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RESEARCH ARTICLE

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Probiotics ameliorates glycemic control of patients with diabetic nephropathy: A randomized clinical study

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Abstract

Objective: This research aimed to explore the effects of probiotic administration on glycemic control and renal function in patients with diabetic nephropathy (DN).

Methods: The 101 participants were randomly divided into two treatment groups and 76 patients were included in the final analysis. In 76 patients with diabetic nephropathy of type 2 diabetes, a randomized double-blind and placebo-controlled clinical trial was conducted to evaluate the administration of 3.2×10^9 CFU probiotic supplements per day (*Bifidobacterium bifidum*, 1.2×10^9 CFU, *Lactobacillus acidophilus* 4.2×10^9 CFU, *Streptococcus thermophilus* 4.3×10^9 CFU) for 12 weeks on glycemic control of patients, including fasting blood glucose, 2 h postprandial blood glucose, glycosylated hemoglobin (HbA1c), microalbuminuria/creatinine (mAlb/Cr) and estimated glomerular filtration rate (eGFR) levels. The placebo group daily received empty capsules filled with starch.

Results: After 12 weeks, the administration of probiotics demonstrated a significant reduction in fasting blood glucose (10.68 ± 3.24 mmol/L before vs. 7.81 ± 2.77 mmol/L after, $p < 0.05$), HbA1c (8.19 ± 1.60% before vs. 7.32 ± 1.20% after, $p < 0.05$) and mAlb/Cr (101.60 ± 22.17 mg/g before vs. 67.53 ± 20.11 mg/g after, $p < 0.05$), while only mAlb/Cr level was significantly lower in the probiotic group than in the placebo group after intervention (67.53 ± 20.11 mg/g vs. 87.71 ± 23.01, $p < 0.05$). Meanwhile, there was no significant reduction of 2 h postprandial blood glucose level (18.95 ± 5.23 mmol/L vs. 17.35 ± 6.28 mmol/L, $p = 0.24$) and eGFR (84.34 ± 6.97 ml/min vs. 82.8 ± 8.72 ml/min, $p = 0.45$) in patients before and after probiotic intake. In addition, the placebo group failed to show any significant change of these parameters.

Conclusion: This clinical study revealed probiotic administration could ameliorate glycemic control of patients with diabetic nephropathy, potentiating its therapeutic potential in clinical application.

KEYWORDS

diabetic nephropathy, glycemic control, probiotics, type 2 diabetes mellitus

1 | INTRODUCTION

Diabetic nephropathy (DN), one of serious diabetic microvascular complications of diabetes mellitus, is regarded as a dominative cause of end-stage renal disease.[1,2] It was reported that patients with DN could result in end-stage renal failure and disability worldwide with high mortality, affecting approximately 40% of diabetic patients.[3,4] Therefore, DN raised great concern in researchers in this field. Patients with DN were usually accompany by metabolic syndrome, such as elevated fasting blood glucose levels, postprandial blood glucose level[5] and microalbuminuria level.[6]

In general, blood glucose elevated beyond the kidney's capacity and failed to reabsorb glucose from the renal ultrafiltration, resulting in redundant glucose diluted in the fluid in early stages of type 2 diabetic mellitus.[7] Consequently, redundant glucose level increased the urine volume and osmotic pressure.[8] Therefore, the treatments of DN based on reducing glucose level were limited, such as the control of glucose intake,[9] the supplementation of high-quality protein diet,[10] intake of angiotensin-converting enzyme inhibitors[11] and angiotensin II receptor blockers.[12] However, these controls failed to demonstrate efficacy and effectiveness on DN. Furthermore, recent studies focus on elucidating the long-term effects of drugs, such as microcirculator, anti-fibrosis chemicals and herbal extracts, on DN.

Upon sufficient intake as living microorganisms in dietary supplements, probiotics would efficiently improve the metabolism of the host and also increase its nutritional intake.[13–15] Numerous reports have illustrated the association between probiotics and gut.[16,17] The researchers demonstrated that the favorable effects of probiotics were closely associated with its abundance of certain beneficial bacteria, which produced anti-inflammatory metabolites. Subsequently, these anti-inflammatory metabolites would modulate the pro-inflammatory immune cell line through the crosstalk between gut and other organs.[18,19] Specifically, it was suggested that probiotics exerted inhibitory effects of metabolic syndrome of diabetes.[20] In details, the results revealed that intake of probiotics had inhibitory effects on blood glucose level, which was essential for modulating the changes of the intestinal microflora in patients with type 2 diabetes mellitus.[20] In addition, it showed that intestinal dysbiosis remained a susceptible factor for the progress of chronic kidney disease in DN. Despite the clinical applications of the probiotic intake in the management of blood glucose, few studies were conducted to investigate the effects of probiotic intake on glycemic control and kidney function amelioration in DN patients.

Therefore, this study aimed to explore the effects of probiotic administration on glycemic control and renal function in patients with DN in type 2 diabetes. And our results revealed that probiotics showed potent effects in decreasing fasting blood glucose and postprandial glucose levels and other diabetic parameters of patients with diabetic nephropathy, potentiating its potential in clinical application.

1.1 | Subjects

This randomized, parallel-group, double-blind, placebo-controlled experiment was performed on patients with DN by China-Japan Union Hospital of Jilin University at an endocrinology and metabolic clinics in Changchun, China, from January 2017 to July 2017. The inclusion criteria were as follows: (1) patient age was ≥18 years and ≤75 years; (2) patients were diagnosed with diabetic nephropathy according to world health organization's standard of type 2 diabetes mellitus[21] and did not intake any antidiabetic drugs within 3 months before the study; (3) the patients' glycosylated hemoglobin (HbA1c) levels was between 7% and 10%; and (4) the microalbuminuria/creatinine (mAlb/Cr) level was ≥30 mg/g per 24 h. The exclusion criteria were as follows: (1) patients with type 1 diabetes mellitus; (2) patients with hypoglycemic coma, diabetic ketoacidosis, hyperosmotic nonketotic coma or diabetes mellitus acute complications; (3) fasting blood glucose was >13.3 mmol/L; (4) total bilirubin was >2.5 times of normal value; (5) serum creatinine was >133 μmol/L in male patients, and >124 μmol/L in female patients; (6) patients with history of hypertension, drug abuse, alcohol dependence or drug allergy; (7) patients' intake of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers within 3 months; and (8) patients' intake probiotic and/or synbiotic supplements within 3 months before this study. Following the selection criteria, the study was conducted on 101 volunteers. However, 25 volunteers failed to complete the trial, and 76 volunteers eventually received the treatment. This clinical trial was approved by the China-Japan union hospital Ethics Committee (Approval number/2016ks095), and the approved date was December 20, 2016. Ethical clearance was taken from ethical clearance committee of the China-Japan union hospital (Ethical clearance number/0431-84995047) (ChiCTR2000038392). The informed consent was signed by all the participants participated in this study.

2 | MATERIALS AND METHODS

2.1 | Random allocation

Randomization of all participants was performed by means of a computer-generated random-numbers table, as to reduce the potential confounding effects. To balance the baseline characteristics between the two groups, subjects were assigned in a 1:1 ratio. The 76 participants were randomly divided into two treatment groups: probiotic group (n = 42) and placebo group (n = 34). The probiotic group received 3.2×10^9 CFU per day of probiotics containing (*Bifidobacterium bifidum* 1.2×10^9 CFU, *Lactobacillus acidophilus* 4.2×10^9 CFU, *Streptococcus thermophilus* 4.3×10^9 CFU) for 12 weeks and then stopped taking probiotics. Simultaneously, the placebo group received empty capsules with similar shape and weight for 12 weeks, and then stopped taking capsules. The probiotic and placebo (starch) were

produced by LactoCare® and Tian San Qi Company, respectively. Moreover, all the participants were required to take their respective supplements on a daily base. Dietary assessment of all participants was performed by the nutritionist to assess the participants' nutrient intake by Nutritionist IV software (First Databank). In order to follow up the treatment, our team contacted the participants once a week for general medical advice and diabetes education, including daily diet, physical exercise, and self-monitoring of blood glucose.

2.2 | Biochemical measurements

The height and weight of all patients were measured before and after 12 weeks treatment. Fasting blood glucose, 2 h postprandial blood glucose level, glycosylated hemoglobin (HbA1c) and serum creatinine were measured by automatic biochemical analyzer. Fasting insulin levels were measured by enzyme-linked immunoassay kit (DRG Company). Microalbuminuria/creatinine (mAlb/Cr) was determined by automatic special protein dry immune scattering chromatographic analyzer (Ariel Afinion AS100). Estimated glomerular filtration rate (eGFR) was calculated by (CKD) - EPI) formula. The formula was HOMA-IR = fasting blood insulin (mIU/L) × fasting blood glucose (mmol/L)/22.5 was used to calculate the homeostasis model assessment index (HOMA-IR).

2.3 | Statistical analysis

Based on the difference between two sample rates, using the estimation formula to calculate the required sample size.[22] The inspection level (α) was 0.05 and power was 0.8 ($\beta = 1$; power = 0.2) were assumed. Based on the two-sided tests, the sample size was estimated to be 74, with 37 subjects per group. Owing to possible patient withdrawal, we increased the sample size by 15%, and a total of 100 subjects were required, with 50 participants in each group. Statistical analysis of the data was performed using SPSS 19.0 (SPSS Inc). Kolmogorov–Smirnov test was used to check the normality of variables distribution. The data were presented as mean ± standard deviation (SD) or *n* (%). Student's *t*-test or Mann–Whitney test was used to assess the statistical significance of the results between probiotic group and placebo group, or before and after intervention. $p < 0.05$ was regarded as statistically significant.

3 | RESULTS

3.1 | Characteristics of probiotic and placebo groups before treatment

101 volunteers were recruited into this research. At the end of the treatment, 25 participants failed to complete the trial, and only 76 participants completed the treatment (probiotic group ($n = 42$) and

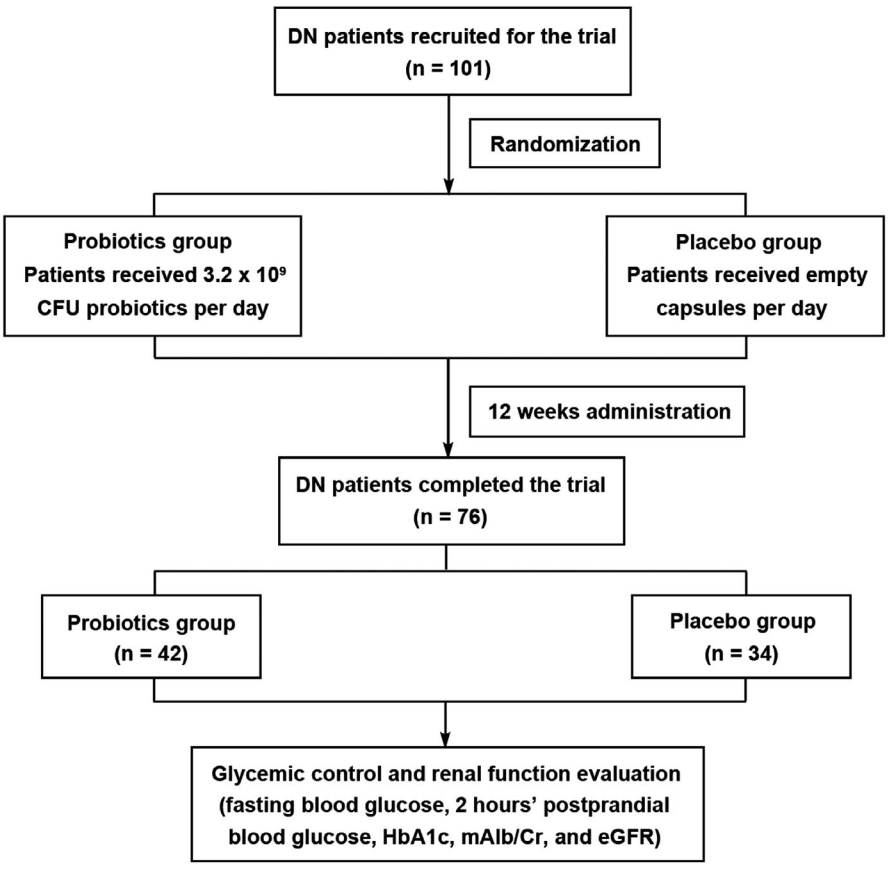

FIGURE 1 The flowchart of study design. DN, diabetic nephropathy; eGFR, estimated glomerular filtration rate; HbA1c, glycosylated hemoglobin; mAlb/Cr, microalbuminuria/creatinine

placebo group (n = 34)). Therefore, the glycemic control and renal function evaluations on these 76 participants were conducted in the following study (Figure 1). The mean value of age and the sex distribution in two groups are listed in Table 1. The results in two groups demonstrated no significant difference regarding levels of fasting blood glucose, 2 h postprandial blood glucose, HbA1c, serum creatinine, mAlb/Cr, BMI, insulin resistance index and eGFR (Table 1).

3.2 | Probiotic administrations reduced glycemic control in DN patients

The probiotic group received 3.2×10^9 CFU per day of probiotics containing, while the placebo group received empty capsules filled with starch, for a total of 12 weeks. After 12 weeks of intervention, probiotic group demonstrated a significant reduction in fasting glucose (7.81 ± 2.77 mmol/L after treatment vs. 10.68 ± 3.24 mmol/L before treatment, $p < 0.05$, Figure 2) and HbA1c (%) (7.32 ± 1.20% after treatment vs. 8.19 ± 1.60% before treatment, Figure 4). However, the probiotic group revealed a slight reduction without significant change of 2 h postprandial blood glucose level (17.35 ± 6.28 mmol/L after intervention vs. 18.95 ± 5.23 mmol/L before intervention, $p = 0.24$, Figure 3). And the placebo group revealed a slight reduction without significant change of fasting glucose (8.78 ± 3.01 mmol/L after intervention vs. 9.83 ± 3.90 mmol/L before intervention, $p = 0.48$, Figure 2), 2 h postprandial blood glucose level (17.13 ± 6.05 mmol/L after intervention vs. 19.00 ± 6.41 mmol/L before intervention,

TABLE 1 The comparison of baseline characteristics between probiotic group and placebo group

	probiotic group(n = 42)	placebo group(n = 34)	*p* value
Age (year)	55.96 ± 8.45	56.12 ± 8.23	0.35
Sex (M/F, %)	M15(35.7%)	M12(35.3%)	0.21
	F27(64.3%)	F22(64.7%)	
BMI (kg/m^2)	27.51 ± 3.22	26.44 ± 2.78	0.47
Fasting blood glucose (mmol/L)	10.68 ± 3.24	9.83 ± 3.90	0.66
2 h postprandial blood glucose level (mmol/L)	18.95 ± 5.23	19.00 ± 6.41	0.18
Glycosylated hemoglobin (%)	8.19 ± 1.60	8.25 ± 2.03	0.22
HOMA-IR	2.73 ± 0.46	2.66 ± 0.52	0.42
mAlb/Cr (mg/g)	101.60 ± 22.17	99.66 ± 25.24	0.56
eGFR(ml·min^{-1}(1.73m^2)$^{-1}$)	82.8 ± 8.72	83.12 ± 7.28	0.43

Note: Data are mean ± SD, p values were obtained by using Student's t-test or Mann–Whitney test and $p < 0.05$ was considered as significant difference between two groups.

Abbreviations: BMI, body mass index; reGFR, estimated glomerular filtration rate; rF, female; rHOMA-IR, homeostasis model assessment index; rM, male; rmAlb/Cr, microalbuminuria/creatinine.

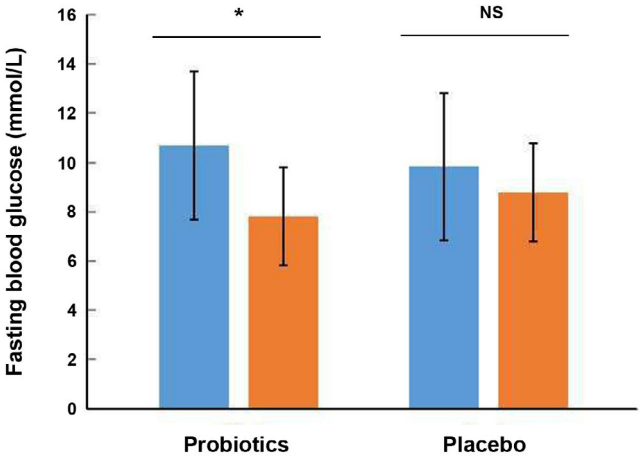

FIGURE 2 Effect of 12-week intake with probiotics or placebo on fasting blood glucose (mmol/L) level of patients with DN. DN, diabetic nephropathy; NS, no significance. *: $p < 0.05$

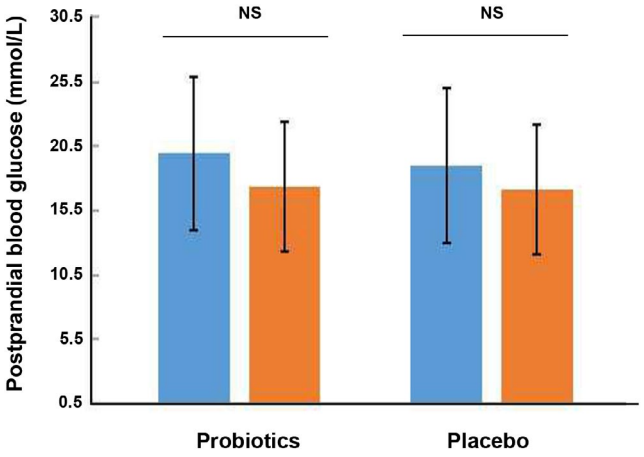

FIGURE 3 Effect of 12-week intake with probiotics or placebo on 2 h postprandial blood glucose level (mmol/L) of patients with DN. DN, diabetic nephropathy; NS, no significance

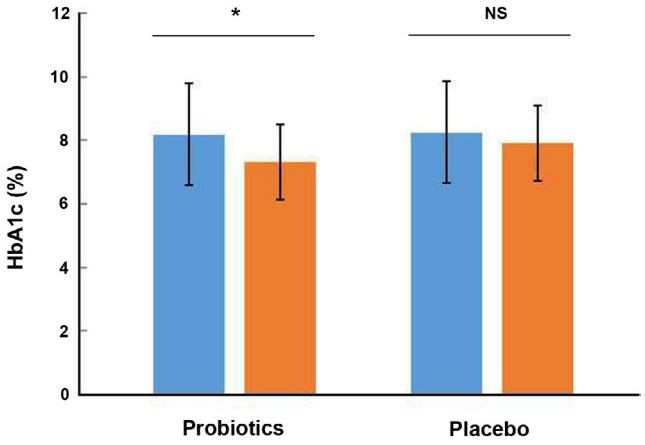

FIGURE 4 Effects of 12-week intake with probiotics or placebo on HbA1c (%) of patients with DN. DN, diabetic nephropathy; HbA1c, glycosylated hemoglobin; NS, no significance. *: $p < 0.05$

$p = 0.51$, Figure 3) and HbA1c (%) (7.92 ± 1.21% after intervention vs. 8.25 ± 2.03% before intervention, $p = 0.67$, Figure 4). Meanwhile, the levels of fasting blood glucose, HbA1c and 2 h postprandial blood glucose showed no significant differences between the probiotic group and the placebo group after intervention ($p > 0.05$, Table 3).

3.3 | Probiotic administration reduced mAlb/Cr in DN patients

After 12 weeks of intervention, probiotic group demonstrated a significant reduction of mAlb/Cr level (67.53 ± 20.11 mg/g vs. 101.60 ± 22.17 mg/g, $p < 0.05$, Figure 5). However, the placebo group revealed a slight reduction without significant change of mAlb/Cr level (87.71 ± 23.01 mg/g vs. 99.66 ± 25.24 mg/g, $p = 0.61$, Figure 5). Meanwhile, mAlb/Cr level was found significantly different between the probiotic group and the placebo group after intervention ($p < 0.05$, Table 3).

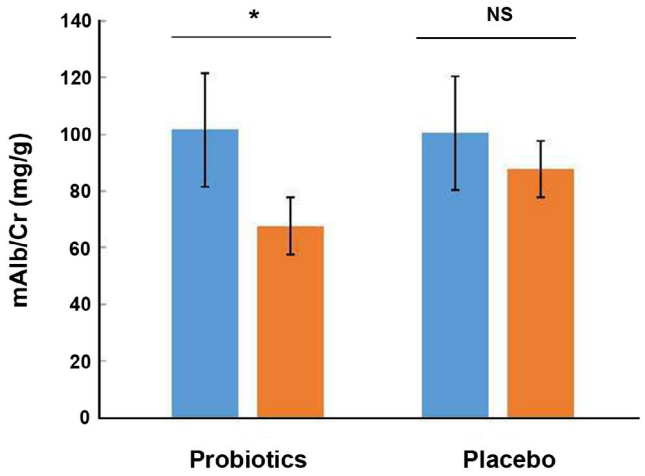

FIGURE 5 Effects of 12-week intake with probiotics or placebo on mAlb/Cr (mg/g) level of patients with DN. DN, diabetic nephropathy; mAlb/Cr, microalbuminuria/creatinine; NS, no significance. *: $p < 0.05$

TABLE 2 Changes of eGFR in probiotic and placebo group after 12 weeks

	Probiotic group ($n = 42$)	Placebo group ($n = 34$)
onset treatment (ml/min)	82.8 ± 8.72	83.12 ± 7.28
12-week treatment (ml/min)	84.34 ± 6.97	84.28 ± 7.13
p value	0.45	0.77

Note: Data are mean ± SD, p values were obtained by using Student's t-test or Mann–Whitney test and $p < 0.05$ was considered as significant difference between two groups.

Abbreviation: eGFR, estimated glomerular filtration rate.

3.4 | The effects of probiotic administration on eGFR

After 12 weeks of intervention, probiotic group demonstrated a reduction of eGFR level (82.8 ± 8.72 ml/min after treatment vs. 84.34 ± 6.97 ml/min before treatment, $p = 0.45$, Table 2). Meanwhile, the placebo group revealed no significant reduction of eGFR (84.28 ± 7.13 ml/min after treatment vs. 83.12 ± 7.28 ml/min before treatment, $p = 0.77$, Table 2). In addition, there was no significant difference of eGFR level between the probiotic group and the placebo group after intervention ($p > 0.05$, Table 3).

4 | DISCUSSION

DN is one of the most important complications of diabetes that can result in end-stage renal failure and disability. Recent studies have revealed that the type 2 diabetes occurrence is associated with reduction of *Lactobacillus* and *B. bifidum*, and the alteration of intestinal flora.[23] Lu et al[24] used *Lactobacillus reuteri* GMNL-263 to treat the diabetic rats with renal fibrosis that induced by streptozotocin and found *Lactobacillus* can reduce the HbA1c and blood glucose levels of the diabetic rats, and protect them from hyperglycemia-enhanced renal fibrosis. Meanwhile, intake of soy milk with *Lactobacillus plantarum* A7 was shown to have a beneficial effect on the renal function of patients with DN.[25] Generally, the probiotics contain *Lactobacillus* and *B. bifidum*, and are commercially available. However, the systematical analysis of probiotic effect on DN patients in a clinical practice, especially regarding the blood glucose level and renal function, is rarely reported. In the present study, we aimed to explore the effects of probiotic administration on glycemic control of DN patients. The probiotics used here is produced by a company and is commercially available. Our results elucidated that probiotic administration ameliorated glycemic control of DN, including exerting beneficial effects on glycemic control. Our research

TABLE 3 The levels of fasting blood glucose, HbA1c, and 2 h postprandial blood glucose between probiotic group and placebo group

	Probiotic group ($n = 42$)	Placebo group ($n = 34$)	p value
Fasting blood glucose (mmol/L)	7.81 ± 2.77	8.78 ± 3.01	0.15
2 h postprandial blood glucose level (mmol/L)	17.35 ± 6.28	17.13 ± 6.05	0.93
Glycosylated hemoglobin (%)	7.32 ± 1.20	7.92 ± 1.21	0.24
mAlb/Cr (mg/g)	67.53 ± 20.11	87.71 ± 23.01	<0.05
eGFR (ml·min^{-1}(1.73 m^2)$^{-1}$)	82.8 ± 8.72	84.28 ± 7.13	0.08

revealed that after 12 weeks, probiotic intake significantly reduced levels of fasting blood glucose, HbA1c, serum creatinine and mAlb/Cr This proved probiotic effect on glycemic control of patients with DN may provide useful information in the clinical practice for DN patients.

It is well known that intestinal microbial populations vary between healthy individuals and patients with type 2 diabetes.[26] Moreover, DN is characterized by chronic hyperglycemia with the metabolic imbalance of carbohydrate, fat and protein digestion resulting from defects in insulin sensitivity.[27,28] Therefore, glycemic control is an essential factor for treatment of DN patients with metabolic syndrome. In this study, we evaluated the changes of glycemic control, indicating that probiotics significantly decreased the levels of blood glucose. In addition, the number of beta cells in the pancreas reduced in DN individuals due to pathological changes, leading to high level of blood glucose, leading to global hyperglycemia.[29,30] In our study, probiotics reduced the level of blood glucose, relieving the unbearable pain of DN patients. Moreover, probiotics reduced 2 h postprandial blood glucose level without significant difference, maybe due to the fact that it is difficult to control the postprandial spike in blood sugar in DN patients.

Furthermore, we estimated the levels of mAlb/Cr before and after the intake of probiotics, which revealed that probiotics reduced the level of mAlb/Cr mAlb level represents the glomerular filtration function, which is the primary indicator of glomerular filtration ability.[31] Under normal circumstances, the majority of mAlb would not get through filtration membrane due to selective barrier of the charge in glomerular filtration membrane with the effect of electrostatic repulsion.[32] However, in DN patients the levels of acetyl sulfate heparin and sialic acid were reduced, resulting in the reduction of the charge selectivity of glomerular filtration membrane, obstructing the extracellular basement affinity and protein polysaccharide, inducing the enlargement of diameter of glomerular filtration membrane filter hole and the change of negative charge structural constitution in glomerular filtration membrane, and this further led to the discharge of mAlb. Simultaneously, in patients who are attacked by kidney disease, serum creatinine variability has a strong effect on GFR level.[33] In previous studies, the researchers demonstrated that level of mAlb/Cr was significantly increased in DN patients by comparison with the healthy individuals.[34] This finding further proved our investigation that probiotics efficiently reduced the level of mAlb/Cr, indicating that probiotics would enhance the ability of glomerular filtration membrane.

In addition, exogenous stimuli, such as high level of blood sugar and urine toxin, may break the balance of angiotensin enzyme and angiotensin enzyme 2 in kidney, leading to a series of cascade reaction, increasing the renal injury and eventually promoting the progress of DN.[35] Furthermore, short-chain fatty acids produced by probiotics bound with G protein-coupled receptors in kidney, thus regulating the hormones, and further affecting the balance between carbohydrate, fat, and protein metabolism. Furthermore, SCFA increased the production of GLP-2 and upregulated the transcriptional expression of tight junction proteins, thus decreasing gastrointestinal permeability; finally, it may improve insulin resistance. Therefore, probiotics exerted favorable effects on DN patients.

Several preclinical and clinical studies have demonstrated the antidiabetic effect of *Lactobacillus* and *Bifidobacteria*.[36–38] Soleimani et al[38] performed a randomized, double-blind, placebo-controlled trial to evaluate the effect of *L. acidophilus*, *Lactobacillus casei*, and *B. bifidum* on diabetes mellitus patients, indicating that probiotics would efficiently reduce the level of fasting blood glucose and HbA1c. Meanwhile, it showed that multi-strains of probiotics significantly reduced the level of fasting blood glucose and HbA1c in diabetes mellitus patients of a randomized experiment.[39] The possible mechanism of hypoglycemic effect is that probiotics could affect intestinal flora to insulinotropic polypeptides and glucagon-like peptide-l, while these peptides induce glucose uptake by muscle.[40] In addition, Ejtahed et al[41] used probiotic yogurt in type 2 diabetic patients and claimed that the reduction of fast blood and HbA1c is probably related to antioxidant activity of probiotic yogurt by multiple interacting pathways. However, others pointed that the probiotic of *Lactobacillus reuteri DSM 17938* failed to reduce the level of HbA1c in patients with diabetes mellitus.[42] Therefore, given that different kinds of probiotics may have different effects on blood glucose and HbA1c, we conducted this trial by selecting *B. bifidum*, *L. acidophilus* and *S. thermophilus* to prove the favorable effects on DN patients. Consistent with the previous results, probiotics significantly reduced the level of fasting blood glucose and HbA1c, simultaneously reducing the level of mAlb/Cr, although our results indicated that probiotics showed no significant reduction of 2 h postprandial blood glucose and eGFR. Together, our research provided the evidence that probiotics ameliorated glycemic control of DN patients via recovering the glycemic control, improving insulin resistance and reducing inflammatory response.

It was reported that probiotic honey consumption for 12 weeks among DN patients had beneficial effects on insulin metabolism, total-/HDL-cholesterol, serum hs-CRP, and plasma MDA levels, but did not affect other metabolic profiles.[43] Another study showed that probiotic supplementation had beneficial effects on glycemic control and markers of cardiometabolic risk.[44] A meta-analysis showed that probiotic supplementation decreased serum insulin and insulin resistance, but it had no beneficial effect regarding kidney function, body weight and lipid profiles, with a moderate positive effect regarding some oxidative stress biomarkers.[45] Another meta-analysis showed the benefits of probiotic supplementation on the reduction of inflammation, oxidative stress and on the amelioration of renal function biomarkers in subjects with diabetic nephropathy.[46] These results were consistent with our study.

There are some limitations that present in this clinical trial. Firstly, the sample sizes analyzed in this study was not very large. This might result in no significant reduction of 2 h postprandial blood glucose and eGFR after probiotic administration. Secondly, the DN patients were not classified under different degrees of renal failure. Therefore, the probiotic effect on glycemic control of DN patients was not extensively evaluated in current study. Further investigations among DN patients with different degrees of renal failure and

large number are suggested to reinforce these findings. In addition, the long-term duration of study may be conducted to validate these data. Finally, the gut microbiota status of the stool sample was not evaluated in this study.

5 | CONCLUSIONS

In summary, our results revealed that intake of probiotic formula *B. bifidum*, *L. acidophilus*, and *S. thermophilus* exerted favorable effects on regulating intestinal flora, glycemic control, reducing mAlb/Cr, thus ameliorating glycemic control of DN in patients with type 2 diabetes.

CONFLICT OF INTEREST

None.

CONSENT FOR PUBLICATION

Informed consent was obtained from all individual participants included in the study.

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