines such as IL-10, suppress chronic inflammation, improve insulin sensitivity to improve glycaemic control and reduce the development of metabolic disorders.

topic.[43] Therefore, to determine the precise impact of probiotic strains on yoghurt, a control group that only consumes yoghurt is required. Toshimitsu et al. administered yoghurt alone to patients in the placebo group and showed a decrease in HbA1c levels in the placebo group, whereas the control participants administered yoghurt alone in the study by Tonucci et al. did not show any change in the value of HbA1c.[25,27] The shorter period of probiotic administration and concomitant use of medication for diabetes may have diminished the effect of yoghurt alone in the latter study. Thus, the combination of probiotics and yoghurt may be more beneficial than probiotics alone.

Novel probiotics for type 2 diabetes have been investigated based on clinical evidence of the probiotics. *Akkermansia muciniphila* is a candidate bacterium that increases the mucus layer thickness and improves diabetes in animal models.[44] Clinical studies on obesity showed that people with greater amounts of intestinal *A. muciniphila* have better insulin sensitivity, less hepatic fat accumulation and better glycaemic control than people with identical BMI and lower amounts of this bacterium.[45] A clinical trial investigated the effects of the administration of *A. muciniphila* in patients with obesity and insulin resistance. Administration for 3 months resulted in a decrease in blood LPS levels and insulin resistance and a tendency to decrease body weight and body fat mass.[46] This finding supports the idea that targeting the intestinal microbiota and the functioning of bacteria as probiotics is a promising new strategy for treating type 2 diabetes.

Furthermore, there is potential for the clinical application of probiotics targeting chronic inflammation in various disorders of type 2 diabetes. Chronic inflammation is thought to occur with ageing, accelerating vascular ageing and exacerbating vascular diseases.[47] Since probiotics suppress chronic inflammation by modulating intestinal function in type 2 diabetes, their administration may prevent cardiovascular disorders. Clinical trials are underway to suppress vascular diseases using monoclonal antibodies targeting inflammatory cytokines. However, probiotics, with their long-term clinical use, may be a therapeutic strategy against inflammation. In addition, supercentenarians have a distinct intestinal microbiota and are less prone to cardiovascular and cerebrovascular disorders as well as type 2 diabetes.[48] Therefore, it is reasonable to target the intestinal tract with probiotics to suppress age-related cardiovascular and cerebrovascular diseases that lead to cognitive impairment. Probiotics suppress chronic inflammation induced by a high-fat diet and/or ageing-related dysfunctions and can prevent metabolic and vascular disorders for longevity by enhancing the action of anti-inflammatory cytokines (Figure 1).

6 | CONCLUSION

The administration of probiotics has been shown to improve glycaemic control and suppress chronic inflammation in patients with impaired glucose tolerance and type 2 diabetes in randomised

controlled trials. Although trends in clinical trial results were consistent, further studies are needed to standardise the dosages and strains of probiotics and the duration of administration to optimise their efficacy in managing type 2 diabetes. In addition, the mechanisms involved in the improvement of glycaemic control through the suppression of inflammation by probiotics should be clarified in clinical settings.

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DATA AVAILABILITY STATEMENT

Data available in article supplementary material.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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