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Impact of Oral Administration of Lactobacillus Acidophilus and Bifidobacterium Lactis (Providac) on the Blood Glucose levels in uncontrolled type 2 Diabetes Mellitus patients

Sai Ram Attla*, Priyanka Vissamraju, Ramanjaneyulu Polisetty, Sahith Rajalingam, Shreya Sangam
Department of Pharm. D (Doctor of Pharmacy), Malla Reddy College of Pharmacy, Osmania University, Hyderabad, Telangana. 500007, INDIA.

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ABSTRACT

Probiotics are dietary supplements containing beneficial bacteria. Diabetes is a metabolic disorder and the prevalence of type 2 Diabetes and its complications are high. It has been advocated that nonpathogenic bacteria like Lactobacillus and Bifidobacterium may undergo antagonistic interactions with other bacterial strains and can be used to control pathogenic bacteria. Probiotics particularly Lactobacilli and Bifidobacteria have recently emerged as the prospective biotherapeutics agents. This study has been taken to find out the effect of probiotic supplementation in patients with uncontrolled type 2 diabetes mellitus in test group (who received probiotic drug in addition to the normal anti diabetic drugs) and control group (who were only on anti diabetic drugs). The results showed percentage decrease in the fasting blood glucose levels to be 18.64% in the test group, whereas in the control group it was 11.64%.The percentage decrease in the postprandial blood glucose levels was found to be 21.37% in the test group, whereas in the control group it was 9.76%. The blood glucose levels were analyzed using ANOVA in SPSS 20.0. A significant reduction in fasting blood glucose levels (p= 0.005) postprandial blood glucose levels (p = 0.000) was observed in the probiotic supplementation group over the course of study. The study showed that administration of a probiotic capsule containing 1 billion organisms of L.acidophilus and B.lactis, improved the fasting blood glucose and postprandial blood glucose levels in uncontrolled Type 2 Diabetes Mellitus patients.

***Key Words**: Probiotic supplementation, Lactobacillus acidophilus, Bifidobacterium lactis, Uncontrolled type 2 Diabetes mellitus, Blood glucose.*

INTRODUCTION

Probiotics are defined live microorganisms which when administered in adequate amounts confer a health benefit on the host. For example, Lactobacillus species, Bifidobacteria species.

Present Indications of Probiotics:

- Metabolic diseases (obesity, diabetes mellitus)
- Allergy and Atopic Diseases of Children
- Hepatic Encephalopathy.
- Hypocholesterolaemic and Cardioprotective Effects
- Cancer Prevention
- Renal health[1]

Role of Probiotics in Type 2 Diabetes Mellitus

- 61.3 million people (20-79 years) had diabetes in 2011; by 2030 this will have risen to 101.3 million in India [2].
- Probiotics increase neutrophil bactericidal activity, phagocytosis, and oxidative burst. Bacteria, such as Lactobacillus acidophilus, increase lymphocyte numbers in the gut. Other studies, also, report that supplementation with L. *acidophilus* in healthy subjects significantly increased the phagocytic activity of polymorphonuclear cells.
- Probiotic bacteria improve insulin sensitivity by attenuating systemic inflammation. The chronic low-grade inflammation with persistently elevated levels of circulation proinflammatory cytokines is considered a principal pathogenetic component of insulin resistance and T2D. Probiotics have immunomodulatory effects. Probiotic supplementation improves high-fat diet-induced insulin resistance and hepatic steatosis.
- The antioxidative mechanisms of probiotics could be assigned to reactive oxygen species scavenging, metal ion chelation, pro-oxidant enzyme inhibition and the reduction activity and inhibition of ascorbate oxidation.
- Probiotic foods have been reported to repress the oxidative stress.
- *L. acidophillus* and *L.casei* attenuate oxidative stress and have antidiabetic effects. Probiotic strain *Bifidobacterium animalis subspecies*. *lactis* could significantly improve the metabolic changes by counter acting the adverse effects of a high-fat diet. The increase in number of *Bifidobacterium* species was significantly and positively correlated with improved glucose-tolerance, glucose-induced insulin secretion and normalized low-grade inflammation [3].

This study would provide an avenue to identify the possibility of probiotic supplementations as an adjuvant therapy in the management of type 2 diabetes.

AIM AND OBJECTIVES

The main aim of this study is to provide a supplement to the patients with uncontrolled diabetes so that it helps the patients to reduce their blood glucose levels and thereby prevent occurrence of the diabetes complications such as retinopathy, nephropathy etc.

Objectives:

- To determine the efficacy of probiotic supplementations as adjuvant therapy to improve blood glucose in individuals with type 2 diabetes.
- To provide patient counseling to the patients regarding the disease, diet and proper use of medications along with any lifestyle modifications if required.

MATERIALS AND METHODS

The study was carried out for a period of seven months from February to August 2013 at Narayana Hrudayalaya, Malla Reddy Hospitals, Hyderabad. It was conducted after approval by

***Corresponding author:**
Sai Ram Attla
Department of Pharm. D (Doctor of Pharmacy),
Malla Reddy College of Pharmacy, Osmania University,
Hyderabad, Telangana. 500007, INDIA. Phone: 7207201181.
**E-Mail: asr2617@gmail.com*

Institutional Human Ethical Committee, Malla Reddy College of Pharmacy, with the approval IRB code IEC/MRGI/PROT/13/0009.

A prospective study was carried out in a total of 60 diabetes mellitus patients. Patients were included into the study only after taking their consent. They were randomly assigned into control (who were only on anti diabetic drugs) and test groups (who received the probiotic drug in addition to the normal anti diabetic drugs). The control group were not given Providac but their weekly blood glucose levels were collected. The patients on same anti diabetic drugs with stabilized doses were continued in the study. The patients in the test group were prescribed with one capsule of Providac per day and their blood glucose levels were collected on weekly basis. The measurements of blood glucose parameters Fasting Blood Glucose, Post Prandial Blood Glucose were done every week for 4 weeks and HbA1c was done once in three months.

Providac information:

Drug: Lactobacillus *acidophilus* (LA-5) and Bifidobacterium *lactis* (BB-12) (Providac)

Category: Probiotic Supplementation

Dosage: 1 billion CFU

Storage: Store below 25^0C in dry place. Protect from light and heat. Keep the container tightly closed. Replace the lid immediately.

Manufacturer: Zydus Healthcare.

All patients were asked to maintain their usual dietary habits and lifestyle and to avoid excess consumption of yogurt and any other fermented foods.

The experimental data was analyzed by SPSS 20.0 and Microsoft excel 2007.The baseline characteristics of the patients (age, weight, gender, BMI, duration of diabetes, HbA1c, Sbp, Dbp) were expressed as Mean ± Standard deviation. The background characteristics of patients (age, weight, BMI, duration) in two groups were compared by independent sample t test. The analysis of fasting blood glucose levels, postprandial blood glucose levels of the patients between the beginning and end of the trial were compared by ANOVA. Results were considered statistically significant with $p<0.05$ for test group and $p<0.1$ for control group.

RESULTS AND DISCUSSION

In this study, six patients were excluded from the statistical analysis as they had a change in the prescription of anti diabetic drugs. Thus, data for 54 patients (20 male and 34 female) was analyzed (n= 27 for each group). The patients demonstrated good compliance with the probiotic capsule consumption and no adverse effects or symptoms were reported. The baseline characteristics of the patients are reported in Table 1 using Independent t test.

The percentage decrease in the fasting blood glucose levels was found to be 18.64% in the test group, whereas in the control group it was 11.64%. The percentage decrease in the postprandial blood glucose levels was found to be 21.37% in the test group, whereas in the control group it was 9.76%.

The mean fasting and post prandial blood glucose levels of test and control group are shown in Table 2.

Fasting Blood Glucose:

Test group:

The results were considered statistically significant if $p<0.05$. A significant reduction in fasting blood glucose levels ($p= 0.005$) was observed in the probiotic supplementation group over the course of study (Table 3).

In the LSD analysis of test group, it was evident that the fasting blood glucose values in the test group reduced in a significant manner from the second week of giving probiotic supplementation. The detailed values are shown in Table 4.

Control Group:

The results were considered to be statistically significant if $p<0.1$ for control group. The FBG values in control group were found to be statistically significant as $p= 0.066$
(Table 5).

In LSD for control group, significant reduction in blood glucose levels was seen from third week (Table 6).

Post Prandial Blood Glucose:

Test Group:

A significant reduction in the postprandial blood glucose levels ($p = 0.000$) was observed in the probiotic supplementation group over the course of study (Table 7).

A significant decrease in the PPBG levels in test group was found in the first week of giving the probiotic supplementation (Table 8).

Control Group:

A significant difference was observed in control group, here, $p<0$ (Table 9). LSD analysis for PPBG in control group showed a statistically significant difference in postprandial blood glucose levels from third week (Table 10).

Table No. 1: The baseline characteristics of study participants.

	Control (n = 27)	Test (n = 27)
Age (Years)	50.85 ± 8.761	47.04 ± 10.581
Men/women	8/19 (29.6%/70.37%)	12/15 (44.4%/55.5%)
Weight (Kg)	65.333 ±11.7244	73.852 ±7.3364
BMI (kg/m²)	24.10 ± 3.206	26.83 ± 2.512
Duration of diabetes (years)	4.03 ± 3.166	3.43 ± 2.858
FBG	165.11 ± 29.236	164.26 ± 38.343
PPG	210.89 ± 35.337	217.78 ± 46.276
HbA1C	7.39 ± 0.478	7.54 ± 0.610
Sbp	129.52 ± 8.622	132.41 ± 14.235
Dbp	81.48 ± 5.853	83.59 ± 4.725

Table No.2: Mean FBG values in Test and Control Group

	Week 0	Week 1	Week 2	Week 3
FBG Test	164.259	156.11	145.7	133.6
FBG Control	172.9	161.6	151.3	151.2
PPBG Test	217.7	195	184.7	171.5
PPBG Control	225.9	215.4	201.6	198.6

Table No.3: Analysis of fasting blood glucose values in test group using ANOVA

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	14102.472	3	4700.824	4.536	.005
Within Groups	107787.852	104	1036.422		
Total	121890.324	107			

Table No.4: LSD for test group(FBG) Dependent variable : FBG values

(I) fbg	(J) fbg	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
fbg1	fbg2	8.519	8.762	.333	-8.86	25.89
	fbg3	18.519*	8.762	.037	1.14	35.89
	fbg4	30.630*	8.762	.001	13.25	48.00
fbg2	fbg1	-8.519	8.762	.333	-25.89	8.86
	fbg3	10.000	8.762	.256	-7.38	27.38
	fbg4	22.111*	8.762	.013	4.74	39.49
fbg3	fbg1	-18.519*	8.762	.037	-35.89	-1.14
	fbg2	-10.000	8.762	.256	-27.38	7.38
	fbg4	12.111	8.762	.170	-5.26	29.49
fbg4	fbg1	-30.630*	8.762	.001	-48.00	-13.25
	fbg2	-22.111*	8.762	.013	-39.49	-4.74
	fbg3	-12.111	8.762	.170	-29.49	5.26

* The mean difference is significant at the 0.05 level.

Table No.5 : Analysis of FBG in control group using ANOVA

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	5806.917	3	1935.639	2.472	.066
Within Groups	81430.000	104	782.981		
Total	87236.917	107			

Table No.6: LSD for control group (FBG)

(I) fbg	(J) fbg	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
fbg1	fbg2	6.000	7.616	.433	-9.10	21.10
	fbg3	13.778	7.616	.073	-1.32	28.88
	fbg4	19.222*	7.616	.013	4.12	34.32
fbg2	fbg1	-6.000	7.616	.433	-21.10	9.10
	fbg3	7.778	7.616	.309	-7.32	22.88
	fbg4	13.222	7.616	.085	-1.88	28.32
fbg3	fbg1	-13.778	7.616	.073	-28.88	1.32
	fbg2	-7.778	7.616	.309	-22.88	7.32
	fbg4	5.444	7.616	.476	-9.66	20.55
fbg4	fbg1	-19.222*	7.616	.013	-34.32	-4.12
	fbg2	-13.222	7.616	.085	-28.32	1.88
	fbg3	-5.444	7.616	.476	-20.55	9.66

Table No.7: Analysis of postprandial blood glucose in test group using ANOVA

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	31259.778	3	10419.93	9.525	.000
Within Groups	113776.519	104	1094.005		
Total	145036.296	107			

Table No.8: LSD for test group (PPBG) Dependent Variable: ppbg values

(I) fbg	(J) fbg	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
ppg1	ppg2	22.778*	9.002	.013	4.93	40.63
	ppg3	33.037*	9.002	.000	15.19	50.89
	ppg4	46.556*	9.002	.000	28.70	64.41
ppg2	ppg1	-22.778*	9.002	.013	-40.63	-4.93
	ppg3	10.259	9.002	.257	-7.59	28.11
	ppg4	23.778*	9.002	.010	5.93	41.63
ppg3	ppg1	-33.037*	9.002	.000	-50.89	-15.19
	ppg2	-10.259	9.002	.257	-28.11	7.59
	ppg4	13.519	9.002	.136	-4.33	31.37
ppg4	ppg1	-46.556*	9.002	.000	-64.41	-28.70
	ppg2	-23.778*	9.002	.010	-41.63	-5.93
	ppg3	-13.519	9.002	.136	-31.37	4.33

*. The mean difference is significant at the 0.05 level.

Table No.9: Analysis of postprandial blood glucose in test group using ANOVA

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	7531.185	3	2510.395	2.547	.060
Within Groups	102487.481	104	985.457		
Total	110018.667	107			

Table No.10: LSD for test group (PPBG) Dependent Variable: ppbg values

(I) fbg	(J) fbg	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
ppg1	ppg2	1.296	8.544	.880	-15.65	18.24
	ppg3	11.444	8.544	.183	-5.50	28.39
	ppg4	20.593*	8.544	.018	3.65	37.54
ppg2	ppg1	-1.296	8.544	.880	-18.24	15.65
	ppg3	10.148	8.544	.238	-6.79	27.09
	ppg4	19.296*	8.544	.026	2.35	36.24
ppg3	ppg1	-11.444	8.544	.183	-28.39	5.50
	ppg2	-10.148	8.544	.238	-27.09	6.79
	ppg4	9.148	8.544	.287	-7.79	26.09
ppg4	ppg1	-20.593*	8.544	.018	-37.54	-3.65
	ppg2	-19.296*	8.544	.026	-36.24	-2.35
	ppg3	-9.148	8.544	.287	-26.09	7.79

*. The mean difference is significant at the 0.1 level.

In the present study, administration of one probiotic capsule (1 billion CFUs) per day for three weeks as a supplementation to the normal anti-diabetic regimen and giving patient counseling regarding disease and dietary habits resulted in a significant decrease in the fasting blood glucose and postprandial blood glucose levels in the test group.

The baseline characteristics such as age, weight, BMI, FBG, PPBG, HbA1c, Sbp, Dbp were analyzed using independent t test.

BMI of the patients was considered as it is an important indicator of obesity, a major predisposing factor to diabetes mellitus. Nadja Larsen et al. reported in a study that type 2 diabetes in humans is associated with compositional changes in intestinal microbiota. Differences between the composition of the intestinal microbiota in humans with type 2 diabetes and non-diabetic persons as control was assessed. The proportions of phylum Firmicutes and class Clostridia were significantly reduced in the diabetic group compared to the control group ($P = 0.03$). Similarly, class Betaproteobacteria was highly enriched in diabetic compared to non-diabetic persons ($P = 0.02$) and positively correlated with plasma glucose ($P = 0.04$) [4].

The number of female patients in the study is more than the males because of more inflow of female patients, during study period.

Hanie S. Ejtahed et al. reported in this randomized, double-blind, controlled clinical trial study that the consumption of probiotic yogurt improved fasting blood glucose and antioxidant status in type 2 diabetic patients. Probiotic yogurt significantly decreased fasting blood glucose ($P < 0.01$) and HbA1c ($P < 0.05$) and increased erythrocyte superoxide dismutase and glutathione peroxidase activities and total antioxidant status ($P < 0.05$) compared with the control group. In addition, the serum malondialdehyde concentration significantly decreased compared with the baseline value in both groups ($P < 0.05$). Results suggest that probiotic yogurt is a promising agent for diabetes management [5].

The present study, was designed based mainly on the above mentioned research article which was probably the first randomised control trial in investigating the effects of probiotic yogurt on blood glucose levels and antioxidant status in type 2 Diabetes Mellitus.

The major limitations of this study are, short duration of the study, small sample size, no blinding was followed and stool culture studies were not performed to assess the change in bacterial composition.

Therefore, further investigations with longer duration and a larger trial with blinding are needed to confirm the positive effect of probiotics in the management of diabetes.

CONCLUSION

The dietary interventions in conjunction with probiotics - a novel multifactorial strategy to abrogate progression and development of diabetes holds considerable promise through improving the altered gut microbial composition and by targeting all the possible risk factors. The efficacy of the probiotics in reducing the blood glucose levels when given as a supplementation in uncontrolled type 2 diabetes mellitus was studied.

In the present study, administration of one probiotic capsule (1 billion CFUs) per day as a supplementation to the normal anti-diabetic regimen and giving patient counseling regarding disease and dietary habits resulted in a significant decrease in the fasting blood glucose and postprandial blood glucose levels, in the probiotic group. The percentage decrease in the fasting blood glucose levels was found to be 18.64% in the test group, whereas in the control group it was 11.64%. In this study, a decrease in the fasting blood glucose levels was observed from the second week of giving the probiotic supplementation whereas, in the control group, the decrease was seen from third week.

Providac capsules were chosen for supplementation because, of convenient handling of the drug by the patient, drug is available as fixed doses in capsule and because of ease of administration by the patient without contamination.

Patient counseling was given to the diabetic patients as a part of the study using patient information leaflets which would help the patient in improving their blood glucose levels. Therefore, giving patient counseling and probiotic supplementation along with anti diabetic drugs helped in improving the blood glucose levels. Further, intense studies are required to confirm the time period for which probiotic effect retains in the patient, who was given probiotic supplementation.

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