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Original Research Article

Effect of probiotic and metformin combination therapy on insulin resistance in polycystic ovary syndrome compared with metformin alone

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ABSTRACT

Background: Insulin resistance in PCOS can be aggravated by gut microbiota dysbiosis. Probiotics may improve microbial balance and insulin sensitivity and, in combination with metformin, improve glycemic control while reducing side effects. This study aimed to compare the effects of probiotic–metformin combination therapy versus metformin alone on insulin resistance in PCOS patients.
Methods: This randomized controlled trial at BSMMU included 60 infertile women with PCOS and insulin resistance. Participants were randomized into two groups: one received probiotics (Lactobacillus and Bifidobacterium, 4 billion CFU twice daily for 12 weeks) plus metformin and the control group received metformin alone. Fasting blood sugar and insulin were measured pre- and post-treatment to assess insulin resistance.
Results: In the experimental group (probiotics+metformin), FBS, fasting insulin and HOMA-IR decreased significantly after 12 weeks (5.1±0.6 vs 5.5±0.9 mmol/l; 10.2±3.8 vs 17.5±5.5 µIU/ml; 2.3±0.9 vs 4.3±1.5). Similar significant reductions were observed in the control group (metformin alone) for FBS (5.3±0.6 vs 5.4±0.5 mmol/l), fasting insulin (10.8±4.3 vs 17.6±7.4 µIU/ml) and HOMA-IR (2.6±1.4 vs 4.2±1.6). However, the mean changes between groups were not statistically significant.
Conclusions: Probiotic–metformin therapy improved insulin resistance, but not significantly more than metformin alone and had fewer, non-significant side effects.

Keywords: Insulin resistance, Metformin, PCOS, Probiotic

INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy in women of reproductive age, affecting 5–10% globally.[1] According to the Rotterdam consensus (2004), diagnosis requires the presence of at least two of the following features: polycystic ovarian morphology on ultrasound, hyperandrogenism or oligo/anovulation.[2] Beyond reproductive challenges, women with PCOS frequently experience metabolic disturbances such as obesity, insulin resistance and dyslipidemia.[3] Insulin resistance is present in 50–75% of women with PCOS and contributes to hyperinsulinemia, which stimulates ovarian androgen production and reduces hepatic sex hormone-

binding globulin (SHBG), thereby amplifying hyperandrogenism.[4,5] In recent years, attention has turned to the gut microbiome, which contains more than 100 trillion microorganisms and plays a vital role in host metabolism, immunity and overall health.[6,7] Dysbiosis has been implicated in a variety of chronic diseases, including type 2 diabetes and liver cirrhosis.[8,9] Studies suggest that gut microbial composition is also altered in PCOS. For example, Zhang et al, (2019) reported higher levels of disease-associated microbes such as Prevotella and Collinsella and lower levels of beneficial genera including Faecalibacterium and Bifidobacterium, in women with PCOS compared to controls.[10] Such findings support a role for the gut microbiota in PCOS pathophysiology.[6]

Beneficial bacteria such as Bifidobacterium and Faecalibacterium produce short-chain fatty acids (SCFAs), including acetate, propionate and butyrate, which stimulate enteroendocrine cells to secrete peptide YY (PYY) and ghrelin. These gut–brain mediators negatively correlate with LH levels, thereby helping regulate androgen production.[11,12] Reduced abundance of these bacteria in PCOS contributes to elevated LH, hyperandrogenism and insulin resistance.

Probiotics, defined as live microorganisms that confer health benefits when administered in adequate amounts, have shown promise in a variety of conditions, including atopic disease, diabetes, gastrointestinal disorders and non-alcoholic fatty liver disease.[13-15]

In women with PCOS, probiotic supplementation has been reported to reduce hyperandrogenism and insulin resistance.[16,17] SCFAs produced by probiotics, particularly propionate, also exert favorable effects on lipid metabolism by reducing hepatic fatty acid synthesis and lowering triglyceride secretion.[18] However, successful colonization of the gut is necessary for these benefits to be sustained.[10]

Among pharmacological treatments, metformin remains the most widely used insulin-sensitizing agent in PCOS.[19] Metformin reduces hepatic gluconeogenesis, inhibits glucagon action, activates the AMPK signaling pathway and enhances adiponectin activity, collectively improving glucose and lipid metabolism.[20,21] It also increases GLUT1 and GLUT4 translocation, decreases ovarian steroidogenesis and improves ovulatory function.[22,23] Despite its efficacy, gastrointestinal side effects, such as diarrhoea, bloating, nausea and vomiting, limit tolerability and up to 5% of patients may discontinue treatment.[24] Evidence suggests these adverse events may be linked to alterations in gut microbiota and probiotics have been shown to mitigate some of these effects when co-administered with metformin.[25]

Given the wide-ranging complications of PCOS, including infertility, metabolic abnormalities and endocrine dysfunction, adjunctive therapeutic approaches are needed. Probiotic supplementation represents a promising strategy to enhance the effects of metformin, improve insulin sensitivity and reduce gastrointestinal side effects. Therefore, the present study aimed to evaluate the effect of combined probiotic and metformin therapy, compared with metformin alone, on insulin resistance in women with PCOS.

Objectives

The main objective was to evaluate the effect of probiotic and metformin combination therapy on insulin resistance in patients with PCOS compared to metformin therapy alone.

METHODS

This was a randomized clinical trial study and was conducted in the Department of Reproductive Endocrinology and Infertility in Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh during the period from April 2023 to March 2024.

The study population consisted of infertile women diagnosed with polycystic ovary syndrome (PCOS) and insulin resistance, attending the outpatient department. A purposive sampling technique was used and enrolment was done based on the availability of patients fulfilling the inclusion and exclusion criteria. A total of 60 patients were enrolled and randomly assigned into two groups using computer-generated random numbers after permuted block randomization. Allocation concealment was ensured using serially numbered, closed opaque envelopes, each containing a card indicating the assigned intervention. Group A (n=30) received probiotic capsules containing Lactobacillus spp. and Bifidobacterium spp. 4 billion CFU twice daily for 12 weeks, along with metformin 500 mg once daily for 7 days, then twice daily for the next 7 days and thrice daily for the remaining 10 weeks. Group B (n=30) received only metformin in the same dosage regimen.

Women included in the study were aged 18–35 years, had a BMI of 18–30 kg/m², were diagnosed with PCOS according to the Rotterdam criteria, had primary or secondary infertility and had insulin resistance with HOMA-IR>1.7. Exclusion criteria included uncontrolled endocrine disorders such as hypothyroidism and hyperprolactinemia, significant medical comorbidities (renal, hepatic, cardiovascular), contraindications to probiotic use (such as infection at screening, immunodeficiency or immunosuppressive drug use) and recent (within 3 months) use of antibiotics, probiotics or medications that could affect insulin resistance or androgen levels (metformin, myoinositol, oral contraceptive pills). After enrolment, patients provided informed written consent following an explanation of the study's purpose, procedure and possible drug side effects.

Baseline demographic and clinical assessments were performed and fasting blood samples were collected after

10 hours of overnight fasting to measure fasting blood sugar and insulin for HOMA-IR calculation. During the 12-week treatment period, patients were followed up monthly via telephone to assess compliance and inquire about any side effects. After completion of therapy, fasting blood samples were recollected to evaluate changes in insulin resistance (fasting blood sugar, fasting insulin and HOMA-IR). In the probiotic plus metformin group, 22 patients completed the full course of treatment, with 7 becoming pregnant and 1 lost to follow-up. In the metformin-only group, 24 patients completed the treatment, with 4 becoming pregnant and 2 lost to follow-up. For each subject, a separate clinical record form was maintained and data were collected through interviews, clinical examination, investigations and review of patient history sheets.

Statistical Analysis: All data were recorded systematically in a preformed data collection form and quantitative data were expressed as mean and standard deviation and qualitative data were expressed as frequency distribution and percentage. Statistical analysis was carried out by using Statistical analysis was done by using SPSS (Statistical Package for Social Science) Version 26 for Windows 10. Chi-square test was used for analyzing categorical variables, while Student's t-test and paired t-test were used for continuous variables. P-value <0.05 was considered as statistically significant. Confidentiality was strictly maintained.

RESULTS

Table 1 shows that mean age was 24.5±3.1 years in experimental group and 24.2±3.6 years in control group. Majority of the patients were housewives in both the groups. Maximum came from urban region and belonged to middle class family. Most of the patients in both the groups had primary infertility. There was no significant difference regarding age, occupational status, residence, monthly income and type of infertility between two groups.

Table 2 shows that majority of the patients in both the groups had oligomenorrhea and acanthosis nigricans. A high percentage of patients had hirsutism as well in both groups. Acne was present in 8 patients in the experimental and 7 patients in the control group. The differences in clinical presentation were not statistically significant between the two arms.

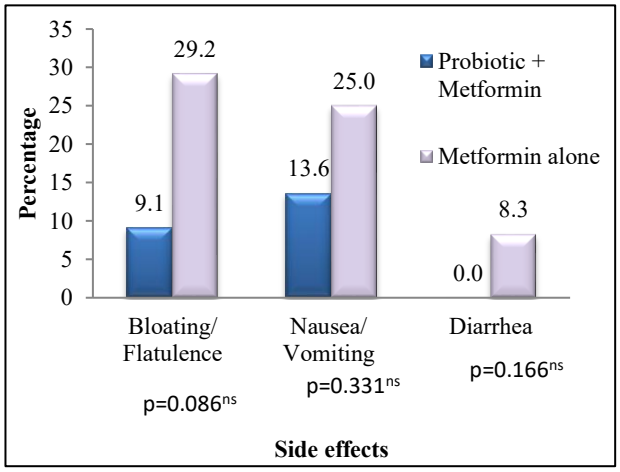

Figure 1: Side effects of the study participants.

Table 1: Demographic characteristics of study participants (n=60).

Demographic characteristics		Experimental group N	%	Control group N	%	P value
Age (in years)	18-21	4	13.33	7	23.33	0.699ns
	22-25	14	46.67	13	43.33	
	26-29	10	33.33	7	23.33	
	30-35	2	6.67	3	10	
	Mean±SD	24.5	±3.1	24.2	±3.6	
	Range (min-max)	19	-30	18	-33	
Occupational status	Housewife	18	60	20	66.67	0.602ns
	Service	7	23.33	4	13.33	
	Student	5	16.67	6	20	
Educational status	Primary					0.582ns
	SSC	5	16.67	8	26.67	
	HSC	13	43.33	10	33.33	
Residence	Rural	12	40	12	40	0.791ns
	Urban					
Monthly income (Taka)	<10,000	12	40	11	36.67	0.582ns
	10,000-25,000	18	60	19	63.33	
	>25,000					
Infertility	Primary	7	23.33	5	16.67	0.573ns
	Secondary	14	46.67	18	60	

ns=not significant; p values were calculated using Student's *t*- test and Chi-square test.

Table 2: Clinical presentations of the study participants (n=60).

Clinical presentations	Experimental group		Control group		P value
	N	%	N	%	
Oligomenorrhea	25	83.33	25	83.33	1.000[ns]
Hirsutism	12	40	17	56.67	0.196[ns]
Acne	8	26.67	7	23.33	0.756[ns]
Acanthosis nigricans	23	76.67	24	80	0.754[ns]

ns= not significant; P-values were calculated using Chi-square test.

Table 3: Comparison of baseline anthropometric and hormonal variables between two groups (n=60).

Variables	Experimental group (n=30)		Control group (n=30)		P value
	Mean	±SD	Mean	±SD	
BMI (kg/m^2)	26.1	±2.1	26.0	±2.8	0.870[ns]
Waist circumference (cm)	89.8	±5.8	87.2	±8.8	0.175[ns]
Serum LH (µIU/ml)	6.2	±3.6	6.9	±3.7	0.502[ns]
Serum FSH (µIU/ml)	5.7	±1.8	5.5	±1.2	0.667[ns]
Serum TSH (µIU/ml)	2.5	±1.2	2.4	±1.1	0.844[ns]
Serum Prolactin (ng/dl)	12.8	±5.2	12.9	±6.0	0.934[ns]

ns=not significant; p values were calculated using Student's *t*- test.

Table 4: Comparison of baseline insulin resistance variables between two groups (n=60).

Variables	Experimental group (n=30)		Control group (n=30)		P value
	Mean	±SD	Mean	±SD	
Fasting glucose (mmol/l)	5.5	±0.9	5.4	±0.5	0.883[ns]
Fasting Insulin (µIU/ml)	17.5	±5.5	17.6	±7.4	0.965[ns]
HOMA-IR	4.3	±1.5	4.2	±1.6	0.865[ns]

ns= not significant; p values were calculated using Student's *t*- test.

Table 5: Pre- and post-treatment insulin resistance variables in experimental group.

Variables	Pre-treatment (n=30)		Post-treatment (n=22)		Mean difference (95% confidence interval)	P value
	Mean	±SD	Mean	±SD		
Fasting glucose (mmol/l)	5.5	±0.9	5.1	±0.6	0.33 (0.15 to 0.50)	0.001[s]
Fasting insulin (µIU/ml)	17.5	±5.5	10.2	±3.8	7.12 (5.15 to 9.09)	0.001[s]
HOMA-IR	4.3	±1.5	2.3	±0.9	1.86 (1.38 to 2.34)	0.001[s]

*7 patients were pregnant and 1 patient was a dropout in follow up period, s=significant; p values were calculated using paired *t*- test.

Table 6: Pre- and post-treatment insulin resistance variables in control group.

Variables	Pre-treatment (n=30)		Post-treatment (n=22)		Mean difference (95% confidence interval)	P value
	Mean	±SD	Mean	±SD		
Fasting glucose (mmol/l)	5.4	±0.5	5.3	±0.6	0.18 (0.09 to 0.27)	0.001[s]
Fasting insulin (µIU/ml)	17.6	±7.4	10.8	±4.3	6.98 (4.05 to 9.91)	0.001[s]
HOMA-IR	4.2	±1.6	2.6	±1.0	1.74 (1.09 to 2.39)	0.001[s]

*4 patients were pregnant and 2 patients were dropouts in follow up period, s=significant; p values were calculated using paired *t*- test.

Table 7: Comparison of changes in insulin resistance variables between two groups.

Variables	Probiotic+Metformin (n=22)		Metformin (n=24)		P value
	Mean	±SD	Mean	±SD	
Fasting glucose (mmol/l)	0.33	±0.39	0.18	±0.21	0.101[ns]
Fasting insulin (µIU/ml)	7.12	±4.44	6.98	±6.94	0.939[ns]
HOMA-IR	1.86	±1.09	1.74	±1.55	0.774[ns]

ns=not significant; p values were calculated using Student's *t*- test.

DISCUSSION

Polycystic ovary syndrome is a heterogeneous endocrine disorder affecting women of reproductive age, characterized by chronic anovulation and hyperandrogenism.[1] Numerous pathophysiological factors contribute to this disease, including genetic and epigenetic factors, environmental influences, oxidative stress and metabolic disturbances, to name a few. A vast majority of PCOS patients suffer from insulin resistance and the compensatory hyperinsulinemia plays a substantial role in the development of androgen abundance and ovarian dysfunction. IR is most notable in phenotypes A and B (80%) followed by type C (65%) and type D (38%).[26]

According to the guidelines, even in cases where there are no appreciable changes in glucose tolerance, women with PCOS who have low insulin sensitivity should adjust their lifestyle and begin insulin sensitivity treatment once detected.[27] The role of intestinal microbiota in the pathogenesis of insulin resistance has garnered a lot of attention in recent years. Dominance of certain pathogenic bacteria can disrupt the gut mucosal permeability, resulting in the entry of their endotoxins into the systemic circulation. This causes chronic low-grade inflammation with dysfunction of insulin receptors. Living microorganisms in the form of probiotic capsules can tilt the microbiota population towards the healthy ones. The net effect is decreased pro-inflammatory cytokines, reduced oxidative stress and improvement in insulin resistance.[28]

Metformin is an already established drug in the treatment of insulin resistance. It helps in achieving better glycemic control via several mechanisms: suppresses gluconeogenesis and adipogenesis, boosts insulin sensitivity of peripheral tissues, facilitates utilisation of glucose and hinders excessive insulin action in the ovary. So far, quite a few studies involving PCOS patients have exhibited superiority of probiotics over placebo in decreasing fasting sugar, fasting insulin and HOMA-IR, although there are conflicting results as well.[29] Clinical trials performed on patients with Type 2 diabetes mellitus have shown that adding probiotics to metformin therapy not only resulted in better amelioration of insulin resistance but also lowered the gastro-intestinal side effects and improved compliance. Therefore, keeping these points in mind, the study was designed to compare the effect of probiotic and metformin combination therapy with metformin alone on insulin resistance in PCOS. In this study the mean age was 24.5±3.1 years in experimental group and 24.2±3.6 years in control group. The difference was not statistically significant between the two groups. In an almost similar study conducted by Zafar et al the mean age was found to be 25.1±5.3 years in probiotic+metformin group and 27.2±4.6 years in metformin alone group.[30] Ahmadi et al, (2017) in another RCT reported that the mean age of their study participants was 25.2±5.4 years in probiotic group.[31] These findings are consistent with our study.

However, Masaeli et al revealed that the mean age in their study was 28.64±4.5 years in metformin group.[32] The difference is maybe because women in our country tend to get married and try for pregnancy at an earlier age and thus when they fail at it, seek for expert help sooner. The majority of the participants had monthly income between 10 to 25000 BDT reflecting the higher prevalence of PCOS patients among middle class families. An increased proportion of patients came from urban region possibly due to the fact that there is increased awareness and easier access to healthcare system in this sub-population. Almost two third of the enrolled women suffered from primary infertility.

This supports the fact that PCOS is a disease of early reproductive period and its detrimental effect on fertility may even start before the average age of marriage. This study observed that the majority of the patients in both the groups (25 in each, 83.33%) had oligomenorrhea. 12 (40%) patients had hirsutism in experimental group against 17 (56.67%) participants with hirsutism in control group. Acne was present in 8 (26.67%) patients in the combination group and 7 (23.3%) patients in the metformin alone group. 23 (76.67%) and 24 (80%) patients presented with acanthosis nigricans in experimental group and control group respectively. The differences were not statistically significant between the two arms. A review article by Kamrul-Hasan et al, exploring the characteristics of women with PCOS in Bangladesh found similar patterns in several studies; oligomenorrhea-79.2%, hirsutism-55%, acne-25%, acanthosis nigricans-77.3%, all of which were conducted at BSMMU.[33] The study participants, at baseline, had a mean BMI of 26.1±2.1 kg/m^2 in probiotic and metformin group and 26.0±2.8 kg/m^2 in metformin alone group. The difference between the two arms was not significant. This is very much close to the mean BMI 26.4±4.3 kg/m^2 of the participants in Ahmadi et al clinical trial. The observation supports the fact that PCOS is more prevalent among overweight women. However, a significant proportion of lean women also suffer from this disease. Masaeli et al study justified this notion as their study participants' mean BMI was 23.51±3.67kg/m^2.[32] Waist circumference, a marker of central obesity, is more noteworthy than BMI as a predictor of insulin resistance.[34] The mean WC found in probiotic plus metformin group was 89.8±5.8 cm which was not significantly different from that found in metformin group (87.2±8.8 cm).

The participants in the study conducted by Shoaei et al had similar findings of 88.8±2.6 cm in probiotic arm and 86.31±2.09 cm in placebo arm.[29] This phenomenon again strengthens the fact that central obesity is a risk factor for IR. Mean serum hormone concentrations (LH, FHS, TSH and prolactin) were not significantly different between the two groups at baseline which eliminate the possibilities of confounding error. Mean serum LH was found more than mean FSH in both the groups, a common hormonal imbalance in PCOS. This is similar to the data extracted

from Zamila et al study where 75.5% of their study participants had altered LH/FSH ratio.[35]

In this study, the baseline values of mean fasting glucose, fasting insulin and HOMA-IR were not statistically significant between the two groups. In the study conducted by Ahmadi et al, (2017), they observed that, at baseline, the mean FBS was 89.5±11.1 mg/dl, mean insulin was 14.4±8.1µIU/ml and HOMA-IR was 3.2±1.9 in probiotic group.[31] These findings are quite similar to ours. Masaeli et al on the other hand, at baseline, had mean FBS of 87.64±7.49 mg/dl, mean insulin level of 12.58±5.541 µIU/ml and mean HOMA-IR of 2.88±1.43 in metformin group which are slightly lower than ours.[32] This study observed that in probiotic plus metformin group after 3 months of intervention, mean FBS significantly decreased from the baseline value (5.1±0.6 from 5.5±0.9mmol/l) with mean difference of 0.33. Mean fasting insulin level was also reduced compared to pre-treatment value (10.2±3.8 versus 17.5±5.5µIU/ml) with a mean difference of 7.12µIU/ml. The same was the case in regard to HOMA-IR (2.3±0.9 from 4.3±1.5, MD=1.86). All of these findings are in line with those obtained in Ahmadi et al, (2017) study where probiotics supplementation for 12 weeks was also linked to substantial decreases in FBS (87.1±7.1 from 89.5±11.1 mg/dl), fasting insulin (12.4±7.1 from 14.4±8.1 µIU/ml) and HOMA-IR (2.7±1.5 from 3.2±1.9).[31] Samimi et al in their study administered synbiotics which were a combination of probiotics and prebiotics (dietary indigestible carbohydrates that nourish the probiotics) also acquired similar results in favour of 12 weeks of synbiotics supplementation on insulin resistance.[36] However contradictory results were exhibited in a clinical trial conducted by Shoaei et al.[29] There were no remarkable differences in FBS (p=0.2), fasting insulin (p=0.5) or HOMA-IR (p=0.2) after 8 weeks of probiotics intervention. This inconsistency may be due to shorter medication duration (8 weeks versus 12 weeks) and so a longer intake of probiotics might be more effective. The

Metformin group in the present study also saw favourable outcomes. FBS decreased from 5.4±0.5 to 5.3±0.6 mmol/l with a main difference of 0.18 mmol/l. Mean fasting insulin after treatment became 10.8±4.3 from 17.6±7.4µIU/l with a mean difference of 6.98µIU/l. HOMA-IR was also reduced (2.6±1.4 versus 4.2±1.6, MD=1.74). All these alterations were significant and supported the efficacy of metformin on insulin resistance. In a study executed by Nawrocka et al, metformin was given at a dose of 850 mg twice daily for 3 months.[37] This resulted in significant decrease in fasting insulin from 25.1 to 15.06 µIU/ml, decline in HOMA-IR from 5.91 to 3.46. These results are consistent with our study findings. A review article by Attia et al explored several studies and supported the metformin doses of 500 mg TDS and 850 mg BD as the most effective ones to overcome IR in PCOS. Syed et al published a meta-analysis where they proposed that metformin could be used as a potential treatment for lean PCOS patients who have substantial insulin resistance.[38,39] This study also found that in the subset of participants with normal BMI (<25 kg/m2), metformin was effective in ameliorating IR.

In this study, although both the groups individually showed significant improvements in IR parameters following respective interventions, the mean changes were not significant when compared against each other. A meta-analysis carried out by Memon et al on type 2 DM patients evaluated the impact of probiotics in addition to metformin versus metformin alone from shortlisted 14 RCTs.[40] Pooled data demonstrates significant decreases in only fasting glucose and HbA1c but not in HOMA-IR, when combination therapy was compared against monotherapy. Kumar et al also had the same arms in their study and could not find significant differences between them.[41] Our findings are consistent with those reported in earlier studies. The reason why some studies report beneficial effects of probiotics while others fail to show additional benefits remains a matter of debate. A variety of factors may contribute to these inconsistent results. Differences in probiotic strains, doses and bioavailability, as well as the intrinsic characteristics of the host intestinal microbiota, may play a role. Additionally, variations in participants' dietary intake could affect the colonization and efficacy of probiotics in the gut. According to Soccol et al an ideal probiotic should consist of strains derived from the human intestinal tract, capable of withstanding the harsh conditions of the gastrointestinal system and successfully colonizing it.[42] They should also be stable and biologically active after going through commercial modification and distribution. These criteria might not have been entirely met before embarking on the studies.

Regarding side effects, they were more in metformin group compared to the combination group (Bloating/flatulence 29.2% versus 9.1%, nausea/vomiting 25.0% versus 13.6%, diarrhoea 8.3% versus 0.0%). However, the differences were not statistically significant, which may be due to the small sample size. The present study findings are similar to those of Memon et al where lower odds of gastro-intestinal adverse events were observed with inclusion of probiotics with metformin therapy (odds ratio 0.18, 95% CI 0.09-0.38). Şahin et al also reported fewer symptoms including abdominal pain (p=0.031 to <0.001), diarrhoea (p=0.005 to <0.001) and bloating (p=0.010 to <0.001) when probiotic was added to metformin.[25,40] It is hypothesized that the gastro-intestinal adverse impacts of metformin are due to the drug disturbing the folate-producing microbiota as well as folic acid absorption; therefore folate-producing probiotics such as bifidobacteria can be co-administered with metformin to diminish its side effects.[43] Overall, both the drugs were found to be well tolerated with only few side effects.

Since our study was conducted at a single center. Due to limited resources and facilities, analysis of the participants' stool samples for changes in bacterial flora and quantification of short-chain fatty acids (SCFAs) could not be performed, making it difficult to assess the actual extent of probiotic colonization. Although efforts

were made to standardize the diet, full compliance could not be ensured, potentially affecting bacterial colonization consistency. The study was also constrained by a small sample size and a short duration due to time limitations. Additionally, neither participants nor investigators were blinded to the treatment after randomization, which could introduce bias. Furthermore, as participants were recruited from a single department of one tertiary-level hospital, the findings may not be entirely generalizable to the broader population due to possible genetic, racial and geographical variations.

CONCLUSION

Although there was remarkable improvement in insulin resistance after three months of probiotic and metformin combination therapy, the change was not statistically significant when compared against metformin monotherapy of the same duration. Patients of the metformin alone group reported more side effects than those in the combination therapy group, though not statistically significant either. Overall, both probiotic and metformin were found to be well tolerated with few side effects.

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