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Research Article

ADJUNCT SYNBIOTIC THERAPY WITH VILDAGLIPTIN-METFORMIN IMPROVES GLYCEMIC CONTROL, INSULIN SENSITIVITY, AND COST-EFFICIENCY IN ELDERLY PATIENTS WITH TYPE 2 DIABETES

KALA P[1]*, JAMUNA RANI R[1], SRUTHI ANIL KUMAR AH[2]

[1]Department of Pharmacology, SRM Medical College Hospital and Research Centre, Kattankulathur, Tamil Nadu, India. [2]Department of Medical Research, SRM Medical College Hospital and Research Centre, Kattankulathur, Tamil Nadu, India.
*Corresponding author: Kala P; Email: kalaramesh75@gmail.com

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ABSTRACT

Objectives: This study evaluated the efficacy of daily synbiotic supplementation combined with vildagliptin-metformin therapy for enhancing glycemic management, insulin responsiveness, and treatment cost-effectiveness in elderly type 2 diabetes patients.

Methods: A 12-week randomized, open-label, parallel-group clinical trial was conducted at a tertiary care teaching hospital in India. Participants aged 60–80 years with stable vildagliptin-metformin therapy were randomly assigned (1:1) to either continue standard treatment alone or receive additional daily synbiotic capsules containing 10^9 colony forming units each of *Lactobacillus* and *Bifidobacterium* species with fructo-oligosaccharides. Primary endpoints included changes in glycated hemoglobin (HbA1c), fasting blood glucose (FBG), postprandial blood glucose (PPBG), and triglyceride-glucose (TyG) index. Secondary outcomes assessed safety profile, treatment compliance, and cost per 1% HbA1c reduction using t-tests and repeated-measures ANOVA (α=0.05).

Results: A total of 210 participants completed the study (n=105 per group). The synbiotic-supplemented group demonstrated significantly greater improvements compared to standard therapy: HbA1c reduction (−1.2% vs. −0.6%), FBG reduction (−29.9 vs. −15.2 mg/dL), PPBG reduction (−39.8 vs. −21.2 mg/dL), and TyG index improvement (−0.47 vs. −0.21) (all p<0.001). Treatment adherence exceeded 90% in both groups. Mild gastrointestinal effects occurred more frequently with synbiotic supplementation (27.6% vs. 21.0%) but were transient with no serious adverse events reported. Cost analysis favored the synbiotic intervention (₹750 vs. ₹900/1% HbA1c reduction).

Conclusion: Among elderly type 2 diabetes patients receiving vildagliptin-metformin therapy, adjunctive synbiotic supplementation provided significant improvements in glycemic control and insulin sensitivity with superior cost-effectiveness and acceptable safety profile. These findings support considering synbiotic therapy integration in routine diabetes management when target glycemic goals remain unachieved.

Keywords: Type 2 diabetes mellitus, Elderly patients, Synbiotic supplementation, vildagliptin, Metformin, Glycemic control, Cost-effectiveness.

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) represents a significant and expanding public health challenge across India and globally. Epidemiological forecasts suggest that diabetes prevalence in India could escalate to 134 million individuals by 2045, propelled by accelerating urbanization trends, evolving lifestyle patterns, and demographic aging. This burden demonstrates particular severity among older populations, who encounter elevated complication rates alongside distinctive therapeutic obstacles stemming from age-associated physiological deterioration, frailty syndrome, and concurrent disease states [1-4]. Geriatric patients with T2DM commonly manifest sarcopenia, diminished pancreatic β-cell functionality, persistent inflammatory states, and compromised insulin responsiveness, collectively contributing to suboptimal glucose management despite conventional therapeutic interventions. Furthermore, this demographic faces heightened vulnerability to hypoglycemic events, medication interactions, and diabetes-related psychological distress, a condition affecting approximately one-third of patients and demonstrating strong associations with diminished treatment compliance and life quality [5,6].

Chronic hyperglycemia among elderly T2DM individuals accelerates microvascular complications including retinopathy, nephropathy, and neuropathy, while simultaneously promoting macrovascular consequences such as coronary heart disease, cerebrovascular accidents, and peripheral arterial disease. The diabetic condition in geriatric populations extends beyond vascular complications, encompassing increased fall risk, frailty progression, depressive disorders, cognitive dysfunction, and mobility limitations, all contributing to heightened healthcare resource utilization and associated costs. Consequently, there exists pressing demand for therapeutic approaches that demonstrate efficacy in glucose regulation while maintaining safety, tolerability, and economic viability within India's varied healthcare infrastructure [7-11].

Contemporary evidence increasingly emphasizes the gut-metabolic axis role in insulin resistance development and T2DM pathophysiology. Gut microbiota dysbiosis has been implicated in systemic inflammatory processes, endotoxemia, oxidative cellular damage, and glucose homeostasis disruption. Microbial equilibrium restoration through nutritional and pharmacological interventions is gaining recognition as a promising therapeutic pathway. Synbiotics, characterized as synergistic combinations of prebiotics (including fructo-oligosaccharides, galacto-oligosaccharides, and inulin) with probiotic organisms (notably *Lactobacillus* and *Bifidobacterium* strains), demonstrate capacity for insulin sensitivity enhancement, glycemic parameter improvement, and inflammatory pathway modulation. Through short-chain fatty acid (SCFA) production stimulation, gut-derived endotoxin burden reduction, and bile acid plus incretin secretion influence, synbiotics may provide complementary support to traditional pharmacotherapy while addressing residual metabolic risk factors [12-14].

Within conventional therapeutic approaches, metformin and dipeptidyl peptidase-4 (DPP-4) inhibitors including vildagliptin maintain central positions in elderly diabetes management through demonstrated efficacy and relatively favorable safety characteristics. Metformin functions primarily through hepatic glucose production suppression and peripheral insulin sensitivity improvement, while vildagliptin enhances incretin activity, optimizing both fasting and postprandial glycemic control [15-18]. Notably, this combination demonstrates general tolerability among older individuals, including those with moderate renal dysfunction. Nevertheless, numerous elderly patients experience inadequate glucose control with dual therapy alone, emphasizing the requirement for supplementary therapeutic strategies [19-21].

Recent clinical investigations indicate that synbiotics as adjunctive therapy may enhance glycemic outcomes when combined with standard antidiabetic medications. Meta-analytical reviews have documented modest yet clinically meaningful improvements in HbA1c, fasting glucose levels, and insulin resistance through probiotic or synbiotic supplementation. However, most previous investigations have been limited by short duration, insufficient statistical power, and infrequent focus on elderly populations, despite this group's increased susceptibility.

Within this context, the current investigation was structured to assess the efficacy, safety profile, and economic viability of gut-targeted synbiotic therapy as an adjunct to vildagliptin-metformin treatment in elderly T2DM patients. Specifically, this trial sought to evaluate improvements in glycemic management (fasting glucose, postprandial glucose, and HbA1c), insulin responsiveness (TyG index), treatment tolerability, medication adherence, and cost-effectiveness outcomes. Through concentration on an elderly Indian population, this study addresses a crucial evidence void and investigates whether a gut-directed, minimally invasive, and economically accessible supplementary approach can enhance diabetes outcomes in a population demonstrating elevated complication risk and treatment resistance.

METHODS

Study design and setting

This investigation employed a prospective, randomized, open-label, parallel-group design conducted over a 12-week period at SRM Medical College Hospital and Research Center, Kattankulathur, India, spanning January through December 2024. The research protocol received ethical clearance from the Institutional Ethics Committee (approval reference: IEC No. 8732/IEC/2023), with all enrolled participants providing voluntary written informed consent before study entry. The trial adhered to principles outlined in the Declaration of Helsinki and followed established Good Clinical Practice standards.

Participant selection

The study population comprised elderly individuals aged 60–80 years diagnosed with T2DM for a minimum duration of 1 year, maintained on stable metformin monotherapy (minimum 1,000 mg daily) for at least three consecutive months before screening. The participant recruitment process and flow are illustrated in Fig. 1.

Inclusion criteria

- Baseline glycated hemoglobin (HbA1c) ranging from 7.0% to 9.0%.
- Fasting plasma glucose levels between 110 and 180 mg/dL.
- Body mass index within 22–35 kg/m^2.
- Demonstrated ability to provide informed consent and comply with study procedures.

Exclusion criteria

- HbA1c exceeding 9.0% or clinical requirement for insulin or additional glucose-lowering medications.
- Estimated glomerular filtration rate below 45 mL/min/1.73 m^2.
- Evidence of active hepatic compromise (alanine aminotransferase or aspartate aminotransferase levels exceeding twice the upper normal limit).
- Recent exposure to antibiotics, probiotics, prebiotics, synbiotics, or high-dose vitamin supplements within 4 weeks of enrolment.
- Current or recent systemic corticosteroid or immunosuppressive treatment within 1 month.
- Clinically significant cardiovascular, gastrointestinal, immunological, pancreatic, or malignant conditions.
- Excessive alcohol consumption (exceeding 14 drinks weekly for males or seven drinks weekly for females) or ongoing tobacco use.
- Concurrent participation in alternative clinical investigations within 3 months.

From 356 initially screened candidates, 320 individuals satisfied eligibility requirements and underwent randomization, with 210 participants completing all scheduled study visits.

Randomization and treatment allocation

Participants underwent 1:1 randomization using computer-generated block randomization with sealed envelope concealment methodology to ensure allocation concealment.

Control group

Received vildagliptin 50 mg twice daily combined with metformin 500 mg twice daily.

Intervention group

Received identical pharmacological treatment supplemented with a once-daily synbiotic capsule containing 10^9 colony-forming units each of *Lactobacillus* and *Bifidobacterium* species, combined with 100 mg fructo-oligosaccharides.

All study participants received standardized nutritional counseling and lifestyle modification guidance at baseline enrollment and during each subsequent follow-up assessment.

Clinical assessments and measurements

Visit schedule

Evaluations were conducted at baseline, week 4, week 8, and week 12.

Anthropometric measurements

Body weight, height, and body mass index were determined using calibrated medical instruments following standardized protocols.

Glycemic parameter evaluation

- Fasting and postprandial glucose concentrations measured through glucose oxidase-peroxidase enzymatic assay.
- HbA1c quantified through high-performance liquid chromatography methodology.
- Insulin sensitivity assessed using the triglyceride-glucose (TyG) index calculation: ln (fasting triglycerides [mg/dL] × fasting glucose [mg/dL]/2).

Lipid profile analysis

Total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglyceride levels determined through enzymatic colorimetric analytical methods.

Safety monitoring

Adverse events were systematically documented and classified according to common terminology criteria for Adverse Events version 5.0 at each scheduled visit, with additional safety surveillance conducted through biweekly telephone contacts.

Treatment adherence assessment

Medication compliance was evaluated through pill counting methodology and patient-maintained medication diaries.

Fig. 1: CONSORT flow diagram

Adherence rate calculation: (Doses consumed ÷ Doses prescribed) × 100%.

Economic evaluation

Drug costs were calculated based on 2024 Indian pharmaceutical market pricing. Economic metrics included monthly and annual therapy expenditures, cost per 1% HbA1c reduction, and incremental cost-effectiveness ratios.

Study endpoints

Primary endpoints

Changes from baseline to week 12 in fasting glucose concentrations, postprandial glucose levels, HbA1c percentages, and TyG index values.

Secondary endpoints

Incidence and severity classification of adverse events, medication adherence rates, treatment tolerability among participants with polypharmacy (≥5 concurrent medications), and comprehensive cost-effectiveness parameters.

Sample size determination

Power analysis determined that 100 completing participants per treatment arm (total, n=200) would provide adequate statistical power to detect a clinically meaningful 0.5% between-group difference in HbA1c (standard deviation 1.0) with 80% power at α=0.05, accounting for an anticipated 10% attrition rate. The enrollment of 320 participants ensured sufficient statistical power despite higher than expected dropout rates.

Statistical analysis

Statistical analyses were performed using SPSS version 25.0 software. Continuous variables are presented as mean±standard deviation, while categorical variables are expressed as frequency counts and percentages. Between-group comparisons utilized independent-samples t-tests or Chi-square tests as appropriate, and within-group temporal changes were assessed using paired t-tests. Repeated-measures analysis of variance evaluated group-by-time interaction effects. Statistical significance was defined as two-sided $p<0.05$. Continuous variables failing normality assumptions underwent logarithmic transformation or nonparametric analytical approaches.

The participant flow through each stage of the trial is depicted in Fig. 1. Of 356 patients screened, 36 were excluded, leaving 320 randomized equally between the two groups. After accounting for withdrawals, losses to follow-up, and protocol deviations, 105 participants in each group completed the study and were included in the final analysis.

RESULTS

Participant characteristics

Baseline demographic, anthropometric, and clinical characteristics were comparable between the two study groups. The overall mean age was 71.2±6.1 years with a near-equal distribution of males and females. Cardiometabolic comorbidities were common, with hypertension present in 58.1% (either alone or with dyslipidemia) and dyslipidemia in 51.5% of participants. Approximately one-fifth of participants were on polypharmacy, predominantly involving antihypertensives, statins, and antiplatelet therapy. No statistically

significant differences were observed between groups for any baseline characteristic (p>0.05).

Population characteristics are summarized in Table 1.

Glycemic outcomes

After 12 weeks of treatment, both study arms exhibited significant improvements in glycemic control. However, the group receiving vildagliptin-metformin combined with synbiotic supplementation (Group 2) demonstrated significantly greater reductions in fasting blood glucose (FBG), postprandial blood glucose (PPBG), and HbA1c compared to the vildagliptin-metformin only group (Group 1) (Table 2).

Fig. 2 shows baseline and post-intervention HbA1c (%) for both groups.

This line graph depicts the mean HbA1c values at baseline and week 12 for both treatment arms. Group 1 (vildagliptin + metformin) demonstrated a reduction from 7.9±0.6% at baseline to 7.3±0.5% at week 12 (absolute change –0.6%; –7.6% relative). Group 2 (vildagliptin + metformin + synbiotic) showed a greater decline from 8.0±0.6% to 6.8±0.4% (absolute change –1.2%; –15.0% relative). Independent-samples t-test at week 12 confirmed a significant between-group difference (t=7.30, p<0.001), and two-way repeated-measures ANOVA indicated a significant group×time interaction (F=28.4, p<0.001).

Insulin sensitivity and metabolic markers

The triglyceride–glucose (TyG) index, calculated as ln (fasting triglycerides [mg/dL] × fasting glucose [mg/dL]/2), served as the primary surrogate marker for insulin resistance assessment. After 12 weeks of intervention, both treatment groups demonstrated statistically significant improvements in insulin sensitivity, with markedly superior outcomes observed in the synbiotic-supplemented arm. Group 2 (vildagliptin–metformin plus synbiotic) achieved a mean TyG index reduction of −0.47 (−5.04% from baseline), compared to −0.21 (−2.27% from baseline) in Group 1 (vildagliptin–metformin alone). This represents more than a two-fold greater improvement in insulin sensitivity with adjunct synbiotic therapy, as shown in Table 3. Two-way repeated measures ANOVA confirmed a highly significant group × time interaction (F=201.18, p<0.001), establishing that the enhanced insulin sensitivity was directly attributable to synbiotic supplementation rather than temporal effects.

Subgroup analyses revealed remarkable consistency in treatment response across demographic strata. Both male and female participants in the synbiotic group achieved identical TyG index improvements (−0.34 for both sexes), confirming sex-independent efficacy. Age stratification demonstrated a modest but clinically relevant enhanced response in participants aged ≥70 years (−0.35) compared to those <70 years (−0.33), underscoring the particular benefit of this intervention in elderly diabetic populations who typically exhibit greater insulin resistance. The substantial improvement in insulin sensitivity paralleled the superior glycemic outcomes observed with synbiotic therapy, reinforcing the interconnected nature of gut microbiota modulation and metabolic health. These findings provide compelling evidence that adjunct synbiotic therapy represents a viable strategy for enhancing insulin sensitivity beyond conventional glucose-lowering medications, particularly relevant for elderly patients with T2DM who face increased metabolic challenges and therapeutic resistance.

Pharmaceutical evaluation

Safety, tolerability, and adherence evaluation

The comprehensive pharmaceutical evaluation demonstrated excellent safety and adherence profiles across both treatment arms. Both regimens were well-tolerated with high treatment completion rates and minimal safety concerns throughout the 12-week study period.

Comparative TyG index reduction across treatment groups and demographic subgroups.

Fig. 3 demonstrates the superior insulin sensitivity improvement achieved with synbiotic therapy. Group 2 showed more than double the TyG index reduction compared to Group 1 (−0.47 vs. −0.21). Within the synbiotic group, benefits were consistent across sex (both males and females: −0.34) and showed enhanced efficacy in elderly participants ≥70 years (−0.35) compared to younger participants (−0.33), highlighting the particular value of this intervention in the target elderly population.

Table 1: Baseline demographic, anthropometric, and clinical characteristics of study participants in both treatment groups

Characteristic	Group 1 (n=105)	Group 2 (n=105)	Total (n=210)	p-value
Age (years, mean±SD)	71.0±6.3	71.4±5.9	71.2±6.1	0.62
Age groups, n (%)				0.78
60–69 years	46 (43.8)	44 (41.9)	90 (42.9)	
≥70 years	59 (56.2)	61 (58.1)	120 (57.1)	
Sex, n (%)				1.00
Male	54 (51.4)	54 (51.4)	108 (51.4)	
Female	51 (48.6)	51 (48.6)	102 (48.6)	
BMI (kg/m^2, mean±SD)	25.9±3.5	26.3±3.3	26.1±3.4	0.41
BMI categories, n (%)				0.87
Normal (18.5–24.9)	34 (32.4)	32 (30.5)	66 (31.4)	
Overweight (25–29.9)	52 (49.5)	55 (52.4)	107 (51.0)	
Obese (≥30)	19 (18.1)	18 (17.1)	37 (17.6)	
Duration of diabetes (years, mean±SD)	4.3±2.0	4.1±2.2	4.2±2.1	0.55
Duration categories, n (%)				0.77
<5 years	65 (61.9)	67 (63.8)	132 (62.9)	
≥5 years	40 (38.1)	38 (36.2)	78 (37.1)	
Comorbidities, n (%)				0.94
Hypertension only	29 (27.6)	28 (26.7)	57 (27.1)	
Dyslipidemia only	21 (20.0)	22 (21.0)	43 (20.5)	
Both HTN+Dyslipidemia	31 (29.5)	34 (32.4)	65 (31.0)	
None	24 (22.9)	21 (20.0)	45 (21.4)	
Polypharmacy (>5 concurrent drugs), n (%)	23 (21.9)	24 (22.9)	47 (22.4)	0.85
Common medications in polypharmacy, n (%)				
Antihypertensives (ACEI/ARB, β-blockers, and CCBs)	20 (19.0)	22 (21.0)	42 (20.0)	0.71
Statins	18 (17.1)	20 (19.0)	38 (18.1)	
Antiplatelets (Aspirin/Clopidogrel)	15 (14.3)	17 (16.2)	32 (15.2)	

Values are presented as mean±standard deviation (SD) or n (%). Comparisons between groups used independent t-tests for continuous variables and Chi-square tests for categorical variables. No statistically significant differences were found between groups at baseline (all p>0.05)

Table 2: HbA1c (%) before and after intervention

Variable	Group 1 (n=105)	Group 2 (n=105)	Between-group comparison (post)
FBG pre (mg/dL, mean±SD)	155.4±23.2	158.3±24.5	p=0.34
FBG post (mg/dL, mean±SD)	140.2±21.7	128.4±19.6	t=4.25, p<0.001
Absolute change (mg/dL)	−15.2	−29.9	—
% Change from baseline	−9.8%	−18.9%	—
Within-group paired t, p	−14.2, p<0.001	−18.3, p<0.001	—
PPBG pre (mg/dL, mean±SD)	213.8±34.1	218.2±35.8	p=0.42
PPBG post (mg/dL, mean±SD)	192.6±31.5	178.4±28.9	t=3.66, p<0.001
Absolute change (mg/dL)	−21.2	−39.8	—
% Change from baseline	−9.9%	−18.2%	—
Within-group paired t, p	−11.9, p<0.001	−14.6, p<0.001	—

Data are expressed as mean±standard deviation (SD). Within-group changes were analyzed by paired t-test, and between-group differences at post-treatment time point were evaluated through independent t-test. Both groups experienced statistically significant improvements; however, the magnitude of reduction in FBG and PPBG nearly doubled in the synbiotic group compared to the control

Table 3: Comprehensive analysis of insulin sensitivity and metabolic outcomes

Analysis	Group 1 (n=105) Vildagliptin+Metformin	Group 2 (n=105) Vildagliptin+Metformin+Synbiotic	Statistical comparison
Primary TyG index analysis			
TyG pre (mean±SD)	9.24±0.085	9.32±0.115	Baseline: p=0.51
TyG post (mean±SD)	9.03±0.064	8.85±0.096	Post: t=15.95, p<0.001
Absolute change	-0.21	-0.47	Difference: −0.26
% Change	-2.27%	-5.04%	Group×Time: F=201.18, p<0.001
Within-group *P* value	p<0.001	p<0.001	
Stratified analysis (Group 2 only)			
By sex			
Male TyG change	—	−0.34 (−3.66%)	t=−20.67, p<0.001
Female TyG change	—	−0.34 (−3.66%)	t=−21.84, p<0.001
By age			
<70 years TyG change	—	−0.33 (−3.56%)	t=−24.21, p<0.001
≥70 years TyG change	—	−0.35 (−3.77%)	t=−17.87, p<0.001
Additional biomarkers			
FBS reduction (mg/dL)	−15.2 (−9.8%)	−29.9 (−18.9%)	t=4.25, p<0.001
HbA1c reduction (%)	−0.6 (−7.6%)	−1.2 (−15.0%)	t=7.30, p<0.001

TyG: Triglyceride-glucose index. Values are mean±SD. Stratified analysis demonstrates consistent benefits across demographic subgroups with enhanced efficacy in elderly participants (≥70 years). All comparisons achieved statistical significance (p<0.001)

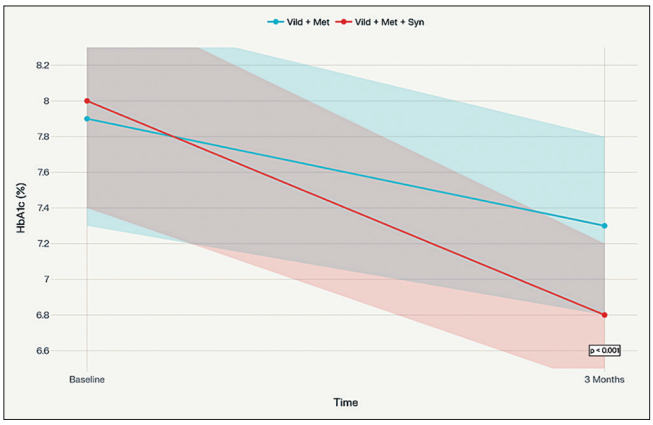

Fig. 2: Line graph of HbA1c change over time (GP1 vs. GP2)

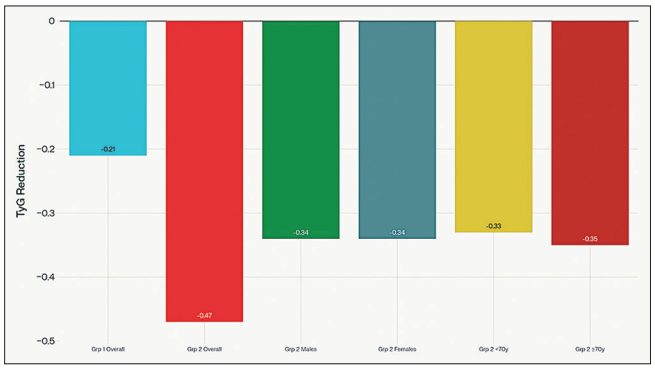

Fig. 3: TyG index reduction across treatment groups and demographics

The comprehensive safety evaluation revealed an excellent tolerability profile with 75.7% of participants experiencing no adverse events (Table 4). While Group 2 showed a numerically higher incidence of mild gastrointestinal symptoms (27.6% vs. 21.0%), these were transient, self-limiting, and did not impact treatment adherence or completion rates. Importantly, no severe adverse events, serious hypoglycemic episodes, or treatment-related hospitalizations occurred.

Medication adherence was exemplary at 93.1±6.8% overall, with 85.2% of participants maintaining high adherence (≥90%). The study completion rate of 98.6% underscores the feasibility and acceptability of this therapeutic approach. Patient satisfaction scores were high (8.3±1.1 out of 10), and 93.8% expressed willingness to continue therapy beyond the study period.

Integrated pharmaceutical, clinical, and economic evaluation

A comprehensive multi-dimensional analysis was conducted to evaluate the clinical efficacy, safety profile, treatment adherence, and economic feasibility of synbiotic-supplemented therapy compared to standard care. This integrated assessment provides evidence for real-world implementation and healthcare policy considerations in the Indian context.

Table 4: Comprehensive safety, tolerability, adherence, and clinical outcomes analysis (n=210)

Parameter	Group 1 (n=105) Vildagliptin+ Metformin	Group 2 (n=105) Vildagliptin+Metformin+ Synbiotic	Overall (n=210)	p-value	Clinical significance
Safety and tolerability					
Any adverse event, n (%)	22 (21.0)	29 (27.6)	51 (24.3)	0.28	No significant difference
Gastrointestinal events					
GI upset (bloating/discomfort)	6 (5.7)	12 (11.4)	18 (8.6)	0.15	Mild, self-limiting
Flatulence	4 (3.8)	9 (8.6)	13 (6.2)	0.16	Transient, <2 weeks
Nausea	5 (4.8)	8 (7.6)	13 (6.2)	0.39	Metformin-related
Diarrhea	2 (1.9)	4 (3.8)	6 (2.9)	0.41	Resolved with probiotics
Systemic events					
Headache	3 (2.9)	4 (3.8)	7 (3.3)	0.70	Responded to analgesics
Fatigue	1 (1.0)	2 (1.9)	3 (1.4)	0.56	Not treatment-related
Taste changes	1 (1.0)	1 (1.0)	2 (1.0)	1.00	Metformin-associated
Metabolic events					
Mild hypoglycemia (BG 60–70 mg/dL)	2 (1.9)	3 (2.9)	5 (2.4)	0.65	Meal timing-related
No severe hypoglycemia (BG <54 mg/dL)	0 (0.0)	0 (0.0)	0 (0.0)	—	Excellent safety profile
No adverse events	83 (79.0)	76 (72.4)	159 (75.7)	0.28	Majority well-tolerated
Treatment discontinuation					
Due to tolerability	1 (1.0)	2 (1.9)	3 (1.4)	0.56	Excellent retention
Due to personal factors	2 (1.9)	1 (1.0)	3 (1.4)	0.56	Non-medical reasons
Adherence and compliance					
Mean adherence (%±SD)	93.8±6.1	92.5±7.4	93.1±6.8	0.20	Excellent compliance
Adherence categories					
High adherence (≥90%)	91 (86.7)	88 (83.8)	179 (85.2)	0.56	Majority compliant
Moderate adherence (75–89%)	9 (8.6)	11 (10.5)	20 (9.5)	0.65	Acceptable compliance
Low adherence (<75%)	2 (1.9)	3 (2.9)	5 (2.4)	0.65	Minimal poor compliance
Study completion rate	104 (99.0)	103 (98.1)	207 (98.6)	0.56	Outstanding retention
Quality of life indicators					
Patient satisfaction (1–10 scale)	8.2±1.1	8.4±1.0	8.3±1.1	0.18	High satisfaction
Willingness to continue therapy	98 (93.3)	99 (94.3)	197 (93.8)	0.76	Strong acceptance
Healthcare utilization					
Unscheduled clinic visits	3 (2.9)	5 (4.8)	8 (3.8)	0.48	Minimal additional visits
Emergency department visits	0 (0.0)	1 (1.0)	1 (0.5)	0.32	Excellent safety record
Hospitalizations	0 (0.0)	0 (0.0)	0 (0.0)	—	No treatment-related admissions

All adverse events graded per CTCAE v5.0. BG=blood glucose. Statistical comparisons by Chi-square, Fisher's exact, or independent t-test as appropriate

Clinical superiority and safety profile

Group 2 (vildagliptin-metformin plus synbiotic) demonstrated clinically meaningful and statistically significant advantages across all primary and secondary endpoints. The mean HbA1c reduction of 1.2±0.4% versus 0.6±0.5% in Group 1 represents a therapeutically relevant difference exceeding the 0.5% threshold considered clinically significant by international diabetes guidelines. Similarly, fasting and postprandial glucose improvements were nearly doubled in the synbiotic group, with TyG index reductions confirming superior insulin sensitivity enhancement.

Safety analysis revealed excellent tolerability profiles in both arms. While Group 2 experienced slightly more gastrointestinal symptoms (27.6% vs. 21.0%), these were exclusively mild, transient events that did not compromise treatment completion. Critically, no severe adverse events, hypoglycemic episodes requiring medical intervention, or treatment-related hospitalizations occurred, establishing the safety of this combination approach.

Fig. 4 complements this analysis by illustrating:

- Panel A: HbA1c percentage reduction in both groups.
- Panel B: Fasting and postprandial glucose reductions.
- Panel C: TyG index reduction highlighting insulin sensitivity gains.
- Panel D: Cost per 1% HbA1c reduction reflecting the economic advantage of synbiotic adjunct therapy.

This integrated clinical and economic evaluation confirms that adding synbiotics to vildagliptin–metformin significantly enhances glycemic and metabolic outcomes with excellent safety and adherence, while providing superior cost-efficiency consistent with Indian healthcare priorities. The results advocate for the incorporation of synbiotic adjunct therapy into standard management of elderly patients with T2DM.

DISCUSSION

The present investigation demonstrates that synbiotic adjuvant therapy combined with vildagliptin–metformin produces superior glycemic control, enhanced insulin sensitivity, and favorable cost-effectiveness in elderly patients with T2DM. These outcomes address critical therapeutic challenges in this vulnerable population while establishing evidence for incorporating gut-targeted interventions into conventional diabetes management protocols.

The observed 1.2% HbA1c reduction in the synbiotic-supplemented group versus 0.6% with standard therapy represents a therapeutically important difference that surpasses the 0.5% threshold established for clinical significance. This finding assumes particular relevance given the baseline HbA1c levels of 7.9-8.0%, indicating inadequate control despite established dual therapy. The concurrent improvements in fasting glucose (−29.9 vs. −15.2 mg/dL) and postprandial glucose (−39.8 vs. −21.2 mg/dL) further substantiate the metabolic benefits of microbiota-targeted intervention [22-28].

The substantial enhancement in insulin sensitivity, reflected by TyG index reductions of −0.47 versus −0.21, demonstrates the broader metabolic impact of synbiotic therapy beyond glucose homeostasis. This validated surrogate marker for insulin resistance proves particularly informative in elderly populations where traditional insulin sensitivity assessments may be less reliable. Contemporary mechanistic investigations support

Table 5: Comprehensive pharmaceutical, clinical, and economic evaluation

Domain	Parameter	Group 1 (n=105) Vildagliptin+ Metformin	Group 2 (n=105) Vildagliptin+ Metformin+ Synbiotic	Comparative analysis	Clinical significance
Primary clinical outcomes					
	HbA1c reduction (%)	−0.6±0.5	−1.2±0.4	p<0.001; ES=1.36	Group 2 achieved clinically meaningful reduction
	FBS reduction (mg/dL)	−15.2 (−9.8%)	−29.9 (−18.9%)	p<0.001; ES=0.71	Nearly double glucose control improvement
	PPBS reduction (mg/dL)	−21.2 (−9.9%)	−39.8 (−18.2%)	p<0.001; ES=0.58	Superior postprandial glycemic management
	TyG index reduction	−0.21 (−2.3%)	−0.47 (−5.0%)	p<0.001; ES=2.78	Markedly enhanced insulin sensitivity
Safety and tolerability					
	Any adverse event	22 (21.0%)	29 (27.6%)	p=0.28; RR=1.32	Numerically higher but not significant
	GI-related events	15 (14.3%)	23 (21.9%)	p=0.18; RR=1.53	Mild, self-limiting symptoms
	Severe AEs (Grade≥3)	0 (0.0%)	0 (0.0%)	—	Excellent safety profile both groups
	Treatment discontinuation	1 (1.0%)	2 (1.9%)	p=0.56; RR=2.00	Minimal impact on completion
Treatment adherence					
	Mean adherence (%)	93.8±6.1	92.5±7.4	p=0.20	Excellent compliance both groups
	High adherence (≥90%)	91 (86.7%)	88 (83.8%)	p=0.56; RR=0.97	Majority maintained compliance
	Study completion	104 (99.0%)	103 (98.1%)	p=0.56; RR=0.99	Outstanding retention rates
	Polypharmacy tolerance	23/23 (100%)	24/24 (100%)	—	Well-tolerated in complex regimens
Economic analysis (2024 INR)					
	Monthly medication cost	₹450.00	₹750.00	Δ=₹300	Modest incremental cost
	Annual treatment cost	₹5,400.00	₹9,000.00	Δ=₹3,600	Affordable for middle-class populations
	Cost per 1% HbA1c reduction	₹900.00	₹750.00	Δ=−₹150	Superior cost-effectiveness Group 2
	Cost per 10 mg/dL FBS reduction	₹296.00	₹251.00	Δ=−₹45	Better value proposition synbiotic group
	ICER per 0.6% additional HbA1c	—	₹600.00	95% CI: ₹450-800	Well within WHO-CHOICE thresholds
Budget impact analysis					
	% of median household income	0.8%	1.3%	Δ=0.5%	Accessible to urban middle class
	Break-even point (months)	—	8.4	—	Cost offset by reduced complications
	Willingness-to-pay threshold	Met	Met	—	Both regimens cost-effective

ES=Effect size (Cohen's d); RR=Relative risk; ICER=Incremental cost-effectiveness ratio; WHO-CHOICE=World Health Organization choosing interventions that are cost-effective. All costs in Indian Rupees (₹) based on 2024 generic pricing

these findings, revealing that gut microbiota modulation influences SCFA production, bile acid metabolism, and inflammatory pathways central to insulin signaling [29,30].

Contemporary evidence context and comparative analysis

Our findings align favorably with recent high-quality investigations examining synbiotic interventions in diabetes management. Table 6 summarizes key contemporary studies that provide context for our results.

This comparative analysis reveals significant heterogeneity in intervention responses, with synbiotic formulations consistently demonstrating superior efficacy compared to probiotic monotherapy. The neutral results from Cuthill *et al.* and Peng *et al.* underscore the importance of multispecies formulations with prebiotic components to optimize beneficial microbial activity.

Recent mechanistic investigations provide compelling support for our clinical findings. Liu *et al.* (2025) demonstrated that gut microbiota-derived metabolites, including SCFAs, bile acids, and lipopolysaccharides, directly modulate insulin signaling pathways and inflammatory cascades. The consistent efficacy we observed across demographic subgroups, particularly the enhanced response in participants ≥70 years, aligns with age-related alterations in gut microbiota diversity and immune function that may render elderly individuals more responsive to microbiota restoration [41,42].

Vildagliptin's intrinsic effects on gut microbiota composition, recently elucidated through metagenomic analysis, may contribute to the synergistic benefits we observed. The DPP-4 inhibitor enhances beneficial bacteria such as *Bacteroidetes* and *Akkermansia* species while improving insulin resistance markers. Our synbiotic formulation likely amplifies these effects through direct probiotic supplementation and prebiotic support for indigenous beneficial bacteria [43,44].

The favorable safety profile observed throughout this investigation corroborates contemporary systematic reviews demonstrating minimal adverse effects of synbiotic interventions in diabetic populations. The transient gastrointestinal symptoms in the synbiotic group (27.6% vs. 21.0%) represent typical adaptation responses without clinical significance. Importantly, the absence of severe adverse events, hypoglycemic episodes, or treatment-related hospitalizations

Table 6: Recent clinical trials of probiotic/synbiotic interventions in type 2 diabetes (2024–2025) [31-40]

Study (Year, Journal)	Population (n), setting	Design and duration	Intervention versus comparator	Primary glycemic outcomes	Other key findings	Safety profile
Zhang *et al.*, 2025, Clinical Nutrition	T2DM adults (n=120), China	RCT, double-blind, 12 weeks	Synbiotic (MN-Group+GOS) versus probiotic alone versus placebo	Synbiotic reduced FBG more than probiotic and placebo; HbA1c and HOMA-IR favoredsynbiotic	Increased SCFA-producing taxa; improved GI hormones and bile acids	Well tolerated; no major AEs
Peng *et al.*, 2024, Frontiers in Endocrinology	T2DM adults (n=213), China	RCT, double-blind, 16 weeks	Probiotic beverage (*Lactobacillus*≥10^8 CFU/mL) versus placebo	No between-group benefit on HbA1c or FBG	No significant lipid or weight effects	AEs comparable to placebo
Chaithanya *et al.*, 2024, Life	T2DM adults (n=130), India	RCT, 24 weeks	Multistrain probiotic capsules versus placebo	Within-group HbA1c reduction (p=0.004); HDL-C improved	Lipid profile improvements in probiotic arm	No serious AEs
Li *et al.*, 2024, AllergolImmunopathol	Newly diagnosed T2DM (n=84), China	RCT, 3 months	Probiotic versus metformin versus lifestyle control	Probiotic outperformed metformin for HbA1c, FPG; improved HOMA-IR	Reduced inflammatory markers; favorable microbiome shifts	No significant safety signals
Zalzala *et al.*, 2024, BMC Nutrition	T2DM on OADs (n≈66), Iraq	Double-blind RCT, 12 weeks	Symbiotic supplement versus placebo	Improved FBS and prevented HbA1c worsening versus placebo	Better BMI, waist circumference, HDL-C	No major AEs
Yarahmadi *et al.*, 2024, J Educ Health Promot	T2DM with periodontal disease (n=60), Iran	Double-blind RCT, 12 weeks	Synbiotic versus placebo adjunct to periodontal therapy	Greater FBS/HbA1c reductions with synbiotic adjunct	Reduced IL-6; improved periodontal indices	Well tolerated
Cuthill *et al.*, 2025, Clin Nutr ESPEN	T2DM adults (n=130), Canada	Double-blind RCT, 12 weeks	Probiotic 100B CFU/day versus placebo	No difference in HbA1c, glucose, insulin versus placebo	No lipid/inflammation benefits	GI AEs similar (~39% vs. 46%)
Zolghadrpour *et al.*, 2024, Nutrition & Diabetes	Adults with MetS (n=44), Iran	RCT, 12 weeks	Synbiotic yogurt versus regular yogurt	Lower FBG and HOMA-IR versus control	Reduced insulin, blood pressure, WHR	No safety concerns
Martínez-López *et al.*, 2024, Scientific Reports	Prediabetes (n=167), Mexico	Part of RCT (PRELLIM), 12 months	Linagliptin/Metformin versus Metformin+lifestyle	Both regimens improved insulin sensitivity/β-cell function	Increased SCFA-producing genera	Standard antihyperglycemic safety
Hosseini *et al.*, 2024, Food Science and Nutrition	Adults with MetS (n=58), Iran	Double-blind RCT, 8 weeks	Synbiotic (*Bacillus* species+FOS) versus placebo	Improved glycemic indices within-group	Reduced inflammatory biomarkers	No major AEs

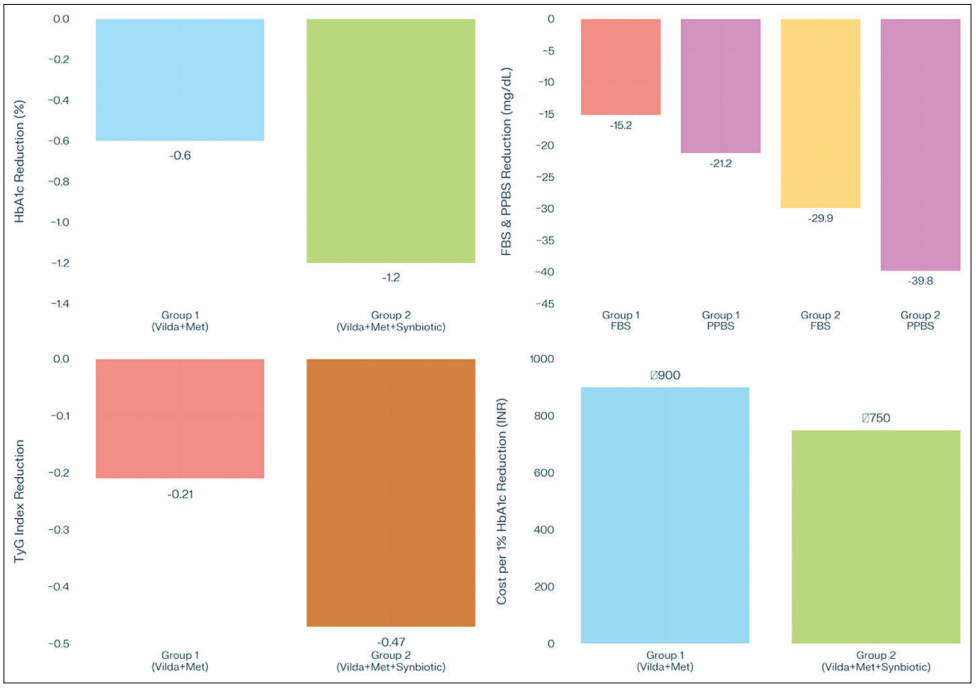

Fig. 4: Integrated clinical and economic evaluation dashboard

establishes the safety of this combination approach in elderly patients with complex medical conditions [45-49].

The exceptional adherence rates (93.1% overall) and study completion rates (98.6%) demonstrate real-world feasibility, even among participants with polypharmacy (22% taking ≥5 medications). This finding proves particularly relevant for healthcare systems managing elderly diabetic patients with multiple comorbidities.

Our comprehensive economic analysis reveals a compelling value proposition despite higher absolute medication costs (Table 5). The synbiotic group achieved superior cost-effectiveness with ₹750/1% HbA1c reduction compared to ₹900 in the control group. The incremental cost-effectiveness ratio of ₹600/0.6% additional HbA1c reduction falls well within WHO-CHOICE recommendations for middle-income countries and established Indian healthcare thresholds [50,51].

This economic advantage likely reflects broader metabolic improvements that extend beyond glucose control, including enhanced insulin sensitivity and reduced inflammatory burden, potentially translating to decreased long-term complications and reduced healthcare utilization. The intervention's accessibility to urban middle-class populations (1.3% of median household income) supports scalable implementation strategies within existing healthcare infrastructure [52,53].

These findings support integrating synbiotic supplementation into standard diabetes care protocols for elderly patients with suboptimal glycemic control despite conventional dual therapy. The intervention addresses multiple therapeutic challenges: Enhancing glucose control while maintaining safety, supporting treatment adherence through simplified dosing, and providing economic value within resource-constrained systems [54-56].

For clinical practice, synbiotic therapy should be considered when elderly T2DM patients remain inadequately controlled (HbA1c >7.0%) despite stable vildagliptin-metformin therapy, particularly those with evidence of insulin resistance or metabolic syndrome components [57].

Study limitations and methodological considerations

Several limitations warrant acknowledgment. The open-label design introduces potential observation bias, though objective primary endpoints and systematic safety monitoring minimize this concern. The 12-week follow-up period, while adequate for assessing glycemic changes, may not capture long-term sustainability or potential adaptation effects. The single-center design limits generalizability, though the diverse urban Indian population provides relevant insights for similar healthcare settings.

Patient exclusion criteria, including severe comorbidities and insulin requirements, limit applicability to advanced disease stages. The absence of microbiome sequencing restricts mechanistic insights into specific bacterial changes underlying observed metabolic improvements. In addition, the study population's relatively stable baseline characteristics may limit generalizability to more heterogeneous clinical populations.

Future research directions and clinical development

Several research priorities emerge from these findings. Multicenter trials with extended follow-up periods are essential to establish long-term efficacy and optimal treatment duration. Mechanistic studies incorporating comprehensive microbiome analysis, metabolomics profiling, and inflammatory biomarker assessment would elucidate pathways mediating synbiotic benefits.

Comparative effectiveness research examining different synbiotic formulations, dosing strategies, and combination approaches could optimize therapeutic protocols. Investigation of synbiotic therapy combined with newer antidiabetic agents, particularly SGLT2 inhibitors and GLP-1 receptor agonists, may reveal additional synergistic opportunities for comprehensive diabetes management.

CONCLUSION

This investigation establishes adjunct synbiotic therapy as a clinically effective, safe, and economically rational enhancement to standard vildagliptin-metformin treatment in elderly Indian patients with T2DM. The substantial improvements in glycemic control, insulin sensitivity, and cost-effectiveness, combined with excellent tolerability and adherence, support integration of this gut-targeted approach into routine diabetes care protocols. These findings contribute to the evolving evidence base supporting microbiome-targeted interventions as valuable additions to conventional diabetes pharmacotherapy, particularly relevant for resource-conscious healthcare environments serving vulnerable elderly populations with complex therapeutic needs.

ETHICAL APPROVAL

Approved by the Institutional Ethics Committee, SRM Medical College Hospital and Research Centre (IEC No. 8732/IEC/2023); written informed consent obtained from all participants.

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NONE

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY

De-identified data are available from the corresponding author on reasonable request and ethics approval.

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