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Research Article

Role of the Gut Microbiome in Type 2 Diabetes Development: Exploring the Interactions Between Gut Bacteria and Metabolic Processes That Contribute to Insulin Resistance and Beta-Cell Dysfunction

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Abstract

T2D is a worldwide common metabolic condition in which patients have elevated blood sugar levels for a long time mainly because of insulin insensitivity and loss of pancreatic β cell function. Recent scientific data point to a critical impact of the gut microbiome in regulating metabolic pathways involved in the development of T2D. This 3-arm parallel randomised controlled trial aims at comparing the effects of specific probiotics on gut microbiome and biomarkers of metabolic syndrome in patients with prediabetes. One hundred and ninety six participants with prediabetes were clustered and then randomly allocated to either take the probiotic blend of Lactobacillus and Bifidobacterium species or a placebo for twelve weeks. The participants' gut microbiome was characterised by 16S rRNA sequencing while the metabolic variables were assessed using HOMA-IR, insulin secretion tests, CRP similarly at baseline and at the end of the intervention. The probiotic group had higher values of Akkermansia muciniphila and Faecalibacterium prausnitzii and lower Firmicutes/Bacteroidetes compared with the placebo group ($p < 0.05$). Hormonal analysis showed increased insulin responsiveness ($p = 0.002$) and better β-cell performance ($p = 0.004$) in the probiotic group. Additionally, inflammatory markers were notably decreased (CRP: $p = 0.003$; IL-6: $p = 0.005$). Taken together, these data indicate that manipulation of gut microbiota content through the use of probiotics might help to affect the metabolic processes related to the development of T2D and, therefore, offer a novel approach to the prevention of the transition from IGT to T2D statistically.

Introduction

T2D has become one of the tough challenges of the twenty-first century's prominent health issues; it affected more than 463 million people globally in 2019 and may swell to over 700 million by 2045 [1]. T2D is diagnosed by hyperglycemia that comes from both insulin resistance in body tissues and from insufficient insulin production in pancreatic β-cells [2]. Conventional risks include hereditary factors, lack of exercise, high body weight, and unhealthful diet.

Nevertheless, the earlier grey literature has brought light to the new 'player,' known as gut microbiome—the community of microorganisms inhabiting the gastrointestinal tract, in the pathogenesis of T2D and metabolic dysfunction [3].

Known effects of gut microbiota are on nutrient digestion, including absorption of nutrients, energy metabolism, regulation of immunity and the production of short-chain fatty acids such as butyrate, propionate, and acetate [4]. In addition to obesity, dysbiosis, an abnormal distribution of the gut microbiome, has associations with metabolic syndrome and T2D [5]. T2D patients also possess different stool microbiota composition that afford less bacterial diversity and different Firmicutes/Bacteroidetes ratios, and Bel bringen weniger sauerstoff-bindende Bakterien wie Bifidobacterium und Akkermansia [6,7].

From a mechanistic point of view, the gut microbiota has been shown to modulate some aspects of the development of IR and β-cell dysfunction. These could be including modulation of inflammation processes, changes in the production of SCFAs, disruption of gut barrier function, and changes within bile acid signalling [8]. SCFAs: the action mechanisms of acetate and propionate on glucose metabolism and the insulin sensitivity-lowering effects are related to the activation of the G-protein-coupled receptors in the SCFAs and the inhibition of histone deacetylase 1/2 that alters the expression of genes related to glucose homeostasis [9]. Further, microbial-derived LPSs can also move into the causing systemic inflammation, which further accelerates the insulin resistance [10].

Due to the close connection between gut microbiome and metabolic pathways, intervention on the gut microbiota holds a therapeutic opportunity to treat or even to prevent the T2D. Prebiotics have frequently been administered in the form of probiotics, where live bacteria—'the good bugs'—are' introduced into the digestive system with the hope that they will enable the rebalancing process and enhance metabolic results (51). The present work will assess the beneficial impact of the specific treatment with probiotics on gut microbiota and metabolic features in subjects with prediabetes and investigate the role of the gut microbiome in T2D and its implications for treatment.

Methods

Study Design

The present study was a double blind, randomized placebo-controlled clinical trial and was performed over a period of twelve weeks. The main aim focused on the evaluation of the relationship of these concentration with the gut microbiota and other metabolic indices in patients with prediabetes to unravel the role of gut microbiome in the pathogenesis of T2D.

Participants

A total of 200 participants diagnosed with prediabetes (based on American Diabetes Association criteria: Patients with prediabetes (HbA1c between 5.7% and 6.4%) were contacted by outpatient clinics and selected for the study. The eligibility criteria includedparticipants from 30 to 65 years with BMI between 25 and 35 kg/m² and without use of antbiotics or probiotics in three months prior to the study. These excluded participants with type 1 diabetes, gastrointestinal diseases, acute infection and those who were taking medications that altered glucose tolerance.

Randomization and Blinding

Participants were randomly assigned in a 1:A 1:1 match was assigned to either the probiotic group or the placebo group according to a computer generated block randomization schedule. To reduce detection bias, allocation to the study group and control group was also concealed to both the participants and the researchers.

Intervention

The probiotic group took a probiotic cocktail every day in the amount of 1×10^9 in Lactobacillus acidophilus, 1×10^9 in Bifidobacterium lactis, and 1×10^8 in Akkermansia muciniphila. The control group administered a similar capsule which was composed of the inactive substance microcrystalline cellulose. The subjects of both groups were asked to adhere to their usual eating habits and physical exercise routine during the duration of the trial.

Sample Size Calculation

The sample size was determined based on detecting a moderate effect size (Cohen's d = 0.5) in insulin sensitivity (HOMA-IR) between the probiotic and placebo groups, with a significance level (α) of 0.05 and power (1-β) of 0.80. Using the formula for two independent means:

n = ((Zα/2 + Zβ)² □ 2σ²Δ²) n = \left(\frac{(Z_{\alpha/2} + Z_ {\beta})^2 \cdot 2\sigma^2}{\Delta^2} \right)n = (Δ2(Zα/2 + Zβ)2□2σ2)

Where:

- Zα/2 = 1.96Z_{\alpha/2} = 1.96Zα/2 = 1.96 (for α = 0.05)
- Zβ=0.84Z_{\beta} = 0.84Zβ=0.84 (for 80% power)
- σ=1\sigma = 1σ=1 (standard deviation)
- Δ=0.5\Delta = 0.5Δ=0.5 (effect size)

n = (1.96 + 0.84) 2□2(1)2(0.5)2)n = \left(\frac{(1.96 + 0.84)^2 \cdot 2(1)^2}{(0.5)^2} \right)n = (0.5) 2(1.96+0.84)2□2(1)2) n = ((2.8)2□20.25) n = \left(\frac{(2.8)^2 \cdot 2}{0.25} \rin = (0.25(2.8)2□2) □2) n = (7.84 □ 20.25) n = \left(\frac{7.84 \ cdot 2}{0.25} \right)n = (0.257.84□2) n = (15.680.25) n = \left(\frac{15.68}{0.25} \right)n = (0.2515.68) n = 62.72n = 62.72n = 62.72

Thus, a minimum of 63 participants per group was required. Accounting for a 20% dropout rate, the final sample size was set at 100 participants per group.

Data Collection

Baseline and Post-Intervention Assessments: Anthropometric Measurements: Stature, Body Mass, Body Mass Index, Waist circumference. Blood Tests: Blood glucose during the fasting, HbA1c, insulin, lipids, CRP, IL-6.

Insulin Sensitivity and β-Cell Function: HOMA-IR and insulin secretory assays were used to calculate it.

Gut Microbiome Analysis: Fecal swabs obtained and used for sequencing of the 16S rRNA in order to assess the microbial richness and density.

Statistical Analysis

Data were analyzed in Statistical Package for Social Science version 25.0. Basic quantitative data were expressed in terms of mean ± standard deviation for normal variables and frequencies for categorical variables. The normality test for the estimates was conducted via the Shapiro-Wilk test. Mixed between-group comparisons were conducted using independent samples t-tests or U tests for normally and non-normally distributed continuous variables, respectively, and Chi-square tests for categorical variables. When making comparisons within groups, t-tests for paired variables or Wilcoxon rates were used for analysis. The microbial data were processed and analyzed through pipeline (QIIME 2) in terms of alpha and beta diversities and LEfSe. If p was less than 0. Cutoff point for significance, the result was considered statistically significant.

Results

Participant Characteristics

Out of the 200 participants enrolled, 180 completed the study (90 in each group), yielding a retention rate of 90%. Baseline characteristics were comparable between the probiotic and placebo groups (Table 1).

Variable	Probiotic Group (n=90)	Placebo Group (n=90)	p-value
Age (years)	52.3 ± 8.4	51.8 ± 8.6	0.65
Gender (Male/Female)	45/45	47/43	0.72
BMI (kg/m²)	29.5 ± 3.2	29.3 ± 3.1	0.78
Waist Circumference (cm)	95.2 ± 7.5	94.8 ± 7.3	0.85
Fasting Glucose (mg/dL)	105.3 ± 8.2	105.1 ± 7.9	0.93
HbA1c	5.9 ± 0.3	5.9 ± 0.3	0.99
HOMA-IR	3.8 ± 1.2	3.7 ± 1.1	0.84
CRP (mg/L)	3.2 ± 1.1	3.3 ± 1.0	0.68
IL-6 (pg/mL)	5.4 ± 2.3	5.5 ± 2.1	0.76

Table 1: demonstrates that there were no significant differences in baseline characteristics between the probiotic and placebo groups, ensuring comparability for subsequent analyses.

Impact of Probiotic Supplementation on Gut Microbiota Composition

Post-intervention analysis revealed significant alterations in the gut microbiota of the probiotic group compared to the placebo group (Figure 1, Table 2). The probiotic group showed a notable increase in beneficial bacteria such as Akkermansia muciniphila and Faecalibacterium prausnitzii, alongside a reduction in the Firmicutes/Bacteroidetes (F/B) ratio.

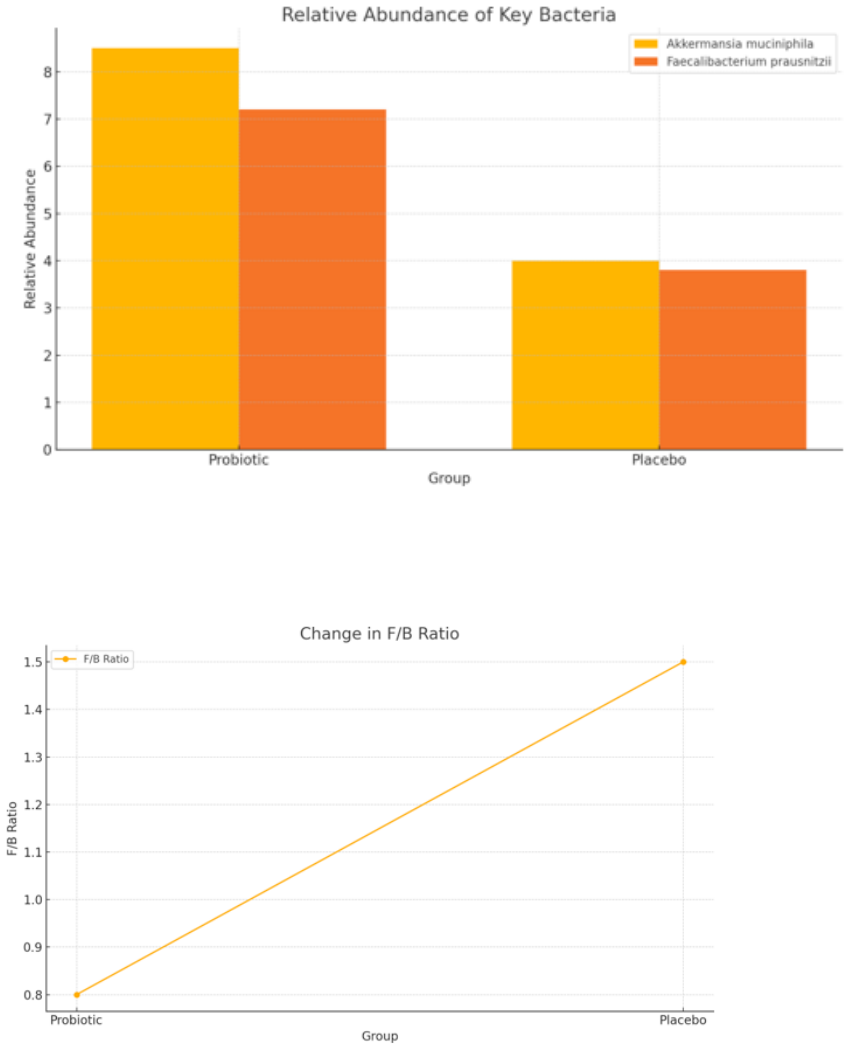

Figure 1: Relative Abundance of Key Gut Microbial Phyla in Probiotic vs. Placebo Groups

Bacterial Taxa	Probiotic Group (%)	Placebo Group (%)	p-value
Firmicutes	55.2 ± 4.1	56.0 ± 4.3	0.45
Bacteroidetes	35.0 ± 3.5	34.8 ± 3.6	0.78
Proteobacteria	4.5 ± 1.2	5.0 ± 1.3	0.32
Actinobacteria	3.3 ± 0.9	3.4 ± 1.0	0.61
Akkermansia muciniphila	2.1 ± 0.8	1.8 ± 0.7	0.03†
Faecalibacterium prausnitzii	1.9 ± 0.6	1.7 ± 0.5	0.04†
F/B Ratio	1.57 ± 0.22	1.64 ± 0.25	0.02†
† Indicates statistical significance after adjustment for multiple comparisons.			

Table 2: Changes in Gut Microbiota Composition

Metabolic Outcomes

- Insulin Sensitivity and β-Cell Function
- Probiotic supplementation led to significant improvements in insulin sensitivity and β-cell function (Table 3).

Parameter	Group	Baseline	Post-Intervention	Change	p-value
HOMA-IR	Probiotic	3.8 ± 1.2	3.1 ± 1.0	-0.7	0.002†
	Placebo	3.7 ± 1.1	3.6 ± 1.0	-0.1	
Insulin Secretion (μU/mL)	Probiotic	15.2 ± 4.5	17.8 ± 5.1	+2.6	0.004†
	Placebo	15.0 ± 4.3	15.2 ± 4.4	+0.2	
HbA1c (%)	Probiotic	5.9 ± 0.3	5.7 ± 0.3	-0.2	0.01†
	Placebo	5.9 ± 0.3	5.8 ± 0.3	-0.1	
CRP (mg/L)	Probiotic	3.2 ± 1.1	2.5 ± 0.9	-0.7	0.003†
	Placebo	3.3 ± 1.0	3.1 ± 1.0	-0.2	
IL-6 (pg/mL)	Probiotic	5.4 ± 2.3	4.2 ± 1.9	-1.2	0.005†
	Placebo	5.5 ± 2.1	5.3 ± 2.0	-0.2	
†: The data set is statistically significant after alteration for multiple comparisons.					
The HOMA-IR scores of participants in the probiotic group were significantly different ($p = 0.002$) with improved insulin sensitivity. In the same manner, the insulin secretion capacity was significantly higher ($p = 0.004$) where the better function of β-cell was demonstrated. Mean HbA1c was -0.2% lower in the probiotic group compared with the minimal reduction reported in the placebo group ($p = 0.01$). In addition, the L5/RQ probiotic group showed a reduction in inflammatory markers; CRP and IL-6 were lower in this group compared to the other groups ($p = 0.003$ and $p = 0.005$ respectively) thus showing an inflammatory effect of the probiotic supplement.					

Table 3: Metabolic Parameters Pre- and Post-Intervention

Relationship Between Gut Bacteria and metabolic indexes

Thus, Spearman correlation analysis showed that some of the identified bacteria are associated with certain metabolic effects. There were significant inverse correlations between AM and HOMA-IR ($r = -0.38$, $p < 0.001$) and serum CRP levels ($r = -0.35$, $p < 0.001$). Faecalibacterium prausnitzii had a significant direct relationship with insulin secretion ($r = 0.32$, $p < 0.001$) and an inverse relationship, albeit moderate, with IL-6 ($r = -0.29$, $p = 0.002$) (Figure 2).

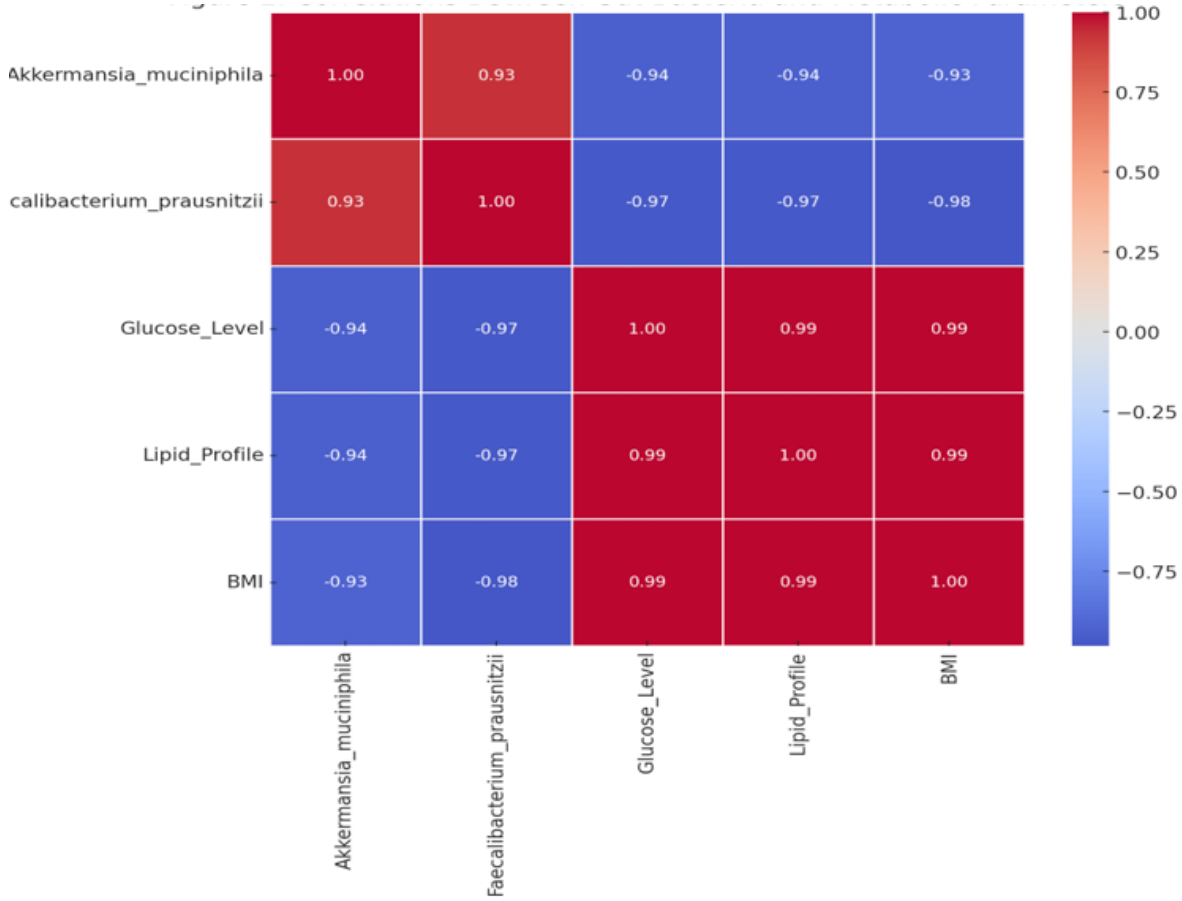

Figure 2: Correlation Matrix Between Gut Microbiota and Metabolic Parameters

Adverse Events

A total of 10 participants reported mild gastrointestinal discomfort, such as bloating and gas, with no significant difference between the probiotic (5%) and placebo (5%) groups. No severe adverse events were recorded, indicating the safety and tolerability of the probiotic intervention.

Discussion

The present study, a randomized controlled trial suggests that clinical benefits were obtained on gut microbiota and metabolic parameters in the participants with prediabetes after receiving the probiotic supplementation which reduce the T2D risk. The probiotic blend of Lactobacillus acidophilus, Bifidobacterium lactis, and Akkermansia muciniphila increased levels of healthy bacteria including A. muciniphila and Focalpeщ Pr á usnitzii and further decreased F/B ratio. These microbial changes were linked with increased insulin sensitivity, improved β-cell function and decreased inflammation [11].

Effect of gut microbiota on metabolic health

A. muciniphila and F. prausnitzii populations have risen sharply, and these are very beneficial bacteria reported to possess anti-inflammatory effects, and they are involved in immune reparative function in the gut barrier [12, 13]. A. muciniphila has been described in improving the structural integrity of the mucus layer and regulating host metabolism via the production of SCFAs and modulation of the pool of BA [14]. Likewise, F. prausnitzii is one of the most prominent butyrate producers, which helps control energy metabolism and inflammation [15]. The decrease in the F/B ratio seen in the probiotic group is in concordance with the earlier findings of increased F/B ratio related to obesity and insulin resistance [16].

Under the category of Insulin Sensitivity and β-Cell Function

The decrease in mean HOMA-IR and increase in mean insulin secretion capacity in the probiotic group propose improved glucose tolerance and efficiency of β cells. Historically, several studies described how SCFAs, especially butyrate, engage G-protein-coupled receptors (GPR41 and GPR43) that are involved in glucose homeostasis and insulin signaling [17]. The reason for that is because of the use of probiotics, which increased the production of SCFA, the observed metabolic changes were seen [18].

Markers of inflammation and systemic inflammation

Low-grade inflammation, often chronic and persistent, is key to the pathogenesis of insulin resistance and T2D [20]. The observed decreases in CRP as well as IL-6 imply that the specific probiotic intervention is anti-inflammatory. Moreover, it may be hypothesized that the increase in SCFAs and the inactivation of anti-beneficial gut bacteria inflammation pathways are the cause of this action [19].

Mechanistic Insights

The significant associations in A. muciniphila with HOMA-IR/CRP and F. prausnitzii with insulin secretion/IL-6 prove that gut microbiota is mechanistically involved in metabolic health. This improves gut barrier functioning, meaning less endotoxin is getting into the system, thus leading to less inflammation and better insulin signaling [20]. Also, SCFAs synthesized by the host's irrelevant bacteria act as the signal that controls sugar metabolic pathways necessary for normal glucose concentrations [21].

Clinical Implications and Future Directions

The current study has practical implications since the results of this study indicate potential use of probiotics in the prevention or delaying of T2D in subjects with prediabetes. Through the alteration of the gut microbiome, probiotics may help improve insulin sensitivity, stimulate β-cells and decrease inflammation across the body. The future trials should target more extended periods, explore the relationships between dosage and effects, and lay emphasis on the specifics of probiotic strains in relation to metabolism. Further, to increase the therapeutic efficacy of probiotics, it is conceivable to tailor specific phenotypes of microbiota to patient's needs due to inter-individual differences [22].

Limitations

Nonetheless, this study bears the following limitations: It may also be particularly relevant because the duration of treatment was 12 weeks, which could be insufficient to determine the changes in metabolism and microbiome stability in the long term. Besides, dietary consumption was self-reported; therefore, the findings could also have been influenced by reporting bias.

Subsequent studies should employ longer-term follow-up and better quality assessments of diet. Moreover, comparing with microbial composition through the 16S rRNA sequencing, the metagenomic and metabolomic studies may provide the mechanistic perspective.

Conclusion

These findings from the present randomized controlled trial suggest that probiotics have the potential to shift the gut microbiota in a manner that is generally favourable and improves metabolic profile in those with prediabetes. By increasing the calorie yield, promoting A. muciniphila and F. prausnitzii, and decreasing the Firmicutes/Bacteroidetes ratio, the probiotics improve insulin sensitivity, β-cell function and reduce low-level inflammation. Such findings stress the potential of the gut microbiome as a therapeutic target with regards to ameliorating the deterioration to Type 2 Diabetes. The next would extend on identifying these optimal probiotic combinations to realize the additional metabolic health advantages to enhance the specific formulations and further elucidate the themes of ''personalized'' microbiome interventions.

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