

Probiotics Efficacy and Safety as add-on Therapy to Metformin in Type 2 Diabetes Mellitus

Valishetti Manoj Kumar¹, Zoha Ahmed², Syed Atiq Ur Rahman³

¹PG MD Pharmacology, Osmania Medical College, Hyderabad., ²MBBS, Deccan College of Medical Sciences, Hyderabad.,
³Professor & Head, Department of Pharmacology, Government Medical College, Mahabubnagar.

How to cite this article: Valishetti Manoj Kumar, Zoha Ahmed et al Probiotics Efficacy and Safety as add-on Therapy to Metformin in Type 2 Diabetes Mellitus. Volume 13 | Issue 4 | October-December 2022

Abstract

Background: Insulin secretion is decreased, and peripheral insulin sensitivity is diminished, resulting in type 2 diabetes mellitus. Diet, oral antihyperglycemic medications, and insulin are all modalities for treatment.

Objective: The goal of this study was to compare the efficacy of probiotics as an add-on treatment to metformin in patients with Type 2 Diabetes Mellitus.

Methods: The study participants were randomly allocated to one of two groups, Group A or Group B, using a computer-generated randomization chart, with each group consisting of 75 patients. **Group A** - For 12 weeks, patients in this group were administered Tab. Metformin 500 mg twice daily with meals. **Group B** - For 12 weeks, patients in this group were administered Tab. Metformin 500 mg twice daily with meals and Cap. Probiotics 1 capsule twice daily with meals. At the culmination of the second, fourth, eighth, and twelfth weeks, all patients were evaluated. Fasting and postprandial blood glucose levels were measured at each visit. The HbA1c test was performed at the end of the 12th week.

Results: The male predominance was seen with males 57% and females 43% in the group A and the male : female ratio was 1.34:1. In Group B males were 55% and females were 45%. The male: female ratio was 1.20 : 1. The mean HbA1C slightly reduced since the start till the end of the study. A total of 37% of the patients experienced minor self-limiting side effects in group A as compared to 6.66% of Group - B.

Conclusion: In treatment for type 2 diabetes mellitus, probiotics as an add-on therapy with metformin was observed to lower fasting blood glucose, postprandial blood glucose, and HbA1c levels when compared to metformin alone. In terms of effectiveness, probiotics have shown no substantial significant outcomes in combination therapy. However, the probiotics study group had fewer reported gastrointestinal adverse effects associated with metformin treatment.

Keywords: Hyperglycaemia, Metformin, Probiotics, T2DM

Introduction

Diabetes mellitus (DM) is a chronic metabolic condition marked by persistent hyperglycaemia. It could be due to a lack of insulin secretion, resistance to insulin's peripheral actions, or both.¹ Chronic hyperglycaemia, when combined with other metabolic irregularities, can impair numerous organ systems, resulting in chronic, progressive, and life-threatening health consequences, the most common

of which are micro and macrovascular complications, which increase the risk of cardiovascular disease by 2- to 4-fold.²

Diabetes is typically categorised into three categories based on aetiology and clinical presentation: type 1(T1DM), type 2(T2DM), and gestational diabetes (GDM). Other, less prevalent kinds of diabetes include monogenic and secondary diabetes.

Corresponding Author:

Dr. Syed Atiq Ur Rahman

Professor & Head, Department of Pharmacology, Government Medical College, Mahabubnagar.

Email: drsyedatiqurrehman@gmail.com

T2DM is the most common type of diabetes, accounting for about 90% of all cases. Insulin resistance is defined as a decreased insulin response in T2DM patients. Because insulin is ineffective in this situation, more insulin must be produced to maintain glucose homeostasis. Insulin production, on the other hand, decreases over time, leading to T2DM.

T2DM is most usually prevalent in those over the age of 45.³ Despite this, it is becoming more common in children, adolescents, and younger adults as a consequence of rising obesity and physical inactivity.

Regardless of the fact that many drugs have been developed to maintain glycaemic control and regulate blood glucose levels, whether through increased insulin production and utilisation, suppressed glucose production and absorption, blocking urine glucose re-absorption and increasing glucose excretion in urine, or a combination of these, these drugs may cause a variety of side effects. Sulphonylureas, for example, have a risk of causing kidney failure.⁴

Metformin is an oral biguanide that reduces gastrointestinal glucose absorption and hepatic glucose production while enhancing peripheral insulin sensitivity. It also has a significant impact on lipid profiles in the blood.⁵

Probiotics modulation of the gut microbiota may be useful in the prevention and control of diabetes, according to clinical data.⁶ Probiotics are living microorganisms that provide a health benefit to the host when given in adequate amounts. These microorganisms are physiologically present in a healthy human body, and they may also be received in the form of over-the-counter dietary supplements. Probiotics, particularly lactobacillus species, have been reported to be effective in the treatment of type 2 diabetes in recent years.^{7,8}

Materials and Methods

Type of study: Randomized Prospective observational study.

Study setting: Department of Pharmacology, Osmania Medical College, Koti, Hyderabad.

Study Duration: May 2019 to January 2020

Sample size: 150 Patients diagnosed with T2DM

Study drugs: Oral drugs were administered

- Tab. Metformin 500 mg
- Cap. Probiotics

Inclusion Criteria:

- All patients diagnosed with T2DM

Exclusion Criteria

- Pregnant women
- Type 1 Diabetes mellitus
- Other anti-diabetic drugs
- Unwilling to give informed consent

A comprehensive medical and drug history was obtained, followed by a thorough clinical examination and laboratory tests that included fasting and postprandial blood glucose, HbA1C, and basic blood tests.

The study participants were randomly allocated to one of two groups, Group A or Group B, using a computer-generated randomization chart, with each group consisting of 75 patients.

Group A (Control group) - For 12 weeks, patients in this group were administered Tab. Metformin 500 mg twice daily with meals.

Group B (Study group) - For 12 weeks, patients in this group were administered Tab. Metformin 500 mg twice daily with meals and Cap. Probiotics 1 capsule twice daily with meals.

At the culmination of the second, fourth, eighth, and twelfth weeks, all patients were evaluated. Fasting and postprandial blood glucose levels were measured at each visit. The HbA1c test was performed at the end of the 12th week. Throughout the trial, adverse events were also monitored.

The decrease in fasting blood glucose, postprandial blood glucose, and HbA1c at the conclusion of 12 weeks was used to determine effectiveness.

The safety assessment was based on spontaneously reported adverse events and changes in laboratory results following the study.

Statistical Analysis: The data was statistically evaluated using SPSS 22 software. The data was analysed using the mean standard deviation method. The student independent t test was used to compare quantitative data between the two groups, while the Chi square test was utilised to compare qualitative data.

Observation and Results

A total of 150 patients were allocated in two groups with 75 patients each.

The male predominance was seen with males 57% and females 43% in the group A and the male : female ratio was 1.34:1. In Group B males were 55% and females were 45%. The male: female ratio was 1.20 : 1.

In group A the majority of the patients belonged to the age group of 51 to 60 yrs with 54.66% followed by 40 to 50 yrs in 44% of the cases and the least belonged to the age group of >60 yrs in 1.33% of the cases. The mean age was 51.06 ± 5.42 yrs.

In group B the majority of the patients belonged to the age group of 51 to 60 yrs with 49.33% followed by 40 to 50 yrs in 48% of the cases and the least belonged to the age group of >60 yrs in 2.66% of the cases. The mean age was 50.90 ± 6.24 yrs.

Table 1: Distribution based on FBS

Fasting blood glucose	Control	Study	p-value
	Mean ± SD	Mean ± SD	
Baseline	133.89 ± 3.49	133.41 ± 4.39	0.976
Week 2	124.91 ± 3.19	122.91 ± 4.19	0.898
Week 4	112.31 ± 5.12	113.11 ± 5.29	0.957
Week 8	103.91 ± 5.39	103.61 ± 6.49	0.983
Week 12	94.81 ± 5.59	93.31 ± 5.31	0.912

Group - A : The Mean FBS reduced from baseline 133.89 ± 3.49 to 94.81 ± 5.59 at the end of week 12.

Group - B : The Mean FBS reduced from baseline 133.41 ± 4.39 to 93.31 ± 5.31 at the end of week 12.

At the end of the 12-week study, there was no statistically significant difference in fasting blood glucose decrease between the group A and group B.

Table 2: Distribution based on PPB

Post prandial blood glucose	Control	Study	p-value
	Mean ± SD	Mean ± SD	
Baseline	227.29 ± 8.39	224.49 ± 9.21	0.895
Week 2	216.39 ± 8.69	210.19 ± 7.81	0.764
Week 4	200.49 ± 8.09	198.39 ± 7.29	0.916
Week 8	188.21 ± 5.91	187.51 ± 7.81	0.971
Week 12	179.71 ± 6.49	175.01 ± 10.15	0.802

Group - A : The Mean PPB reduced from baseline 227.29 ± 8.39 to 179.71 ± 6.49 at the end of week 12.

Group - B : The Mean PPB reduced from baseline 224.49 ± 9.21 to 175.01 ± 10.15 at the end of week 12.

At the end of the 12-week study, there was no statistically significant difference in Post prandial blood glucose decrease between the group A and group B.

Table 3: Distribution based on Haematological parameters

Parameter	Group	Baseline	End of 12 th week
		Mean ± SD	Mean ± SD
Haemoglobin	Group - A	11.55 ± 1.34	11.67 ± 1.33
	Group - B	11.65 ± 1.55	11.46 ± 1.35
Total Count	Group - A	8260.59 ± 1931.84	8338.59 ± 1812.70
	Group - B	9013.79 ± 2946.75	8896.95 ± 2892.95
Urea	Group - A	21.63 ± 6.09	21.65 ± 5.75
	Group - B	20.40 ± 5.35	19.77 ± 5.19
S. Creatinine	Group - A	0.62 ± 0.21	0.62 ± 0.21
	Group - B	0.69 ± 0.16	0.65 ± 0.16
Total Cholesterol	Group - A	165.50 ± 21.91	162.65 ± 20.74
	Group - B	161.52 ± 22.03	159.29 ± 22.09
HDL	Group - A	45.85 ± 4.86	44.83 ± 4.40
	Group - B	44.95 ± 3.75	44.48 ± 3.95
LDL	Group - A	99.81 ± 24.65	98.71 ± 24.67
	Group - B	112.13 ± 15.55	111.85 ± 15.51
TGL	Group - A	161.89 ± 25.55	160.49 ± 24.59
	Group - B	174.64 ± 12.33	173.45 ± 12.75
Total Bilirubin	Group - A	0.51 ± 0.19	0.46 ± 0.20
	Group - B	0.40 ± 0.16	0.34 ± 0.15
SGOT	Group - A	22.81 ± 5.65	22.26 ± 5.15
	Group - B	22.10 ± 4.65	21.90 ± 4.15
SGPT	Group - A	22.85 ± 5.95	22.88 ± 5.35
	Group - B	24.95 ± 4.79	24.64 ± 4.15

Parameter	Group	Baseline	End of 12 th week
		Mean \pm SD	Mean \pm SD
Na	Group - A	136.25 \pm 4.25	136.08 \pm 3.95
	Group - B	139.55 \pm 4.29	138.26 \pm 4.35
K	Group - A	3.99 \pm 0.35	3.95 \pm 0.35
	Group - B	4.25 \pm 0.45	4.15 \pm 0.45

In both groups A and B, there were no substantial variations between baseline and end-of-study values.

HbA1C:

The mean HbA1C slightly reduced since the inception from 6.77 till the end of the study, 6.41 in Group A

The mean HbA1C slightly reduced since the inception from 6.71 till the end of the study, 6.39 in Group B.

Table 4: Distribution based on Adverse effects

Adverse effects	Group A	Group B
Abdominal discomfort	5(6.66%)	3(4%)
Flatulence	3(4%)	2(2.66%)
Diarrhoea	9(12%)	0(0%)
Nausea	5(6.66%)	0(0%)
Indigestion	3(4%)	0(0%)
Metallic taste	3(4%)	0(0%)
Total	28(37.33%)	5(6.66%)

Around 37% of the patients experienced minor self-limiting side effects in group A as compared to 6.66% of Group - B.

Discussion

Probiotics have been shown to be beneficial in disorders such as infective diarrhoea, chronic inflammatory bowel disease, lactose intolerance, and allergies, and their potential in diabetes has been studied. It has been demonstrated that there is a correlation between pathogenic microorganisms and persistent low-grade inflammation. The processes through which inflammation causes insulin resistance are also well documented. Clinical research have demonstrated that using probiotics to restore normal gut flora has resulted in improvements in glycaemic indices.

The most commonly administered probiotics in these studies were Lactobacillus and Bifidobacterium species.^{9,10} Because each bacterium has a unique method of action, using numerous species is preferred until trials identify a single strain. When probiotics were utilised for a modest to considerable length of time, the effectiveness increased (around 12 weeks). However, in several experiments, probiotics had no effect on glycemic indices, yielding contradictory results. This might be due to subtherapeutic dosages or a short research duration. The mean FBS, PPB, HbA1c levels were considerably lower in both the groups. However, there was no statistically significant difference in HbA1c decrease between the two groups.

Study	Probiotics used	Participant age	Duration	Outcome
Mazloom et al ¹¹	L. acidophilus, L. bulgaricus, L. bifidum, L. casei	25 - 65yrs	6 weeks	Non-significant declining trend in the level of TG, MDA, and IL-6 and insulin resistance
Ejtahed et al ¹²	Yogurt containing L. acidophilus LaS, B. lactis Bb12	30 - 60 yrs	6 weeks	Improved fasting blood glucose and antioxidant status
Moroti et al ¹³	L. acidophilus, B. bifidum, fructooligosaccharides	50 - 60 yrs	30 days	Significant increase in HDL and a significant decrease of glycaemia
Andreasen et al ¹⁴	L. acidophilu	55 - 62 yrs	4 weeks	Preserved insulin sensitivity, but did not affect the systemic inflammatory response
Asemi et al ¹⁵	L. sporogenes and inulin as prebiotic 35-70	35-70 yrs	6 weeks	Significant effects on serum insulin, hs-CRP, uric acid, and plasma total GSH levels
Tonucci et al ¹⁶	L. acidophilus La-S, B. animalis subsp lactis BB-12	35 - 60 yrs	6 weeks	Improved glycaemic control, decrease in inflammatory cytokines (TNF-a and resistin) and increase in acetic acid
Firouzi et al ¹⁷	Lactobacillus and Bifidobacterium	30-70 yrs	12 weeks	Modest improvement in HbA1c and fasting insulin

The haematological parameters were unaltered by probiotics. In contrast to metformin monotherapy, the study group was depicted to have less side effects. The study group had less reported gastrointestinal adverse effects related with metformin medication, which was statistically significant. In both groups, there were no severe side effects.

Despite limited research, the use of probiotics as add-on therapy is recommended, owing to the significant preclinical and clinical evidence in treating diabetes, as well as their favourable tolerability profile. Further studies should determine the best strain, therapeutic dosage, and study period for the optimum outcome.

Conclusion

In treatment for type 2 diabetes mellitus, probiotics as an add-on therapy with metformin was observed to lower HbA1c, fasting blood glucose and postprandial blood glucose levels when compared to metformin alone. In terms of effectiveness, probiotics have shown no substantial significant outcomes in combination therapy. However, the probiotics study group had fewer reported gastrointestinal adverse effects associated with metformin treatment.

Ethical Clearance: The ethical clearance was obtained from the Osmania medical college and hospital institutional ethics committee prior to the commencement of the study

Conflict of interest: Nil

Source of Funding: Self

References

1. Alvin C. Powers. Diabetes Mellitus, Harrison's principles of internal medicine. 18th edition, pg 2968.
2. Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of Diabetes Res Clin Prac. diabetes for 2010 and 2030. 2010;87:4-14.
3. Stephen J. McPhee, Maxine A. Papadakis, Ralph Gonzales, Roni Zeiger. Diabetes Mellitus and Hypoglycaemia Current Medical Diagnosis & Treatment 2010. 49th edition pg 1192
4. Aline Corado Gomes, Allain Amador Bueno, Rávila Graziany Machado de Souza et al. Nutrition Journal 2014, 13:60 doi:10.1186/1475-2891-13-6.
5. Isolauri E: Probiotics: from anecdotes to clinical demonstration. J Allergy Clin Immunol 2001, 108.
6. Sanders ME: Probiotics: considerations for human health. Nutr Rev 2003, 61:91-99.
7. Burcelin R, Serino M, Chabo C, Blasco-Baque V, Amar J: Gut microbiota and diabetes: from pathogenesis to therapeutic perspective. Acta Diabetol 2011, 48:257-273.
8. Gomes et al. Gut Microbiota, Probiotics and Diabetes. Nutrition Journal 2014 13:60 pg no 2.
9. Voreades, Diet and the development of the human intestinal microbiome. Front Microbiol. 2014;5:494
10. Salvetti S, Rapid determination of vitamin B2 secretion by bacteria growing on solid media. J Appl Microbiol. 2003;95(6):1255-60.
11. Mazloom Z, Effect of probiotics on lipid profile, glycemic control, insulin action, oxidative stress, and inflammatory markers in patients with type 2 diabetes: a clinical trial. Iran J Med Sci. 2013;38(1):38-43.
12. Ejtahed HS, Probiotic yogurt improves antioxidant status in type 2 diabetic patients. Nutrition. 2012;28(5):539-43.
13. Moroti C, Effect of the consumption of a new symbiotic shake on glycemia and cholesterol levels in elderly people with type 2 diabetes mellitus. Lipids Health Dis. 2012;11:29.
14. Andreasen AS, Effects of lactobacillus acidophilus NCFM on insulin sensitivity and the systemic inflammatory response in human subjects. Br J Nutr. 2010;104(12):183-8.
15. Asemi Z, Effects of synbiotic food consumption on metabolic status of diabetic patients: A double-blind randomized cross-over controlled clinical trial. Clin Nutr. 2014;33(2):198-203.
16. Tonucci LB, Clinical application of probiotics in type 2 diabetes mellitus: A randomized, double-blind, placebo-controlled study. Clin Nutr. 2017;36(1):85-92.
17. Firouzi S, Effect of multi-strain probiotics (multi-strain microbial cell preparation) on glycemic control and other diabetes-related outcomes in people with type 2 diabetes: A randomized controlled trial. Eur J Nutr. 2017;56(4):1535-50.