

The Beneficial Effects of a Multispecies Probiotic Supplement on Glycaemic Control and Metabolic Profile in Adults with Type 1 Diabetes: A Randomised, Double-Blinded, Placebo-Controlled Pilot-Study

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Objective: In this pilot-study, the effects of a multispecies probiotic supplement on glycaemic control and metabolic parameters in adults with type 1 diabetes (T1DM) were explored.

Material and Methods: A total of 50 T1DM patients were enrolled and randomly placed into a group receiving capsules containing multi-probiotic strains (*Bifidobacterium longum*, *Lactobacterium bulagricumi*, *Streptococcus thermophilus*) and insulin (probiotics group, n = 27) or a group receiving a placebo and insulin (placebo group, n = 23). All patients underwent continuous glucose monitoring at baseline and 12 weeks after intervention. The primary outcomes were determined by comparing factors such as changes in fasting blood glucose (FBG) and haemoglobin A1c (HbA1c) between the groups.

Results: Probiotic supplementation significantly reduced FBG (-1.0 ± 4.7 vs 1.8 ± 4.7 mmol/L, $p = 0.048$), 30 min postprandial glucose (-0.5 ± 4.6 vs 1.9 ± 3.3 mmol/L, $p = 0.0495$), and low-density lipoprotein cholesterol (-0.07 ± 0.45 vs 0.32 ± 0.78 mmol/L, $p = 0.0413$), compared with the placebo. Although not statistically significant, probiotic supplementation also lowered HbA1c levels by 0.49% (-5.33 mmol/mol, $p = 0.310$). Besides, no significant difference was observed in the continuous glucose monitoring (CGM) parameters between the two groups. Further subgroup analysis revealed a significant reduction in mean sensor glucose (MSG; -0.75 ($-2.11, 0.48$) mmol/L vs 1.51 ($-0.37, 2.74$) mmol/L, $p = 0.010$) and time above range (TAR; -5.47 ($-20.1, 3.04$)% vs 18.9 ($-1.11, 35.6$)%, $p = 0.006$), as well as an greater improvement in the time in range (TIR; 9.32 ($-4.84, 16.6$)% vs -19.9 ($-31.4, 0.69$)%, $p = 0.005$) in male patients than female patients in the probiotics group.

Conclusion: Multispecies probiotics exerted beneficial effects on fasting and postprandial glucose and lipid profiles in adult T1DM patients, especially for male patients and those with higher baseline FBG levels.

Keywords: continuous glucose monitoring, glycaemic variability, lipid profile, probiotics, type 1 diabetes mellitus

Introduction

Type 1 diabetes mellitus (T1DM) is one of the most common autoimmune disorders in the world.¹ It is characterised by the progressive destruction of insulin-producing beta (β)-cells in the pancreatic islets. Managing T1DM is a challenging task that requires constant daily self-management, relying on insulin therapy. Despite considerable advances in insulin infusion techniques, T1DM patients still suffer from a high risk of both acute and chronic complications. Over the past

two decades, the prevalence of T1DM among young children has increased by approximately 70%,² with an annual growth of around 3–4% globally.³ This has incurred a tremendous medical, social, and economic burden worldwide.

The rapid growth in T1DM cases cannot be fully explained by genetic predisposition alone.

Accumulating evidence suggests that gut microbiota and their metabolites, deeply affected by the living environment, play a vital role in the pathophysiology of T1DM. Gut microbiota contribute to both the development and subsequent progression of islet autoimmunity, ultimately leading to hyperglycaemia and clinical disease.⁴ Murri et al demonstrated that the alteration of bowel flora, especially with an increased number of bacteria belonging to the Bacteroidetes phylum and a relative decrease in the number of Lactobacillus, Bifidobacterium and Clostridium strains, contributed to the development of T1DM.⁵ It has been demonstrated that due to increased intestinal permeability, immune stimulants enter the circulation to trigger systemic inflammation and aberrant immunity.⁶ Additionally, anti-inflammatory bacteria promote gut epithelial integrity and immune homeostasis by producing short-chain fatty acids (SCFAs) such as butyrate, propionate, and acetate.⁶

Probiotics improve the gut microbiota when administered in appropriate amounts and may confer health benefits on the host. For instance, Bifidobacterium lactis has been reported to improve insulin tolerance as well as lipid profiles.⁷ Besides, Lactobacillus johnsonii alleviates host oxidative stress and is associated with intercellular tight junction assembly and maintenance in the gut, mitigating the development of T1DM.⁸ Considering the limited current therapies for T1DM, probiotics hold tremendous promise for the adjuvant treatment of T1DM. However, most studies on the gut microbiome and clinical outcomes of diabetes focus on type 2 diabetes (T2DM)⁹ and T1DM in the young.¹⁰ However, more than half of T1DM cases have been reported in those over 20 years old.⁴ Also, because of the progression in diabetes management, an unprecedented number of older adults are living with this disease. Moreover, some studies did not perform blinded experiments and very few papers have demonstrated the impact of probiotic supplementation on glycaemic variability (GV) in T1DM. Although regarded as the gold standard for glycaemic control evaluation, haemoglobin A1c (HbA1c) alone cannot provide a complete picture of glucose control. A growing body of evidence suggests that continuous glucose monitoring (CGM), which provides comprehensive blood glucose profiles using different parameters, shows great promise in improving glucose control, glucose variability, and consequently quality of life.¹¹ To the best of our knowledge, there are very few reports on the impact of commercial compound probiotics on GV in adult T1DM patients. Therefore, in this study, we evaluate the effect of the supplementation of the Bifid triple viable capsule, a multi-species compound probiotic, on fasting blood glucose (FBG), HbA1c, GV, and other metabolic parameters in adults with T1DM.

Materials and Methods

Methods and Patients

This 12-week randomised, double-blinded, controlled clinical trial was approved by the Ethics Committee of the Shenzhen People's hospital (The Second Clinical Medical College, Jinan University, Ethics approval number: LL-KT-2018248) and was registered at clinicaltrials.gov (NCT03556631). Besides, the trial was conducted in observance of the Declaration of Helsinki and the International Conference of Harmonization - Good Clinical Practice guidelines. Subjects with T1DM were consecutively recruited between September 2020 and September 2021 at both the outpatient and inpatient clinics of the Department of Endocrinology and Metabolism of our hospital. Written informed consent was obtained from all the patients before their enrolment in the study.

The inclusion criteria were an age range of 18 to 75 years, T1DM (positive for more than one diabetes mellitus-associated autoantibody), treated with continuous subcutaneous (s.c.) insulin infusion or multiple daily injections with a stable regimen, $6.5\% \leq \text{HbA1c} \leq 10.0\%$, and $7.0 \leq \text{FPG} \leq 13.3 \text{ mmol/L}$ at screening. Self-monitoring of blood glucose (SMBG) at least three times a day for at least 1 month was required for all participants before enrolment in the study. The exclusion criteria included severe gastrointestinal diseases, gastrointestinal or abdominal surgery within a year, medications affecting insulin sensitivity (eg, immunosuppressants, steroids), severe hepatic, renal, cardiovascular, autoimmune, psychiatric, or infectious diseases, acute diabetic complications in the past 3 months, administration of other probiotics or

probiotic products in the past 3 months, and pregnancy. All the patients were provided with the same dietary and physical activity guidance by the same dietician and diabetes educator before being randomly assigned a group.¹²

Study Design

After preliminary screening, the randomization number was generated by a research statistician who had no contact with the participants. The corresponding author randomly assigned (1:1) the 50 patients to receive either the placebo or multispecies probiotic supplements for 3 months using a random digit table. Insulin therapy remained the same for all patients. Chief investigators and statisticians were masked to group allocation.

All participants were asked to take one supplement three times a day. Each multispecies probiotic supplement (Jinshuangqi Co., Inner Mongolia, China) consisted of three viable freeze-dried strains: *Bifidobacterium longum* (2×10^7 CFU), *Lactobacterium bulagricumi* (2×10^6 CFU), and *Streptococcus thermophilus* (2×10^6 CFU). The placebo containing the same substances but without the bacteria was packed into identical-looking tablets. All the supplements were coded by the producer to guarantee blinding and were distributed to participants monthly. Besides, the participants were advised to avoid consuming any other probiotic products during the study. Every participant underwent a thorough evaluation at baseline and a 12-week follow-up visit.

Laboratory Measurements

HbA1c, serum insulin, and C-peptide analyses were performed in a central laboratory at Shenzhen People's Hospital. HbA1c was measured using an automated high-performance liquid chromatography gradient elution analyser (Arkray Adams A1c HA-8180, Arkray Inc., Japan). Additionally, a biochemical analyser (Modular Analytics, Roche, Germany) was used to measure serum glucose, total cholesterol (TC), triglyceride (TG), high-density lipoprotein-cholesterol (HDL-C), low-density lipoprotein-cholesterol (LDL-C), high sensitivity C-reactive protein (Hs-CRP), estimated glomerular filtration rate (eGFR), alanine aminotransferase (ALT), and aspartate aminotransferase (AST). The parameters above were evaluated in all participants at baseline and the measurements were subsequently repeated after 12 weeks.

CGM Measurements and Parameter Calculation

Glucose data were collected continuously for 7 days by professional retrospective CGM (iPro™2, Medtronic Minimed Inc., Northridge, CA, USA) in all patients at baseline and the end of the 3-month intervention. To calibrate the CGM data, all participants underwent pre-prandial SMBG four times a day, before breakfast, lunch, dinner, and bedtime, using a glucometer (Accu-Chek Mobile, Roche Diagnostics, Germany) calibrated by fasting plasma glucose, as measured by the central laboratory. These consecutive calibrated glucose profiles were recorded by the iPro™2 sensor and downloaded via Carelink iPro for further statistical analysis. To analyse GV, the standard deviation of blood glucose (SDBG), the largest amplitude of glycaemic excursions (LAGE), mean amplitude of glucose excursions (MAGE), mean of daily differences (MODD), and coefficient of variation (CV) were calculated. The parameters reflecting glycaemic control such as mean sensor glucose (MSG), time in range (TIR; glucose range of 3.9–10.0 mmol/L in 24 hours), time above range (TAR; glucose range over 10.0 mmol/L in 24 hours), and time below range (TBR; glucose range under 3.9 mmol/L in 24 hours) were also calculated using the CGM data.

Outcomes

The primary outcomes included changes in FBG and HbA1c from baseline to 12 weeks. Moreover, the secondary outcomes were changes in SD, LAGE, CV, MODD, TIR, body mass index (BMI), Hs-CRP, lipid profiles, and daily insulin dose at the 12-week follow-up. The incidence of symptomatic or biochemical hypoglycaemic events (< 2.8 mmol/L), as well as medication adverse events, were recorded for safety data analysis.

Statistical Analysis

As a pilot study, the sample size was calculated according to the feasible execution of the study. Hence, a sample size of 50 was ultimately adopted. Descriptive statistics were presented as mean \pm SD for normally distributed data and median (interquartile range, IQR) for abnormally distributed data. Besides, categorical variables were presented as percentages.

Continuous variables were checked for the distributional assumption of normality using the Shapiro–Wilks tests, while the Wilcoxon rank-sum test was used for abnormally distributed data. Categorical variables were compared using the chi-square test or Fisher's exact test. Moreover, a two-tailed P-value < 0.05 was considered statistically significant. All statistical analyses were performed using the Statistical Package for the Social Sciences (version 23.0; SPSS Inc.).

Results

A total of 60 patients were enrolled in the study, with ten of them being excluded (five refused to participate and five did not take part for other reasons). Among the 50 eligible randomised participants, two participants in the probiotics group withdrew from the study (one became pregnant, while another required antibiotic treatment). Ultimately, 48 participants (probiotics group, $n = 25$; placebo group, $n = 23$) completed the study (Figure 1). The baseline characteristics are summarised in Table 1. The average age of the participants was 39 ± 11 years, with a median diabetes duration of 10 years (interquartile range: 6–16 years). The mean daily insulin dose was 38.7 ± 18.3 U and the mean BMI was 21.1 ± 2.4 kg/m². There was no significant difference in sex, age, duration of diabetes, BMI, blood pressure, transaminase, Hs-CRP, fasting C-peptide, or parameters of metabolic control (HbA1c level, fasting blood glucose, lipid profiles) between the probiotics group and the placebo group at baseline. Moreover, CGM parameters including SDBG, LAGE, MAGE, MODD, TIR, TAR, TBR, CV, and MSG were found to be comparable between the two groups at baseline. Furthermore, no serious adverse events were reported throughout the study.

Effect of Probiotics on Glycaemic Endpoints

The changes in glycaemic control and GV between the probiotics group and the placebo group after the 12-week intervention are presented in Table 2. There was a significant reduction in FBG in the probiotics group, compared to the placebo group (-1.0 ± 4.7 vs 1.8 ± 4.7 mmol/L, $p = 0.048$, Figure 2A). Additionally, 30 min postprandial blood glucose (30min-PBG) levels in the probiotics group were significantly lower than in the placebo group (-0.5 ± 4.6 vs 1.9 ± 3.3 mmol/L, $p = 0.0495$, Figure 2B). HbA1c expression tended to decrease in both the probiotics and placebo groups, but the difference was not statistically significant ($-0.49 \pm 1.15\%$ (-5.33 ± 12.60 mmol/mol) vs $-0.22 \pm 0.60\%$ (-2.38 ± 6.59 mmol/mol), $p = 0.310$). Meanwhile, there were no noticeable differences in either the CGM parameters of glycaemic control (MSG, TIR, TAR, and TBR) or GV (SDBG, LAGE, MAGE, CV, and MODD) between the two groups.

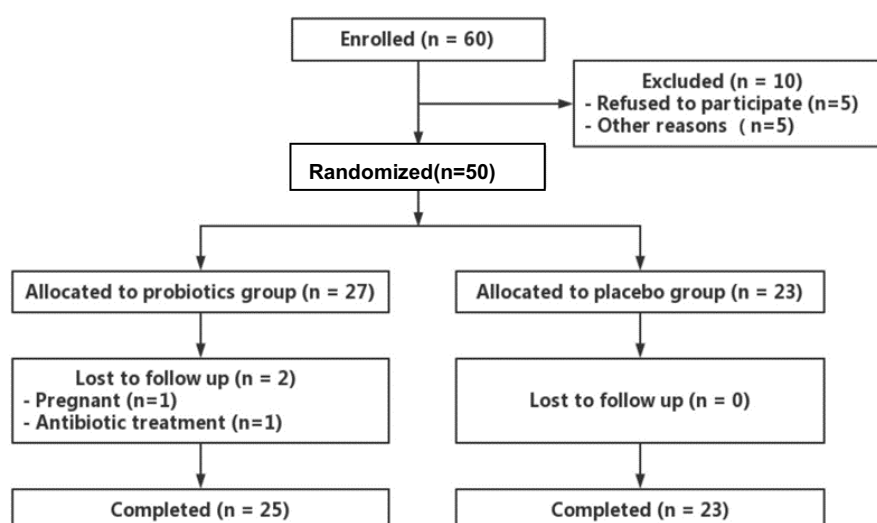


Figure 1 Diagram of clinical trials in participants with type 1 diabetes mellitus. f/u, follow-up.

Table 1 General Baseline Characteristics of the Study Participants

	Total (N=50)	Placebo (N=23)	Probiotics (N=27)	p-value
Age (years)	39±11	39±8	38±14	0.834
Sex, female/male, n (%)	23 (36.0)/27 (54.0)	10 (43.5)/13 (56.5)	13 (48.1)/14 (51.9)	0.741
Diabetes duration (years)	10 (6, 16)	10(7, 16)	10 (4, 16)	0.718
Daily insulin dose (U)	38.7±18.3	34.7±21.2	42.4±14.6	0.154
Body weight (kg)	57.8±8.6	56.2±8.0	59.3±9.0	0.216
BMI (kg/m ²)	21.1±2.4	20.5±2.4	21.7±2.2	0.085
SBP (mmHg)	114±14	111±13	116±15	0.147
DBP (mmHg)	74±10	74±9	75±10	0.608
HbA1c (%)	7.5±1.5	7.3±1.5	7.8±1.5	0.251
HbA1c (mmol/mol)	58.65±16.55	55.76±16.76	61.31±16.24	0.251
Fasting C-peptide (ng/ml)	0.17±0.35	0.14±0.40	0.19±0.31	0.616
Hs-CRP (mg/L)	0.75±0.55	0.63±0.50	0.86±0.58	0.132
ALT (U/L)	17.8±13.8	20.3±18.6	15.5±6.6	0.258
AST (U/L)	21.2±10.9	21.7±11.0	20.8±10.9	0.759
TG (mmol/L)	1.05±1.98	0.757±0.23	1.32±2.73	0.312
TC (mmol/L)	5.19±1.00	5.31±0.98	5.08±1.03	0.422
HDL-c (mmol/L)	1.80±0.45	1.91±0.42	1.69±0.45	0.098
LDL-c (mmol/L)	3.01±0.78	3.11±0.85	2.92±0.72	0.403
eGFR (mL/min/1.73 m ²)	107.51±16.82	104.09±15.94	110.65±17.30	0.178
FBG (mmol/L)	8.7±4.0	7.6±3.5	9.8±4.2	0.052
30min PBG (mmol/L)	12.8±3.6	11.9±3.0	13.6±4.0	0.098
2h PBG (mmol/L)	23.1±4.4	22.6±4.4	23.5±4.5	0.521
SDBG (mmol/L)	2.85 (2.15, 3.39)	2.85 (2.08, 3.09)	2.81 (2.28, 3.80)	0.410
LAGE (mmol/L)	12.50(10.05–16.40)	11.80(9.70–15.33)	12.95(11.40–16.78)	0.471
MAGE (mmol/L)	6.45 (5.03, 7.90)	6.10 (5.13, 7.65)	6.55 (5.08, 8.40)	0.520
MODD (mmol/L)	2.85 (2.20, 3.40)	2.70 (2.20, 3.93)	2.95 (2.18, 3.33)	0.767
CV(%)	34.0±9.92	33.3±9.35	34.6±10.6	0.674
MSG(mmol/L)	8.58±2.34	8.47±2.51	8.69±2.22	0.752
TAR (%)	29.9±24.5	28.4±24.6	31.3±24.8	0.701
TBR (%)	4.82±7.29	5.13±7.63	4.53±7.11	0.782
TIR (%)	65.3±23.5	66.4±23.6	64.2±23.8	0.754

Note: Normally distributed quantitative variables are presented as the mean ± s.d., and nonnormally distributed quantitative variables are presented as the median (interquartile range, IQR).

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CV, coefficient of variation; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FBG fasting blood glucose; HbA1c, haemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; Hs-CRP, high sensitivity C-reactive protein; LAGE, largest amplitude of glycaemic excursions; LDL-C, low-density lipoprotein cholesterol; MAGE, mean amplitude of glucose excursions; MODD, mean of daily differences; SBP, systolic blood pressure; SDBG, standard deviation of blood glucose; TC, total cholesterol; TG, total triglyceride; TAR, time above range; TBR, time below range; TIR, time in range, 2h PBG, 2-hour postprandial blood glucose; 30min PBG, 30 minutes postprandial blood glucose.

Effect of Probiotics on Lipid Profile and CRP

A significant reduction in LDL-C levels was observed in the probiotics group in comparison to the placebo group (-0.07 ± 0.45 vs 0.32 ± 0.78 mmol/L, $p = 0.0413$, Figure 2C). However, no statistical differences were detected in the other lipid indicators or Hs-CRP (Table 2).

Subgroup Analysis of Changes in the Probiotics Group

A subgroup analysis was conducted for baseline BMI, HbA1c, FBG, and sex in T1DM patients with probiotics supplementation. Table 3 and Table 4 list the results of the subgroup analysis, which was stratified according to the median baseline BMI (20.8 kg/m²), HbA1c (7.35%), FBG (8.62 mmol/L), and sex. The patients with a higher baseline FBG level presented a greater decrease in FBG (-2.87 ± 4.53 vs 1.51 ± 3.65 mmol/L, $p = 0.013$) and 30min-PBG (-2.16 ± 4.98 vs 1.69 ± 3.09 mmol/L, $p = 0.027$) after three months of treatment with probiotics, compared to those with a lower

Table 2 The Between-Group Comparisons of Metabolic Profiles, CGM Data, and Hs-CRP After Supplementation

	Placebo (N=23)	Probiotics (N=25)	p-value
ΔHbA1c (%)	-0.22±0.60	-0.49±1.15	0.310
ΔHbA1c (mmol/mol)	-2.38±6.59	-5.33±12.60	0.310
ΔFasting C-peptide (ng/mL)	-0.02±0.28	-0.01±0.14	0.979
Δ30 minutes postprandial C-peptide (ng/mL)	-0.07±0.39	0.01±0.11	0.406
Δ2 hour postprandial C-peptide (ng/mL)	-0.17±0.71	-0.01±0.15	0.302
ΔFBG (mmol/L)	1.8±4.7	-1.0±4.7	0.048
Δ30min PBG (mmol/L)	1.9±3.3	-0.5±4.6	0.050
Δ2h PBG (mmol/L)	0.5±4.7	0.1±5.0	0.727
ΔSDBG (mmol/L)	0.40 (0.02, 0.81)	0.11 (-0.44, 0.81)	0.296
ΔLAGE (mmol/L)	1.30 (-1.68, 2.93)	-0.05 (-3.23, 2.33)	0.281
ΔMAGE (mmol/L)	0.60 (-0.65, 1.88)	-0.00 (-2.53, 1.65)	0.195
ΔMODD (mmol/L)	0.45 (-0.48, 1.05)	0.850 (-0.08, 1.18)	0.448
ΔCV (%)	1.97 (-1.63, 7.33)	1.92 (-7.19, 5.37)	0.624
ΔMSG (mmol/L)	0.40 (-0.56, 1.41)	-0.15 (-1.24, 1.43)	0.725
ΔTAR (%)	2.26 (-2.21, 7.52)	0.82 (-11.82, 21.29)	0.991
ΔTBR (%)	0.00 (-2.41, 3.10)	0.00 (-2.12, 2.73)	0.965
ΔTIR (%)	-1.66 (-7.44, 3.43)	-1.84 (-20.33, 11.98)	0.700
ΔTG (mmol/L)	0.00±0.20	0.52±2.39	0.297
ΔTC (mmol/L)	0.52±1.05	0.16±0.64	0.156
ΔHDL-C (mmol/L)	0.00±0.21	0.00±0.13	0.925
ΔLDL-C (mmol/L)	0.32±0.78	-0.07±0.45	0.041
ΔHs-CRP (mg/L)	0.08±0.47	0.20±0.43	0.374

Notes: Normally distributed quantitative variables are presented as the mean ± s.d., and nonnormally distributed quantitative variables are presented as the median (interquartile range, IQR). Delta (Δ) value = 3-month value – baseline value.

Abbreviations: CV, coefficient of variation; FBG fasting blood glucose; HbA1c, haemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; Hs-CRP, high sensitivity C-reactive protein; LAGE, largest amplitude of glycaemic excursions; LDL-C, low-density lipoprotein cholesterol; MAGE, mean amplitude of glucose excursions; MODD, mean of daily differences; SDBG, standard deviation of blood glucose; TC, total cholesterol; TG, total triglyceride; TAR, time above range; TBR, time below range; TIR, time in range; 2h PBG, 2-hour postprandial blood glucose; 30min PBG, 30 minutes postprandial blood glucose.

baseline FBG. Also, TBR decreased more significantly in patients with higher baseline FBG (-1.07 (-4.57, -0.26)% vs 2.43 (0.41, 5.19)%, $p = 0.007$). However, no significant differences in the changes of SDBG, LAGE, MAGE, MODD, CV, MSG, TIR, TAR, and C-peptide were found between the two subgroups. Regarding sex, male patients showed

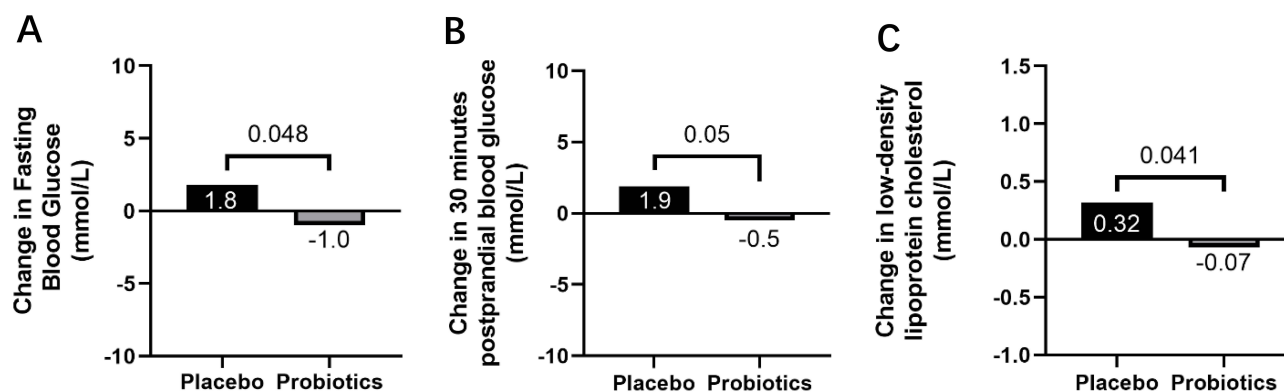


Figure 2 Probiotics improved fasting blood glucose (FBG) and 30 minutes postprandial blood glucose (PBG) as well as low-density lipoprotein cholesterol (LDL-C). **(A)** Change in FBG (mmol/L) in response to Probiotics group vs Placebo group. **(B)** Change in 30 minutes PBG (mmol/L) in response to Probiotics group vs Placebo group. **(C)** Change in LDL-C (mmol/L) in response to Probiotics group vs Placebo group. Significant reductions in FBG, 30 minutes PBG as well as LDL-C were observed in the patients in the Probiotics group, and the changes were significantly different compared with those in Placebo group.

Table 3 Subgroup Analysis of C-Peptide and Glucose Level in the Probiotics Group After Intervention

	Δ Fasting C-Peptide (ng/mL)	Δ 30 Minutes Postprandial C-Peptide (ng/mL)	Δ 2 Hour Postprandial C-Peptide (ng/mL)	Δ FBG (mmol/L)	Δ 30Min PBG (mmol/L)	Δ 2h PBG (mmol/L)
BMI (kg/m ²)						
>20.8	-0.04±0.10	0.00±0.09	-0.01±0.17	-1.5±3.5	-0.6±4.5	0.3±5.1
≤20.8	0.02±0.17	0.01±0.15	-0.02±0.12	-0.2±6.1	-0.2±5.0	-0.2±5.1
P-value	0.307	0.965	0.774	0.558	0.850	0.835
Sex						
Male	-0.05±0.13	-0.03±0.08	-0.04±0.15	-0.33±5.00	-0.16±5.23	-0.20±4.65
Female	0.02±0.14	0.04±0.13	0.02±0.15	-1.61±4.34	-0.80±4.03	0.37±5.52
P-value	0.245	0.125	0.354	0.501	0.736	0.784
HbA1c (%)						
>7.35	-0.02±0.09	0.01±0.10	-0.00±0.16	-2.34±4.75	-1.60±5.29	-0.77±5.89
≤7.35	-0.01±0.18	0.00±0.13	-0.03±0.14	0.83±4.04	0.98±3.23	1.14±3.52
P-value	0.835	0.917	0.670	0.085	0.148	0.325
FBG (mmol/L)						
>8.62	-0.03±0.09	-0.01±0.10	-0.03±0.14	-2.87±4.53	-2.16±4.98	-1.37±5.60
≤8.62	0.00±0.19	0.03±0.13	0.01±0.17	1.51±3.65	1.69±3.09	1.91±3.51
P-value	0.676	0.388	0.440	0.013	0.027	0.087

Notes: Data are the mean ± s.d. Delta (Δ) value = 3-month value – baseline value.

Abbreviations: FBG, fasting blood glucose; 30min PBG, 30 minutes postprandial blood glucose; 2h PBG, 2-hour postprandial blood glucose.

a significant reduction in MSG (-0.75 (-2.11, 0.48) mmol/L vs 1.51 (-0.37, 2.74) mmol/L, $p = 0.010$) and TAR (-5.47 (-20.1, 3.04)% vs 18.9 (-1.11, 35.6)%, $p = 0.006$) and greater improvement in TIR (9.32 (-4.84, 16.6)% vs -19.9 (-31.4, 0.69)%, $p = 0.005$), compared to the female patients in the probiotics group. Meanwhile, a significant increase in TIR (1.09 (0.09, 4.59)% vs -1.07 (-4.57, 1.39)%, $p = 0.039$) was identified in patients with lower basal HbA1c levels in the probiotics group. However, there were no major differences in the changes in blood glucose, SDBG, LAGE, MAGE, MODD, CV, MSG, TAR, TBR, and C-peptide between patients with different levels of HbA1c. Also, no significant differences in glycaemic control and GV were found in patients with different baseline BMI values.

Safety Data

Among the 50 randomized participants, only 3 participants (6%) failed to complete the study protocol. Among these patients, 2 was dropped from the study due to the initiation of antibiotics and 1 was pregnant. No severe adverse events were reported during the study in two groups.

Discussion

In the analysis, we observed slight declines in the FBG and 30min-PBG levels in participants who consumed multi-species probiotic supplements, compared to those who had the placebo. Additionally, LDL-C expression was significantly lower in the probiotics group. However, there were no statistically significant differences regarding HbA1c, CGM parameters (SDBG, LAGE, MAGE, MODD, CV, MSG, TAR, TBR, and TIR), and Hs-CRP between the two groups after the 12-week trial.

The effect of probiotics on glycaemic control in individuals with diabetes has received increased attention in recent years. Researchers speculate that amelioration of gut dysbiosis using specific probiotics is associated with a decline in the risk of islet β -cell autoimmunity, reduction of Toll-like receptor 4 signalling (a type of inflammatory signalling), and improvement in gut integrity. This subsequently leads to the amelioration of T1D pathology.¹³ Furthermore, beneficial gut bacteria may increase the synthesis of glucagon-like peptide 1 (GLP-1), which contributes to the improvement of glucose homeostasis.¹⁴ For instance, as the most commonly-found gut microbiota in probiotic supplements, Bifidobacterium and Lactobacillus species have been reported to improve glucose homeostasis in several clinical

Table 4 Subgroup Analysis of Glycaemic Variability and Glycaemic Control in the Probiotics Group After Intervention

	ΔSDBG (mmol/L)	ΔLAGE (mmol/L)	ΔMAGE (mmol/L)	ΔMODD (mmol/L)	ΔCV (%)	ΔMSG (mmol/L)	ΔTAR (%)	ΔTBR (%)	ΔTIR (%)
BMI (kg/m ²)									
>20.8	0.08 (−0.47, 0.44)	−0.80 (−3.25, 2.15)	−0.40 (−2.90, 0.95)	0.20 (−0.35, 0.90)	2.58 (−0.38, 5.11)	−0.37 (−1.88, 0.55)	−0.95 (−16.44, 6.78)	0.56 (−0.25, 2.78)	0.68 (−12.56, 12.39)
≤20.8	0.30 (−0.34, 1.24)	1.00 (−2.70, 3.60)	0.40 (−0.60, 3.50)	1.10 (1.00, 1.40)	−6.36 (−9.75, 9.33)	0.95 (−0.02, 2.52)	14.47 (2.66, 23.37)	−1.74 (−3.99, 0.35)	−19.58 (−20.95, 7.87)
P-value	0.519	0.796	0.114	0.374	0.848	0.120	0.121	0.100	0.197
Sex									
Male	−0.20 (−0.44, 0.26)	−0.45 (−3.23, 1.33)	−0.50 (−2.75, 0.15)	0.30 (−0.33, 1.03)	3.57 (−1.76, 5.23)	−0.75 (−2.11, 0.48)	−5.47 (−20.13, 3.04)	0.99 (−0.13, 2.92)	9.32 (−4.84, 16.6)
Female	0.44 (−0.54, 1.00)	1.00 (−3.33, 3.30)	1.05 (−1.98, 3.20)	0.95 (0.43, 1.43)	−0.14 (−10.50, 6.28)	1.51 (−0.37, 2.74)	18.92 (−1.11, 35.56)	−1.37 (−4.25, 0.88)	−19.85 (−31.39, 0.69)
P-value	0.588	0.941	0.076	0.660	0.367	0.010	0.006	0.317	0.005
HbA1c (%)									
>7.35	−0.20 (−0.49, 0.70)	−0.25 (−3.53, 2.30)	−0.50 (−2.40, 1.50)	0.35 (−0.23, 1.33)	−0.14 (−8.90, 3.76)	0.015 (−1.25, 2.67)	0.62 (−13.25, 26.78)	4.28 (−22.22, 13.02)	−1.07 (−4.57, 1.39)
≤7.35	0.36 (−0.13, 0.71)	−0.05 (−2.35, 2.30)	0.25 (−1.85, 1.33)	0.95 (0.65, 1.00)	4.64 (−3.43, 9.19)	−0.15 (−0.38, 0.65)	2.20 (−1.44, 13.89)	−9.67 (−17.93, 1.30)	1.09 (0.09, 4.59)
P-value	0.526	0.521	0.968	0.727	0.170	0.531	0.843	0.764	0.039
FBG (mmol/L)									
>8.62	0.015 (−0.40, 0.89)	−0.50 (−3.53, 2.98)	−0.50 (−2.58, 1.43)	0.85 (0.13, 1.33)	1.92 (−8.90, 5.66)	0.17 (−1.21, 2.16)	2.03 (−11.03, 22.68)	−1.07 (−4.57, 0.26)	−1.84 (−20.74, 12.32)
≤8.62	0.22 (−0.43, 0.45)	−0.05 (−2.23, 2.23)	0.25 (−1.23, 1.33)	0.55 (−0.38, 1.00)	1.57 (−4.21, 4.92)	−0.15 (−1.39, 0.48)	0.03 (−13.08, 11.90)	2.43 (0.41, 5.19)	−3.25 (−17.93, 9.17)
P-value	0.931	0.675	0.735	0.579	0.478	0.479	0.509	0.007	0.931

Notes: Data are the median (interquartile range, IQR). Delta (Δ) value = 3-month value – baseline value.

Abbreviations: CV, coefficient of variation; LAGE, largest amplitude of glycaemic excursions; MAGE, mean amplitude of glucose excursions; MODD, mean of daily differences; MSG, mean sensor glucose; SDBG, standard deviation of blood glucose; TAR, time above range; TBR time below range; TIR, time in range.

trials.^{15,16} However, some studies were not clearly blinded and the bacterial strains used in other studies were not used routinely in commercial probiotics preparations.

As far as we know, this is the first double-blinded randomised controlled trial that evaluates the effect of commercial probiotics on glycaemic control in T1DM patients. Existing studies have provided either inconclusive results or reported only modest effects of probiotics supplementation on glycaemic control in diabetes patients. Several meta-analyses have shown a significant reduction in FBG with probiotics or synbiotics supplementation compared with placebos. Besides, HbA1c levels exhibited a downward trend, but without statistical significance.^{9,17} It is noteworthy that most studies included in the aforementioned meta-analyses focused on T2DM, while only one paper investigated T1DM with synbiotics as a supplement.¹⁰ Interestingly, an observational study conducted by Aila et al witnessed a significant reduction in HbA1c levels in T1DM using probiotics after 12 weeks.¹⁸ They inferred that the discrepant results of different trials concerning HbA1c could be explained by different intervention lengths, since those less than 8 weeks may be too short to reveal significant changes in HbA1c expression. Further subgroup analyses revealed that probiotics were more effective in T2DM patients who were not on insulin therapy or those with poor glycaemic control. Likewise, Firouzi et al reported that a 12-week probiotics intervention resulted in greater improvements in HbA1c levels in T2DM patients with a normal weight than in those who were overweight or obese.¹⁹ The similar result was also revealed by Kumar et al in children with new-onset T1DM. They found that patients treated with high dose multi-strain probiotics had a significant decrease in HbA1c as well as a significant decline in daily insulin requirement compared with those in the placebo group after 3-month intervention.²⁰ However, in our 12-week trial, the HbA1c levels in the probiotics group tended to decrease over time, but the difference was statistically insignificant.

Interestingly, both FBG and 30min-PBG levels decreased significantly in the T1DM patients who used probiotics in this study. This is an aspect that has only been examined by a limited number of other studies. Accepted as an independent predictor of cardiovascular events, PBG is marked by postprandial glycaemic peaks that result in inflammation, oxidative stress, and endothelial dysfunction. Besides, it is related to the development of insulin resistance and T2DM.²¹ Indeed, an early study reported that gut microbiota was a co-determinant of PBG response.²² Similarly, Oh et al found that daily administration of *L. plantarum* HAC01 over eight weeks significantly reduced 2h-PBG levels in a population with impaired glucose tolerance (IGT), compared to the placebo group.²³ One possible hypothesis for this is that selective increases of bifidobacterial in gut microflora improve glucose tolerance, glucose-induced insulin secretion and normalised inflammatory tone through decreasing endotoxaemia, plasma and adipose tissue proinflammatory cytokines in high-fat-diet-induced diabetes in mice.²⁴ Another mechanism may be found in the association between gut bacterial metabolism and intestinal transit time. Roager et al found that increased gut microbiota richness due to decreased intestinal transit time is accompanied by a shift in colonic metabolism from carbohydrate fermentation to protein catabolism.²⁵ However, the detailed mechanism remains largely undetermined and needs to be further explored.

Glycaemic variability, another key metric of the glucose profile other than HbA1c, has been associated with hypoglycaemia, chronic complications of diabetes, and reduced quality of life.²⁶ However, the association between gut microbiota and GV has hardly been discussed before. In this study, we observed no improvements in GV metrics in the overall study population with probiotics supplementation. However, further subgroup analysis based on gender indicated that, compared with female patients, probiotic supplements were more effective in reducing MSG and TAR and enhancing TIR in males. Popularised as an intuitive and valid measure of glucose control, TIR has been proved to be a marker of microvascular risk. For every 10% decrease in TIR, the risk of retinopathy and microalbuminuria increases by 64% and 40%, respectively.²⁷ Thus, it seems that men benefit more from probiotics supplementation. A previous study reported that men had lower gut microbial diversity and a lower abundance of multiple species conferring beneficial effects on host metabolism compared to women.²⁸ Also, in an animal experiment, Zhang et al stated that male mice had a smaller transition in the gut microbiota than female mice during the development of T1DM.²⁹ Further correlation network analysis demonstrated that gut microbiota exerted a significant effect on host metabolic changes induced by T1DM in a sex-specific manner, mainly through four different pathways: short-chain fatty acid (SCFA) metabolism, energy metabolism, amino acid metabolism, and choline metabolism.²⁹ Therefore, we speculate that probiotics, which are live microorganisms that help maintain host physiology and immune homeostasis and shape the host immune system,³⁰ have a more potent effect on men than women.

Additionally, in this study, probiotics were more effective than the placebo in reducing serum LDL-C from the baseline, but they did not affect TC, HDL-C, and TG levels. Although several pioneering studies have demonstrated the lipid-lowering effect of probiotics administration to maintain cardiovascular health,³¹ some reported results were inconsistent or contradictory. Zarezadeh et al reported that supplementation with probiotics enhanced TC, LDL-C, and TG levels but had no effect on HDL-C, and these effects occurred in a time-dependent manner.³² Furthermore, probiotics had the greatest modifying effect on the lipid profile of T2DM and non-alcoholic fatty liver disease (NAFLD) patients.³² Furthermore, Aila et al found that the TG and the TG-HDL-cholesterol ratio was lower in T1DM patients with self-reported use of probiotics.¹⁸ Several papers have proposed the mechanisms that are potentially responsible for the lipid-regulating effect of probiotics. The first possible mechanism is the deconjugation of bile salts, which involves the coprecipitation of intestinal cholesterol. Alternatively, lipometabolism regulation may allow the cell membrane of the probiotic to incorporate and assimilate cholesterol. Another potential mechanism is the reduction in intestinal cholesterol absorption through various pathways, which inhibits the expression of the intestinal cholesterol transporter Niemann–Pick C1-Like 1 (NPC1L1) in the enterocytes.³³

Low-grade chronic inflammation is a critical factor in the pathogenesis of numerous chronic conditions such as diabetes and cardiovascular disease. Although Hs-CRP did not improve with the supplementation of probiotics in this study, several other studies have observed a reduction in inflammatory biomarkers such as Hs-CRP, IL-6, and the complement system, by using probiotics in patients with diabetes.^{34,35} The reasons for these discrepant findings are unclear. We speculate the following reasons. Firstly, Type 1 diabetes and type 2 diabetes share different pathogenesis. Secondly, the relationship between inflammation and type 2 diabetes has long been established. Nevertheless, the mechanisms behind the aforementioned effects remain to be investigated.

There are several strengths and limitations of note in this study. First, this paper was a carefully designed and well-conducted clinical study and was the first paper to evaluate the effect of probiotics administration on GV in adult T1DM patients. Besides, we chose commercially available probiotic supplements as the intervention, to realise a cost-effective method that utilised probiotics in the management of T1DM. Also, the patients of this study were recruited from both the inpatient and outpatient departments of our hospital, so our findings could be generalised to include all patients in a primary care setting. Finally, the patients in both groups adhered closely to the CGM procedures with a high follow-up rate. However, this study has certain limitations. It was an exploratory clinical study conducted in a single centre and the sample size was relatively small, due to a relatively low prevalence of T1DM compared with T2DM. Moreover, although a prolonged duration (2–4 weeks) of CGM is recommended by current guidelines to reduce the likelihood of statistical bias, we only collected the CGM data for 7 days due to restrictions related to the CGM recorder.³⁶ Additionally, the impact of dietary factors and exercise on GV cannot be underestimated. To minimise such a bias, the participants received advice regarding diet and physical activity and were urged to follow a consistent diet and exercise regularly during the CGM periods.

Conclusion

This randomised, double-blind, placebo-controlled trial confirmed for the first time that the intervention with a multispecies probiotic supplement containing *Bifidobacterium longum*, *Lactobacterium bulagricumi*, and *Streptococcus thermophilus* for 12 weeks exerted a beneficial effect on fasting and postprandial glucose and lipid profiles in adult T1DM patients without any serious adverse events, especially for male patients and those with higher baseline FBG levels. However, this compound probiotic did not improve GV in adult T1DM patients. In conclusion, probiotics supplementation may serve as a safe adjuvant strategy for the amelioration of cardiometabolic health parameters in adult T1DM patients.

Data Sharing Statement

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

Statement of Ethics

The study was approved by the Ethics Committee of the Shenzhen People's hospital (The Second Clinical Medical College, Jinan University, China. Ethics approval number: LL-KT-2018248). All patients provided written informed consent.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors have no personal or financial conflicts of interest.

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