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RANDOMIZED STUDY ON GLUCOSE AND LIPID METABOLIC PARAMETERS IN TYPE-II DIABETICS BY MULTISTRAIN PROBIOTIC SUPPLEMENTATION

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ABSTRACT
Diabetes Mellitus type 2 patients were assessed over a six-month period for metabolic and glycemic responses. Sixty participants were divided into two groups and received standard treatment and probiotic treatment. Baseline, three month, and six month measurements were taken of anthropometric and biochemical parameters. The probiotic group had significantly higher average ages, BMIs, waist-hip ratios, and blood pressures at baseline in comparison to Group I (standard treatment group), with p-values of 0.0321, 0.006, 0.0158, and 0.0223 (systolic) and 0.0297 (diastolic), respectively. Over the study period, Group II exhibited a significant reduction in glucose levels from 174.20±3.708 mg/dl to 147.63±5.275 mg/dl (p=0.0327). It does not appear that there is a statistically significant difference between the two groups, despite the fact that insulin and C-peptide levels were lower in both groups (p=0.829 and p=0.623, respectively). Although the difference wasn't significant (p<0.567), HOMA-IR values decreased more significantly in Group II. There were significant improvements in lipid profiles in both groups, with HDL-cholesterol in Group II increasing from 47.69 to 55.933mg/dl (p=0.0299). Also, triglycerides and LDL cholesterol levels decreased more in Group II, but not significantly (p=0.1219 and p=0.1758). Over the course of six months, glucose control and HDL cholesterol levels were significantly improved in T2DM patients who were treated with probiotics. The findings suggest that probiotics may be a helpful adjunct therapy for the treatment of diabetes type 2.

Keywords: Diabetes Mellitus, lipid profiles, gastrointestinal microbiota, Probiotics, Anthropometric parameters

INTRODUCTION
In diabetes mellitus, glucose levels are elevated, glycosuria occurs, lipid levels are elevated, and nitrogen levels are negatively influenced by insulin deficiency [1,2]. Type I diabetes causes an absolute insulin shortage due to the destruction of pancreatic islets by an autoimmune process. In Type 2 Diabetes, liver and skeletal muscle resists insulin's effects along with elevated insulin levels [3]. There are 422 million diabetics in the world, and 1.5 million are diagnosed and die each year from the disease. Most of these people live in low- and middle-income countries. During the past few decades, diabetes has steadily increased both in prevalence and in frequency [4]. Globally, India ranks second behind China in terms of diabetics with 77 million. By 2045, 27.5 million people will

be over 65 years old, up from 12.1 million in 2014 [5]. Type 2 diabetes pathophysiology leads to increased peripheral insulin resistance and hepatic glucose output. In many people, insulin and C-peptide blood levels are either hyper- or normo-insulinemic [6]. Adipocytes and skeletal muscle engage in greater lipolysis, which leads to gluconeogenesis, accelerated liver glycogenolysis, chronic inflammation, and insulin resistance. These factors together cause type 2 diabetes. Recent research shows that obesity-associated insulin resistance can be caused by altering the gastrointestinal microbiota [7-9]. In recent years, antibiotics have become widely used, sanitation has improved, and high-processed foods are devoid of fiber and prebiotics, causing our bodies' natural flora to change. There is a connection between metabolic diseases such as diabetes, obesity, hypertension, and dyslipidemia, as well as dysbiosis, or changes in bacteria [10]. Obesity, insulin resistance, dyslipidemia, hypertension, and diabetes are caused by a variety of mechanisms, including altered gut microbiota that affect energy harvest, alter fatty acid metabolism, modulate gut peptides, activate lipopolysaccharide toll-like receptor-4, and disrupt the intestinal barrier [11]. The term "probiotic" refers to "living microorganisms that, in adequate quantities, can benefit the health of the host" [12]. Probiotic supplements usually contain Lactobacillus, Bifidobacterium, Saccharomyces, Bacillus, Clostridium, and Streptococcus strains. The gut microbiota may be modulated with probiotics to provide more effective management of T2DM. In this study, we assessed whether multi-strain probiotic supplementation coupled with anti-diabetic treatment could improve glycaemic control and anthropometric measurements. It may therefore be beneficial to alter gut microbes with probiotics in the future for patients with Type 2 diabetes as an add-on therapy.

Study objectives

This study examines whether probiotic supplementation combined with anti-diabetic drugs impacts glycemic control in patients with Type II Diabetes.

An evaluation of the effects of giving anti-diabetic treatment with lipid-lowering supplementation and anthropometric parameter reduction in comparison with anti-diabetic treatment alone on serum lipids and anthropometric parameters

METHODOLOGY

Study protocol

It was conducted at the Sri Lalithambigai Medical College and Hospital in Chennai. A detailed explanation of the study's purpose and procedures was provided to patients. Those who were interested in taking part in the trial were required to fill out a consent form in their regional language. The study was enrolled with the Institutional Ethical Board, Sri Lalithambigai Medical College and Hospital and procured approval (IEC-EC/NEW/INST/2022/2769). The demographic information of the patients was collected. Diabetic patients were evaluated by their physician based on their history, vital parameters, and general and systemic examinations, and referred to appropriate specialists in order to rule out micro- and macrovascular complications. A random assignment was conducted for participants who met the inclusion criteria either in the control group or in the test group.

Study duration: Treatment period of 6 months (180 days) and post treatment follow up period of 1 month (30 days) per patient.

Composition	**Approx. per serving**
L. acidophilus	500 million
L. rhamnosus	1 billion
L. paracaesi	2.5 billion
B. lactis	275 million
S. boulardii	30 million
B. clausi spores	2 billion

S. faecalis	30 million
C. butyricum	4 million
B. mesentricus	2 million

Criteria for selection

I. Inclusion of subjects

- Age 30 – 70 yrs
- Gender – Male and Female
- Patients with Type II Diabetes who have been treated with standard methods for at least five years.
- Patients with Fasting Blood glucose greater than or equal to 126mg/dl and Post prandial blood glucose >=200mg/dl
- Patient with abnormalities in serum lipid profile.
- Patients with BMI >=25kg/m^2 - <=30kg/m^2
- Informed consent given by patient and willingness to participate.

II. Exclusion of subjects

- Type 1 diabetic patients, pre-diabetic patients with FBG <126mg/dl and PPBS <200mg/dl.
- Patients who are on Insulin.
- Type II diabetic patients with macrovascular complications like coronary artery disease, stroke.
- Type II diabetic patients with microvascular complications like retinopathy, neuropathy and nephropathy.
- Patients who have taken anti-biotics, anti-fungals, anti-parasites, or anti-virals in the previous 30 days.
- Patients who are on anti-tuberculous drug and / or anti-retroviral therapy for HIV.
- Patients who were on probiotics in the past two months.
- Patients with blood pressure more than 160/110 mm Hg.
- Patients with renal, hepatic dysfunction.
- Pregnant and lactating women.
- Patients enrolled in any other study.

Study randomization

In the study, subjects were randomized to receive either the study drug or standard therapy based on a simple randomization process.

Treatment protocol

GROUP A (n=30): Patients received standard treatment for Diabetes mellitus.

GROUP I (n=30): Patients received standard treatment along with a multi-strain probiotic capsule once a day (*C. Cyraflora*) taken on an empty stomach with a glass of water before breakfast daily.

The study medication was issued for 2 weeks during the first 3 months. After assessing compliance, the study medication was issued every 4 weeks up to 24 weeks.

STATISTICS

A statistical analysis was performed using the Graph Pad prism 8.3.0. To assess the impact of probiotics on the outcome variables, a sample t-test was performed to compare the study group with the control group at the end of each follow-up period (3^{rd} and 6^{th} months). In order to analyze categorical variables, one way ANOVA was used. Alpha levels of $p<0.05$ were used to determine statistical significance.

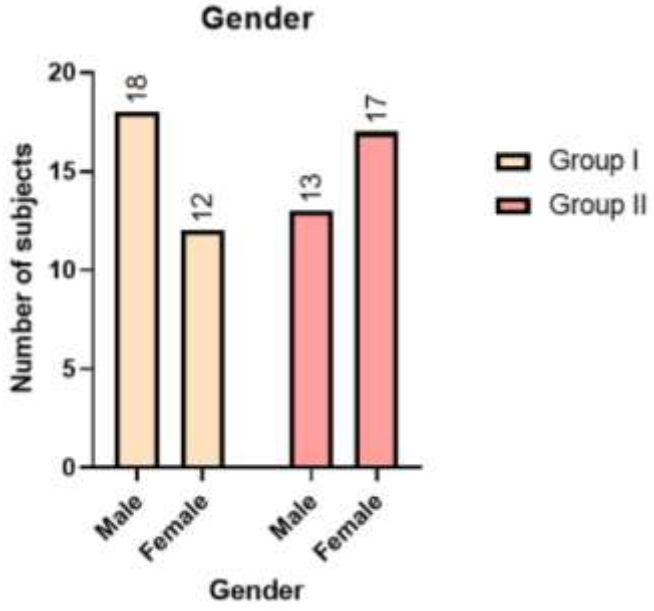
RESULTS AND DISCUSSION

Table: 1 Baseline Characteristics

Characteristics	Group I	Group II	P
Gender			
Male	18	13	
Female	12	17	
Age	46.16±6.103	51.06±5.81	**0.0321***
BMI	28.15±1.37	27.62±1.25	**0.006****
Waist Hip Ratio	0.88±0.06	0.84±0.08	**0.0158***
Systolic BP	128.54±1.34	137.96±2.07	**0.0223***
Diastolic BP	77.17±1.85	84.73±1.489	**0.0297***
Mean Arterial Pressure	94.74±2.52	104.78±3.0	**0.0320***
Glycemic Profile			
Glucose (mg/dl)	171.46±3.104	174.20±3.708	**0.005****
Insulin (IU/ml)	13.96±0.55	10.20±1.14	**0.0983**
C-Peptide (ng/ml)	0.16	0.57	**0.3787**
HOMA-IR	5.620	7.14	**0.0756**
Lipid Profile			
Triglycerides (mg/dl)	137.10±4.63	143.86±3.37	**0.052***
Serum Cholesterol (mg/dl)	188.10±4.57	189.03±4.99	**0.0016*****
HDL-Cholesterol (mg/dl)	51.26±4.65	53.23±7.20	**0.012***
LDL-cholesterol (mg/dl)	135.46±2.71	136.03±2.29	**0.0013*****

*P<0.05-significant; **P<0.005- Moderately significant, ***P<0.001- Highly significant

Figure: 1 Gender characteristics



Study subjects with Type II DM received standard treatment versus multi-strain probiotic supplementation in Group II. Group II received standard treatment along with multi-strain probiotic supplementation. In accordance with the baseline characteristics, the two groups differed significantly on a number of parameters. Group II had a higher average age (51.06±5.81 years) compared to Group II (46.16±6.103 years), with a p-value of 0.0321, indicating a significant difference. The BMI was significantly lower in Group II (27.62±1.25) compared to Group I (28.15±1.37), with a p-value of 0.006. Waist-hip ratio also showed a significant difference, with

Group II having a lower ratio (0.84±0.08) compared to Group I (0.88±0.06), and a p-value of 0.0158. Blood pressure parameters were notably different between the groups, with Group II exhibiting higher systolic BP (137.96±2.07) and diastolic BP (84.73±1.489) compared to Group I (128.54±1.34 and 77.17±1.85, respectively), and corresponding p-values of 0.0223 and 0.0297. Mean arterial pressure was also significantly higher in Group II (104.78±3.0) than in Group I (94.74±2.52), with a p-value of 0.0320.

In terms of glycemic profile, Group II had higher glucose levels (174.20±3.708 mg/dl) compared to Group I (171.46±3.104 mg/dl), with a p-value of 0.005. Insulin levels were lower in Group II (10.20±1.14 IU/ml) compared to Group I (13.96±0.55 IU/ml), with a p-value of 0.0983. The C-peptide levels in Group II (0.57ng/mL) were higher than those in Group I (0.16ng/mL), with a p-value of 0.3787; the HOMA-IR level was higher in Group II (7.14), compared to Group I (5.620), with a p-value of 0.0756.

The triglycerides were slightly higher in Group II (143.86±3.37mg/dl) compared to Group I (137.10±4.63 mg/dl), with a p-value of 0.052. Group II had higher serum cholesterol (189.03±4.99mg/dl) compared to Group I (188.10±4.57mg/dl), with a p-value of 0.0016. HDL-cholesterol was lower in Group II (53.23±7.20 mg/dl) compared to Group I (51.26±4.65mg/dl), with a p-value of 0.012. There was an increase in LDL cholesterol in Group II (136.03±2.29mg/dl) compared to Group I (135.46±2.71mg/dl), with a p-value of 0.0013. As a result of these findings, it is possible to determine whether probiotic supplementation can impact the management of type 2 diabetes in a positive way.

Table: 2 Measurements of anthropometry before and after intervention in groups I and II

Characteristics	Group I			Group II			P value
	Baseline	III- month	VI-month	Baseline	III-month	VI- month	
BMI (kg/m^2)	28.15±1.37	28.34±1.16	27.45±1.11	27.62±1.25	27.21±1.12	27.8±1.23	0.8896
Waist Hip ratio	0.88±0.06	0.89±0.05	0.89±0.04	0.84±0.08	0.84±0.082	0.859±0.080	0.8839
SBP (mmHg)	128.54±1.34	129.00±0.92	129.2±0.82	137.96±2.07	135.57±4.16	137.32±1.91	0.9813
DBP (mmHg)	77.17±1.85	78.27±1.246	76.29±1.318	84.73±1.489	81.75±0.696	83.81±1.387	0.9736
MAP	94.74±2.52	96.34±1.38	100.16±1.56	104.78±3.0	102.09±1.44	99.2±1.15	0.9923

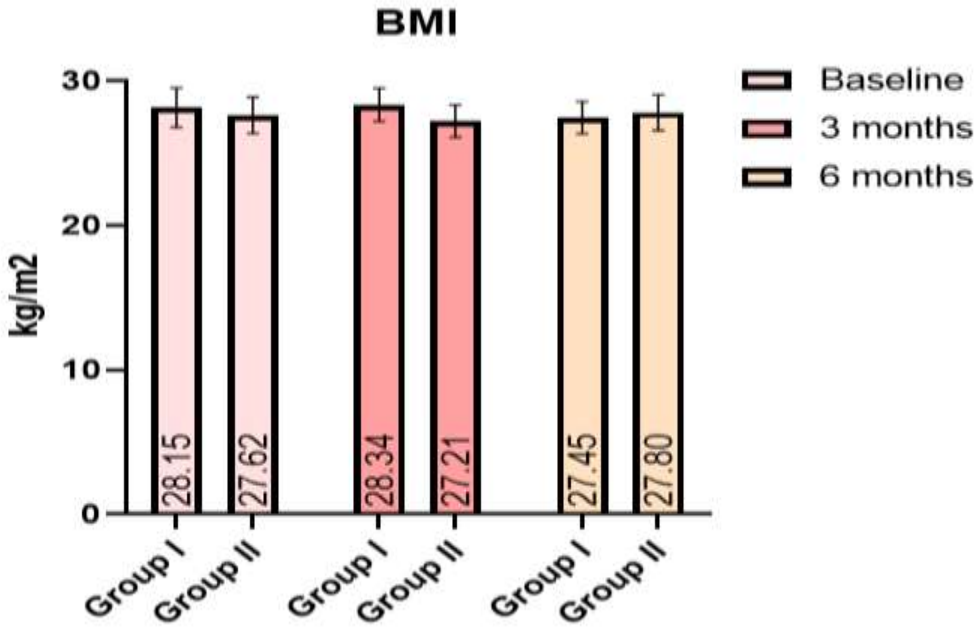
*P<0.05-significant; **P<0.005- Moderately significant, ***P<0.001- Highly significant

The study assessed the anthropometric measures of patients in two groups, Group I (standard treatment) and Group II (standard treatment plus probiotics), over a six-month period.

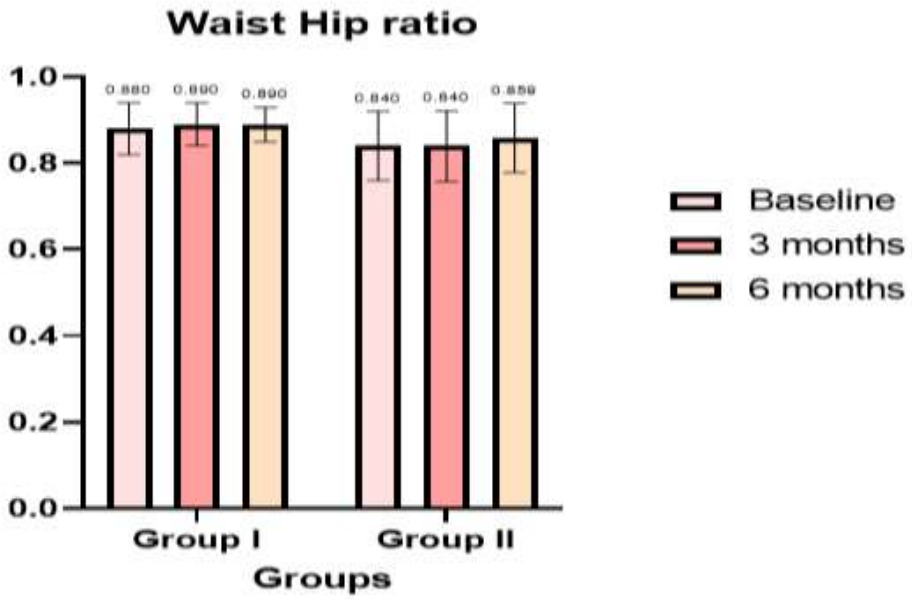
The table compares several parameters between two groups of participants over a six-month period. Group I (n=30) received standard treatment, while Group II (n=30) received standard treatment plus probiotics. The Body Mass Index (BMI) for Group I was 28.15±1.37 kg/m² at baseline, slightly increased to 28.34±1.16 kg/m² at three months, and decreased to 27.45±1.11 kg/m² at six months. For Group II, BMI started at 27.62±1.25 kg/m², decreased to 27.21±1.12 kg/m² at three months, and increased slightly to 27.8±1.23 kg/m² at six months. The p-value for BMI changes was 0.8896, indicating no significant difference between the groups. The waist-hip ratio in Group I remained relatively stable, with values of 0.88±0.06 at baseline, 0.89±0.05 at three months, and 0.89±0.04 at six months. Group II also showed minimal changes, with a baseline value of 0.84±0.08, 0.84±0.082 at three months, and 0.859±0.080 at six months. The p-value was 0.8839, indicating no significant difference. For systolic blood pressure (SBP), Group I showed a slight increase from 128.54±1.34 mmHg at baseline to 129.00±0.92 mmHg at three months, and to 129.2±0.82 mmHg at six months. Group II exhibited a decrease from 137.96±2.07 mmHg at baseline to 135.57±4.16 mmHg at three months, with a slight increase to 137.32±1.91 mmHg at six months. The p-value for SBP was 0.9813, showing no significant difference. Diastolic blood pressure (DBP) in Group I increased

from 77.17±1.85 mmHg at baseline to 78.27±1.246 mmHg at three months, then decreased to 76.29±1.318 mmHg at six months. In Group II, DBP decreased from 84.73±1.489 mmHg at baseline to 81.75±0.696 mmHg at three months, and then increased to 83.81±1.387 mmHg at six months. The p-value for DBP was 0.9736, indicating no significant difference. Mean arterial pressure (MAP) in Group I increased from 94.74±2.52 mmHg at baseline to 96.34±1.38 mmHg at three months and further to 100.16±1.56 mmHg at six months. In Group II, MAP decreased from 104.78±3.0 mmHg at baseline to 102.09±1.44 mmHg at three months, and further to 99.2±1.15 mmHg at six months. The p-value for MAP was 0.9923, indicating no significant difference between the groups. Overall, the differences between the two groups across all measured parameters did not reach statistical significance despite variations within each group over time.

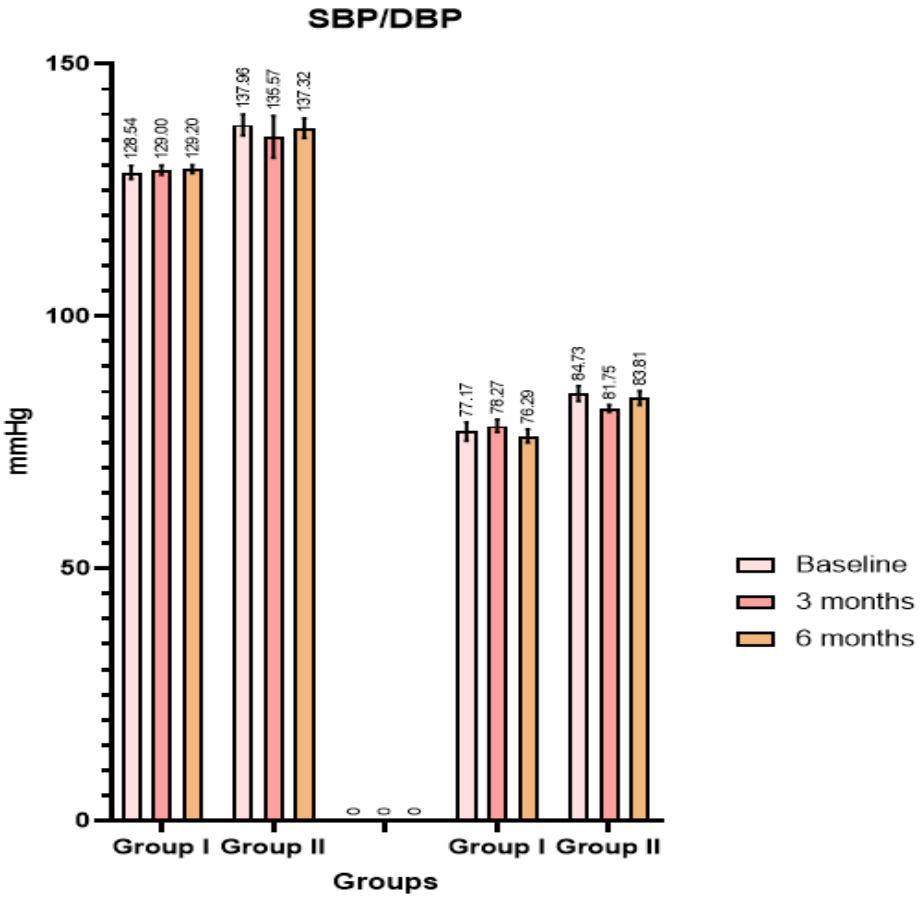
Figure: 2 **Measurements of anthropometry before and after intervention in groups I and II (A-BMI; B-Waist Hip Ratio; C-SBP/DBP; D- MAP)**



(A)



(B)


SBP/DBP
150
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mmHg
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135.57
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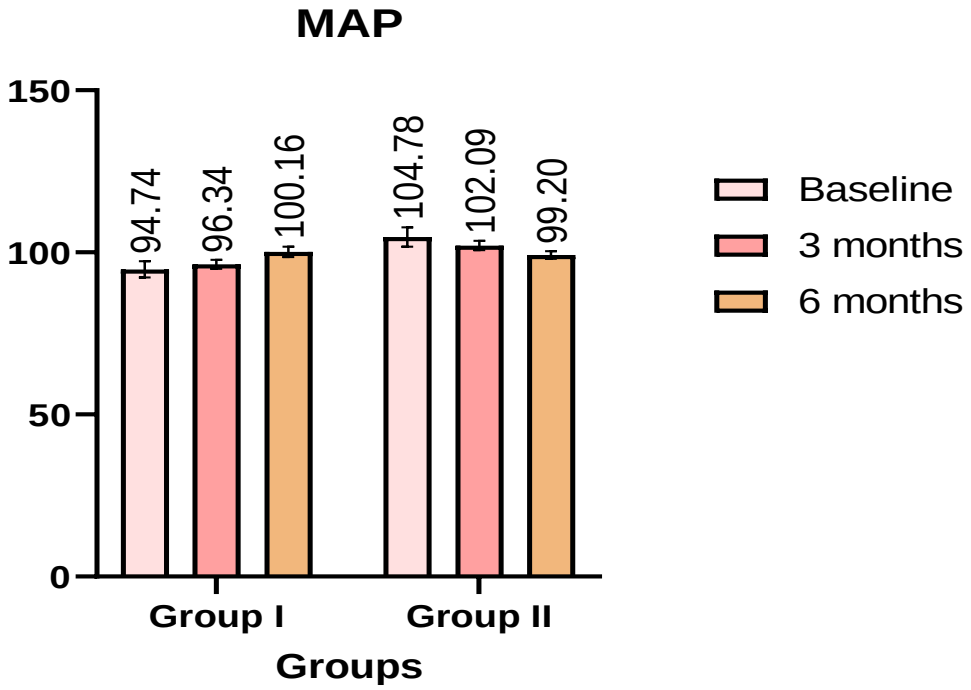
81.75
83.81
Group I Group II
Group I Group II
Groups
Baseline
3 months
6 months

(C)


MAP
150
100
50
0
94.74
96.34
100.16
104.78
102.09
99.20
Group I
Group II
Groups
Baseline
3 months
6 months

(D)

Table: 3 Comparison of glycemic parameters before and after intervention with Groups I and II

Characteristics	Group I			Group II			P value
	Baseline	III-month	VI-month	Baseline	III - month	VI- month	
Glucose (mg/dl**)**	171.46±3.104	163.10±1.965	156.43±2.40	174.20±3.708	159.36[a]±3.275	147.63[ab]±5.275	0.0327[*]
Insulin (IU/ml)	13.96±0.55	11.94±0.42	13.60±0.37	10.20±1.14	8.31[a]±0.489	7.88[a]±0.35	0.829
C-Peptide (ng/ml)	0.16	0.11	0.8[a]	0.57	0.16[a]	0.13[a]	0.623
HOMA-IR	5.620	5.6	6.3	7.14	4.4[a]	3.08[a]	0.567

[a] Significance compared to baseline; [b] significance compared to 3rd month; [*]P<0.05 significance

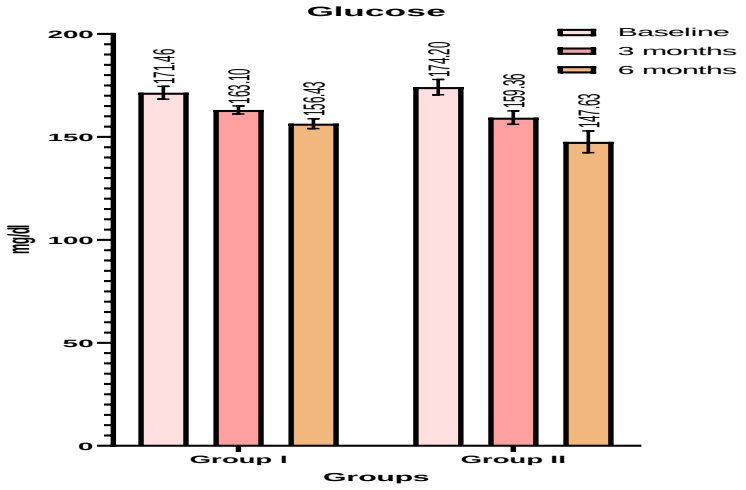
The table presents glycemic parameters for two groups of participants over a six-month period. Group I (n=30) received standard treatment, while Group II (n=30) received standard treatment plus probiotics. The glucose levels in Group I decreased from 171.46±3.104 mg/dl at baseline to 163.10±1.965 mg/dl at three months, and further to 156.43±2.40 mg/dl at six months. In Group II, glucose levels also decreased from 174.20±3.708 mg/dl at baseline to 159.36±3.275 mg/dl at three months, and significantly to 147.63±5.275 mg/dl at six months. Group II showed the greatest reduction in glucose levels, with a p-value of 0.0327 indicating a statistically significant difference.

Insulin levels in Group I decreased from 13.96±0.55 IU/ml at baseline to 11.94±0.42 IU/ml at three months, and then slightly increased to 13.60±0.37 IU/ml at six months. In Group II, insulin levels decreased from 10.20±1.14 IU/ml at baseline to 8.31±0.489 IU/ml at three months, and further to 7.88±0.35 IU/ml at six months.

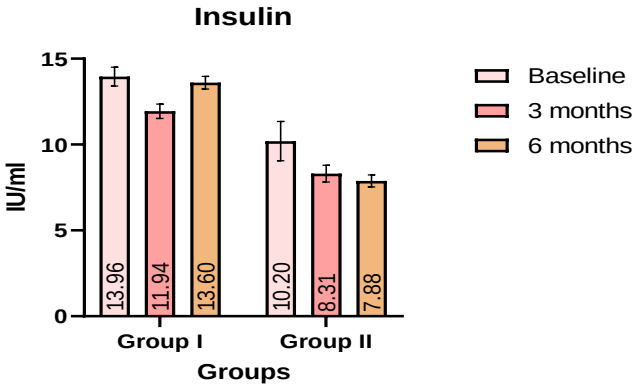
The p-value for insulin levels was 0.829, indicating no significant difference between the groups. C-peptide levels in Group I changed from 0.16 ng/ml at baseline to 0.11 ng/ml at three months, and increased to 0.8 ng/ml at six months. In Group II, C-peptide levels decreased from 0.57 ng/ml at baseline to 0.16 ng/ml at three months, and further to 0.13 ng/ml at six months. The p-value for C-peptide levels was 0.623, indicating no significant difference between the groups. HOMA-IR values in Group I were 5.620 at baseline, slightly decreased to 5.6 at three months, and increased to 6.3 at six months. In Group II, HOMA-IR values decreased from 7.14 at baseline to 4.4 at three months, and further to 3.08 at six months.

The p-value for HOMA-IR was 0.567, indicating no significant difference between the groups. Overall, while there were improvements in glycemic parameters within each group over time, the most notable significant difference was observed in glucose levels, with Group II showing a more substantial reduction compared to Group I.

Figure: 3 **Comparison of glycemic parameters before and after intervention with Groups I and II (A-Glucose level; B-Insulin; C-C peptide; D-HOMA IR)**



(A)



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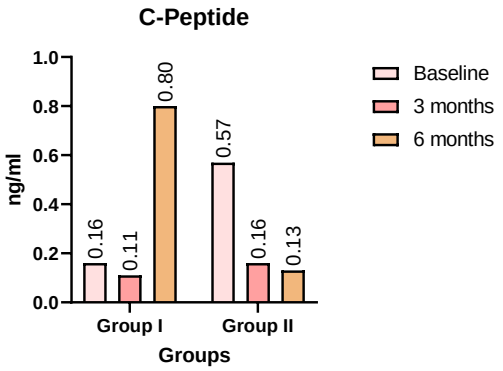

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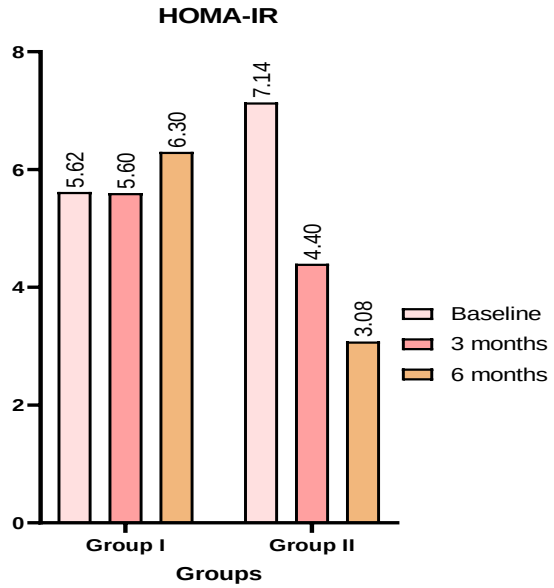


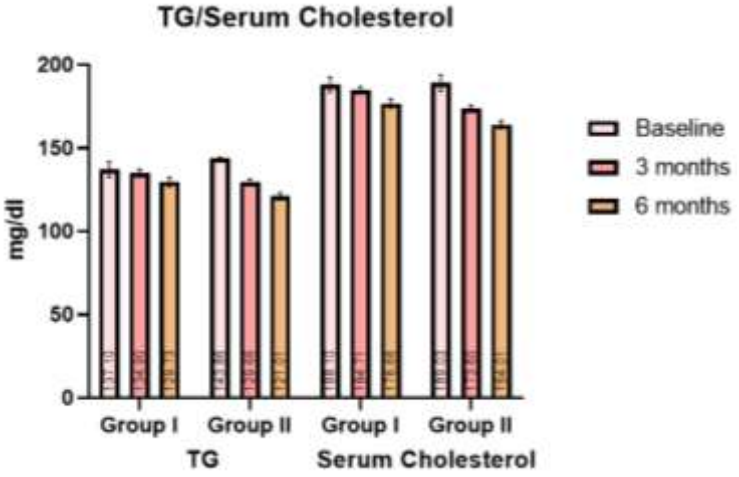
(D)

Table: 4 Comparison of lipid profiles before and after Group I and Group II interventions

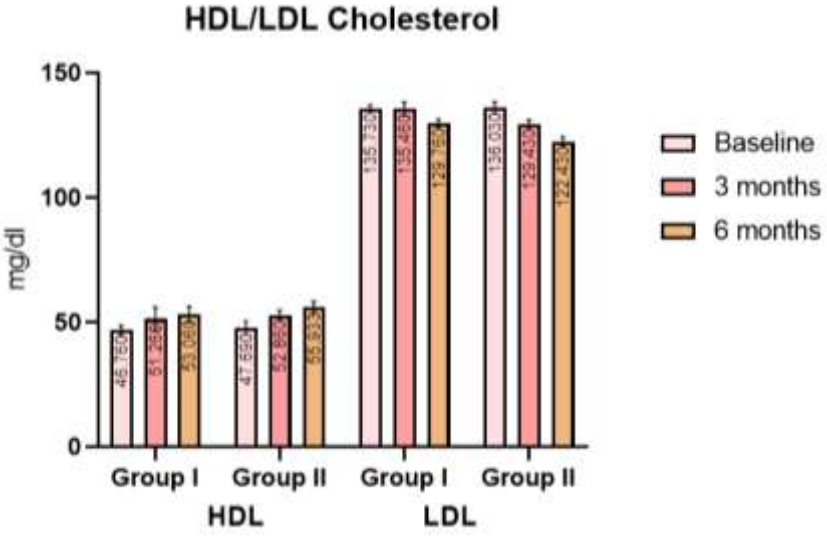
Characteristics	Group I			Group II			P value
	Baseline	III-month	VI-month	Baseline	III-month	VI-month	
TG (mg/dl**)**	137.10±4.63	134.9±2.38	129.73±2.82	143.86±0.33	129.66±1.749[a]	121.01±2.364[ab]	0.1219
Serum Cholesterol (mg/dl)	188.10±4.57	184.71±2.168	176.66±2.695	189.03±4.99	173.60±1.904[a]	164.01±2.464[ab]	0.1639
HDL-Cholesterol (mg/dl)	46.76±1.85	51.26±4.65	53.06±3.205	47.69±2.64	52.86±1.99[a]	55.933±2.34[ab]	0.0299[*]
LDL-cholesterol (mg/dl)	135.73±1.337	135.46±2.71	129.76±1.69	136.03±2.29	129.43±1.870[a]	122.43±1.92[ab]	0.1758

[a] Significance compared to baseline; [b] significance compared to 3rd month; [*]P<0.05 significance

Figure: 4 Comparison of lipid profiles before and after Group I and Group II interventions (A-TG/Serum Cholesterol; B- HDL/LDL)



(A)



(B)

The table outlines the changes in lipid profiles over a six-month period for two groups of participants, Group I (n=30) receiving standard treatment, and Group II (n=30) receiving standard treatment plus probiotics. In Group I, TG levels slightly decreased from 137.10±4.63 mg/dl at baseline to 134.9±2.38 mg/dl at three months, and further to 129.73±2.82 mg/dl at six months. In Group II, TG levels started higher at 143.86±0.33 mg/dl, but showed a significant reduction to 129.66±1.749 mg/dl at three months and further to 121.01±2.364 mg/dl at six months. The p-value for TG levels was 0.1219, indicating no statistically significant difference between the two groups, although the reduction within Group II was notable. In Group I, serum cholesterol levels decreased from 188.10±4.57 mg/dl at baseline to 184.71±2.168 mg/dl at three months, and further to 176.66±2.695 mg/dl at six months. Group II also showed a reduction from 189.03±4.99 mg/dl at baseline to 173.60±1.904 mg/dl at three months, and to 164.01±2.464 mg/dl at six months. The p-value for serum cholesterol was 0.1639, indicating no significant difference between the groups. HDL-cholesterol levels in Group I increased from 46.76±1.85 mg/dl at baseline to 51.26±4.65 mg/dl at three months, and further to 53.06±3.205 mg/dl at six months. In Group II, levels increased from 47.69±2.64 mg/dl at baseline to 52.86±1.99 mg/dl at three months, and to 55.933±2.34 mg/dl at six months. The p-value for HDL-cholesterol was 0.0299, indicating a statistically significant

difference, with Group II showing a more pronounced increase. In Group I, LDL-cholesterol levels slightly decreased from 135.73±1.337 mg/dl at baseline to 135.46±2.71 mg/dl at three months, and further to 129.76±1.69 mg/dl at six months. Group II saw a reduction from 136.03±2.29 mg/dl at baseline to 129.43±1.870 mg/dl at three months, and to 122.43±1.92 mg/dl at six months. The p-value for LDL-cholesterol was 0.1758, indicating no significant difference between the groups. Overall, while there were improvements in lipid profiles within each group over time, the most notable significant difference was observed in HDL-cholesterol levels, with Group II showing a more substantial increase compared to Group I.

DISCUSSION

This study investigates how probiotic supplementation in combination with anti-diabetic drugs affects glucose control in Type II diabetics. In comparison to treating diabetic patients alone, anti-diabetic medication may be effective when combined with lipid-lowering supplements and anthropometric measurements.

Earlier studies have shown the probiotics group was significantly reduced post-intervention, while the standard group was not affected. Additionally, probiotics significantly improved insulin sensitivity when compared to other groups in the HOMA-IR study. When total cholesterol/HDL ratios and glycemic control have been compared between baseline and after probiotics treatment, probiotics have been found to significantly improve HOMA-IR in other diet or medical intervention studies in T2DM patients [13,14].

According to our study, no differences were observed between the standard treatment group and the probiotic group based on baseline biochemical data. There has been research on the benefits of probiotics in the treatment of type 2 diabetes in the past, but these effects may take more than three months to manifest, and our study suggests 6 months may be the most beneficial period [15-19].

Many studies have been conducted on the effects of probiotics on diabetics type II. Although this was not the first interventional study to be conducted, it addressed previous concerns regarding use of a longer period of time and multiple strains of probiotics within a study, which highlighted differences between baseline and six months in the probiotic group between the baseline and control groups [20]. A recent meta-analysis by previous study found that trials involving more than one strain of probiotic were more effective than trials involving shorter durations, which confirms the most significant changes were noted after a six-month observation period. The same study found that trials involving more than one strain of probiotic had a more positive effect on type 2 diabetes patients than trials involving shorter durations [21,22].

According to our findings, weight loss did not result in probiotic supplementation having any effect on weight loss. It has been shown that probiotics can affect weight in a significant way when combined with either a hypocaloric diet or bioactive compounds [23]. If the probiotics are taken along with prebiotics or symbiotics [24] or are administered as part of a prescribed diet [25], these factors have not been considered in our study. Thus, the degree to which probiotics affect further research may depend on whether insulin sensitivity and intestinal barrier function improve rather than whether probiotics directly affect them.

CONCLUSION

It was found that adding multi-strain probiotics to standard treatment in T2DM patients led to a significant improvement in glucose control and HDL cholesterol levels over a period of six months. Even though the probiotic group had higher baseline measurements for age, BMI, waist-hip ratio, and blood pressure, glucose levels were significantly reduced, and HDL cholesterol levels increased,

despite higher baseline measurements for these variables. Probiotics may improve diabetes metabolic health, according to these results.

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