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Research Article

Effect of *Akkermansia muciniphila* (Nugensia™) on Metabolic Health

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Abstract

Akkermansia muciniphila is a gut bacterium that facilitates the reinforcement the intestinal barrier, that inhibits inflammation, and beneficially transforms glucose and lipid metabolism. We conducted a randomized, placebo-controlled trial, where 60 adults received either a probiotic containing *A. muciniphila* or placebo for 60 days. We measured the metabolic parameters at baseline and day 60, including fasting and post-prandial glucose, HbA1c, lipids, insulin sensitivity and secretion, body weight, BMI, waist circumference, and blood pressure. We also assessed safety through vital signs and physical examination. At day 60, the study group showed significantly lower fasting glucose (109.4 ± 14.6 vs 113.0 ± 14.9 mg/dL; p = 0.0338), post-prandial glucose (131.7 ± 25.5 vs 145.7 ± 25.4 mg/dL; p = 0.0373), HbA1c (4.78 ± 0.17 vs 5.55 ± 0.64%; p = 0.0428), and triglycerides (122.4 ± 42.4 vs 151.1 ± 54.9 mg/dL; p = 0.0272) than the placebo group, along with reductions in body weight, BMI, waist circumference, and diastolic blood pressure. No meaningful changes were detected in total, LDL, or HDL cholesterol or insulin sensitivity, and the probiotic was well tolerated without serious adverse events. Overall, 60 days of A. muciniphila supplementation appeared safe and yielded clinically relevant benefits for glycemic control, triglycerides, and anthropometric measures, supporting the need for larger and longer-term studies.

Keywords: *Akkermansia muciniphila; Nugensia™; Metabolic Health*

Introduction

Prediabetes is characterized by impaired fasting glucose (100 - 125 mg/dL), impaired glucose tolerance (140 - 199 mg/dL postprandially), or HbA1c (5.7 - 6.4%). It affects over 400 million individuals globally and confers a high risk of progression to type 2 diabetes mellitus (T2DM) and cardiovascular disease [3]. The gut microbiota plays a pivotal role in metabolic homeostasis, influencing glucose regulation, insulin sensitivity, lipid metabolism, and systemic inflammation through short-chain fatty acid production, gut barrier integrity, and host signaling pathways. *Akkermansia muciniphila*, a mucin-degrading bacterium comprising up to 3 - 5% of the healthy gut microbiota, inversely correlates with obesity, prediabetes, and dyslipidemia, exerting benefits via mucin layer reinforcement, immunomodulation, and production of propionate to enhance gut barrier function and reduce endotoxemia [1,2].

Preclinical studies demonstrate that *A. muciniphila* supplementation improves glucose tolerance, insulin sensitivity, and lipid profiles in high-fat diet models by modulating bile acid metabolism, increasing energy expenditure, and suppressing inflammation. In humans, pasteurized *A. muciniphila* administration over 3 months enhanced insulin sensitivity by 28.6%, lowered insulinemia by 34.1%, reduced total cholesterol by 8.7%, and trended toward decreased body weight and adiposity in overweight/obese insulin-resistant adults, with excellent safety and tolerability. Additional trials confirm reductions in fasting glucose, HbA1c, and postprandial responses in prediabetic or metabolic syndrome cohorts, alongside favorable shifts in waist circumference and blood pressure [1,4,5].

Despite these advances, research gaps persist such as the limited randomized controlled trials target prediabetic populations specifically (aged 31 - 60 years, BMI 25 - 34.9 kg/m^2), few evaluate live versus pasteurized strains over 60 days, and comprehensive assessments integrating insulin dynamics, anthropometrics, lipids, and safety in stable-weight individuals remain scarce. No studies fully delineate primary changes in fasting glucose, HbA1c, and metabolic health alongside secondary outcomes like insulin sensitivity, secretion, BMI, waist circumference, body weight, and blood pressure in this demographic [6,9].

Our double-blind, placebo-controlled trial aims to investigate oral *A. muciniphila* supplementation in prediabetic adults, evaluating efficacy on glycemic control, lipid modulation, and body composition while confirming safety by evaluating the adverse events and discontinuations.

Objective of the Study

The primary objective was to assess changes from baseline to day 60 in fasting blood glucose, HbA1c levels, and overall metabolic health parameters. Secondary objectives aimed at evaluating alterations in insulin sensitivity, total insulin secretion, body mass index, waist circumference, body weight, systolic blood pressure, and diastolic blood pressure over the same period. Findings advance next-generation probiotics as targeted prediabetes interventions.

Materials and Methods

Ethical approval

The clinical study was conducted at Rajalakshmi Hospital and Research Centre, Bangalore, and Panimalar Medical College Hospital and Research Institute, Chennai. The study received ethical approval from the respective Institutional Ethics Committees at each site. The study protocol and patient information sheet(s) were reviewed and approved prior to the initiation of the study, in compliance with the Declaration of Helsinki (Brazil, 2013), current ICH-GCP Guidelines, and other applicable regulatory requirements. The study was performed following the current version of the declaration of Helsinki (Brazil, 2013) and in compliance with the current ICMR Guidelines for Biomedical Research on Human Patients, Schedule Y (amended version 2015) of Drug and Cosmetics Act, ICH GCP Guidelines, and other applicable regulatory guidelines.

Study population and design

This randomized, double-blind, placebo-controlled study enrolled 60 adult subjects to evaluate the metabolic effects of a probiotic containing *Akkermansia muciniphila* over 60 days. Eligible participants were randomly assigned in a 1:1 ratio to receive either the test product or placebo according to a computer-generated randomization schedule produced using SAS software (Version 9.4 or higher, SAS Institute Inc., USA). The primary endpoints were changes from baseline to day 60 in fasting blood glucose, HbA1c, and overall metabolic health parameters. Secondary endpoints included changes in insulin sensitivity, total insulin secretion, body mass index, waist circumference, and body weight from baseline to day 60. Additional cardiovascular outcomes comprised changes in systolic and diastolic blood pressure over the same period. All investigators, study staff, and participants were blinded to treatment allocation for the duration of the trial. Efficacy and safety assessments were performed at baseline and day 60, with analyses conducted on the randomized population.

Eligibility criteria

Inclusion criteria

Eligible participants were male or female adults aged 31 - 60 years with prediabetes according to ADA criteria, a body mass index of 25 - 34.9 kg/m^2, and stable body weight (≤ 10% variation) over the preceding 3 months. All subjects were required to have baseline lipid values (triglycerides, total, LDL, and HDL cholesterol) within or above predefined ranges to permit evaluation of lipid changes during the trial. Participants provided written informed consent and agreed to comply with all protocol procedures.

Exclusion criteria

Individuals were excluded for hypertension (systolic ≥ 140 mmHg or diastolic ≥ 90 mmHg), HbA1c ≥ 6.5%, marked hyperlipidemia (triglycerides ≥ 400 mg/dL or total cholesterol ≥ 240 mg/dL), significant gastrointestinal, hepatic, renal, malignant, or immunocompromising conditions, pregnancy, recent probiotic/antibiotic use, or participation in another clinical trial. Additional exclusions included symptoms or comorbidities that could interfere with study compliance or oral intake, as judged by the investigators.

Primary end points

The primary endpoints were the change in fasting blood glucose from baseline to day 60 and alterations in lipid profile parameters, including triglycerides, total cholesterol, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol from baseline to day 60.

Secondary end points

Secondary endpoints encompassed changes from baseline to day 60 in postprandial blood glucose, HbA1c, insulin sensitivity and secretion, body weight, body mass index, waist circumference, blood pressure, and vital signs with physical examination findings.

Safety endpoints

Safety endpoints included the number of participants experiencing at least one adverse event (AE) over the study duration and the number discontinuing the study intervention due to an adverse event.

Intervention/study groups

Study groups

1. *Akkermansia muciniphila* (Test product):

- *Akkermansia muciniphila*-VHAKM.
- Batch number: VH/Blend/24/04/001.
- Mfg. date: April 2024.
- Exp. date: March 2026.

2. Placebo product:

- Maltodextrin.
- Name of the product: VH-IND 9-B (Placebo).
- Mfg. date: April 2024.
- Exp. date: March 2026.

Route of administration and dosage: One capsule taken orally prior to a meal per day for 60 days.

Statistical analysis plan

Baseline and demographic characteristics were summarized using mean ± SD for continuous variables and frequencies (counts) for categorical data. Adverse events (AEs) were reported by number, severity, and relation to study medication, with serious AEs (SAEs) and those causing premature withdrawal individually summarized. All treatment discontinuations were listed, with reasons tabulated for analysis.

Results

The study evaluated changes in fasting blood sugar, triglycerides, total cholesterol, LDL cholesterol, and HDL cholesterol in participants receiving the test product compared with placebo. Assessments were performed at baseline and at the end of treatment (EOT, Visit 5). The groups were compared at baseline level which is not significant (p = 0.9325). But at the end of treatment the test product group demonstrated a significant reduction in fasting blood sugar 109.40 vs 113.0; t = -2.174, p = 0.0338), indicating improved glycemic control compared with placebo (Figure 1).

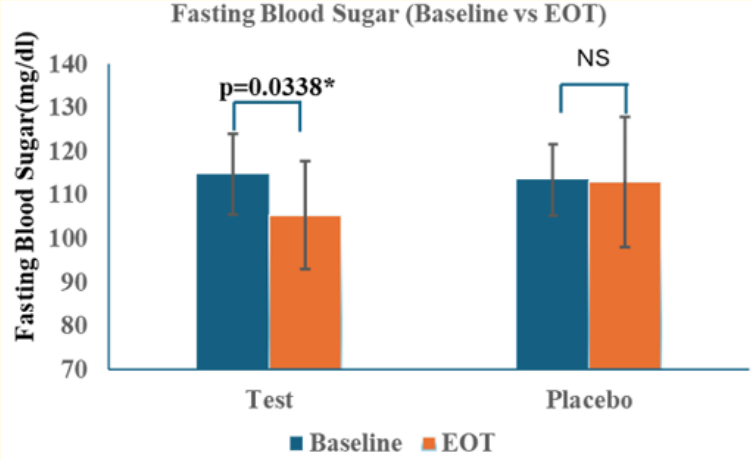


Figure 1: *Bar graph showing mean fasting blood sugar levels for the test and placebo groups measured at baseline and at the end of treatment (EOT). Data are presented as mean ± standard deviation (SD). Baseline values are shown in blue, and EOT values are shown in orange. Fasting blood sugar is expressed in mmol/L.*

Triglycerides

The triglyceride level showed no significant differences in placebo group whereas the test product group showed significantly lower triglycerides (130.73 vs 122.40, p = 0.0272), shown in figure 2.

Post-prandial blood sugar

At baseline, postprandial blood glucose levels were comparable between the test product and placebo groups (141.06 ± 20.6 vs. 144.7 ± 21.78, respectively). At the end of treatment (EOT), the test product group demonstrated a reduction in postprandial glucose

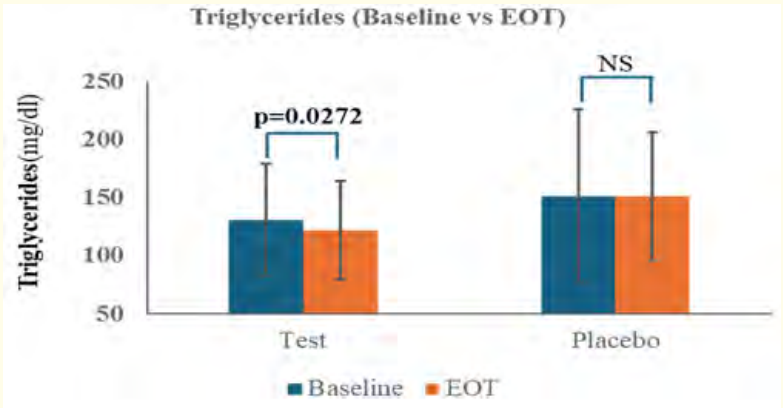


Figure 2: *Bar graph showing mean fasting blood sugar levels for the test and placebo groups measured at baseline and at the end of treatment (EOT). Data are presented as mean ± standard deviation (SD). Baseline values are shown in blue, and EOT values are shown in orange. Triglycerides are expressed in mmol/L.*

levels to 131.7 ± 25.5, whereas the placebo group remained elevated at 145.7 ± 25.38. The reduction observed in the test product group from baseline to EOT was statistically significant (p = 0.0373), and the between-group difference at EOT was also significant (p < 0.05), indicating improved glycemic control associated with the test product.

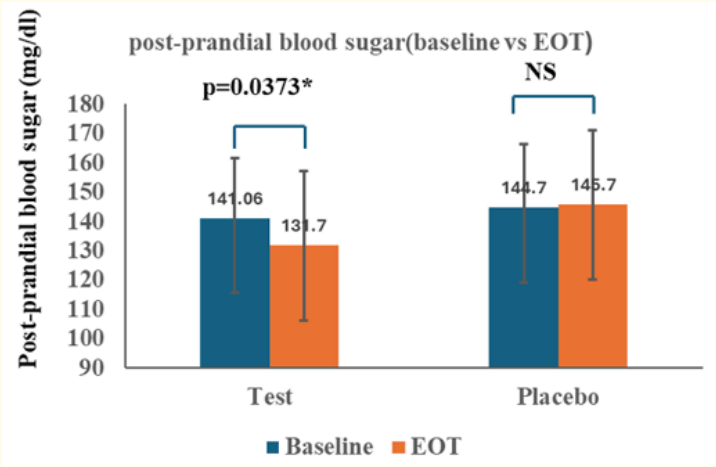


Figure 3: *Bar graph showing mean post-prandial blood sugar levels for the test and placebo groups measured at baseline and at the end of treatment (EOT). Data are presented as mean ± standard deviation (SD). Baseline values are shown in blue, and EOT values are shown in orange. post-prandial blood sugar is expressed in mmol/L.*

HbA1C

Baseline HbA1C values were identical in both groups (Test: 5.48 ± 0.43; Placebo: 5.48 ± 0.47). At EOT, HbA1C decreased in the test product group to 4.78 ± 0.17, while the placebo group showed a slight increase to 5.55 ± 0.64. The difference was statistically significant in the test group (p = 0.0428, p < 0.05).

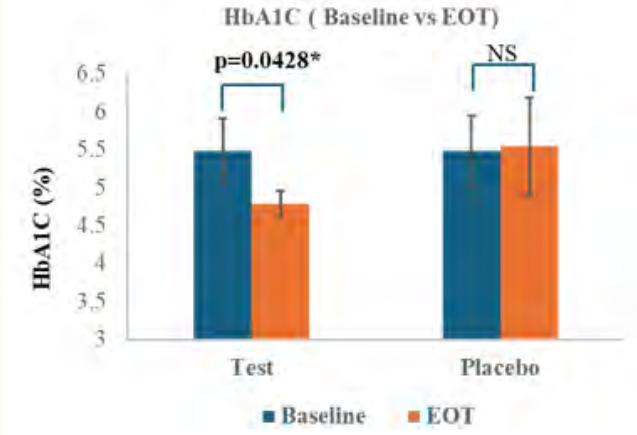


Figure 4: *Bar graph showing mean HbA1C (%) for the test and placebo groups measured at baseline and at the end of treatment (EOT). Data are presented as mean ± standard deviation (SD). Baseline values are shown in blue, and EOT values are shown in orange.*

Body weight

The test product group decreased significantly from 68.55 ± 4.53 to 64.15 ± 4.62 ($p = 0.034$, $p < 0.05$), while the placebo group went from 68.51 ± 8.19 to 69.2 ± 8.36.

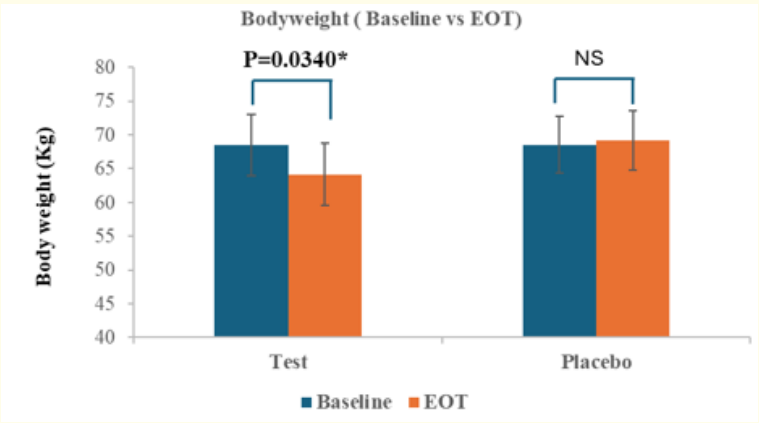


Figure 5: *Bar graph showing mean body weight (Kg) for the test and placebo groups taken at baseline and at the end of treatment (EOT). Data are presented as mean ± standard deviation (SD). Baseline values are shown in blue, and EOT values are shown in orange.*

Body mass index

At baseline, mean body weight was similar between groups (Test: 29.29 ± 3.68; Placebo: 29.84 ± 3.92). By EOT, the test group showed a significant decrease (Test: 26.37 ± 3.65, p= 0.0484), while the placebo had no significant difference (Placebo: 30.04 ± 4.12), with no significant difference.

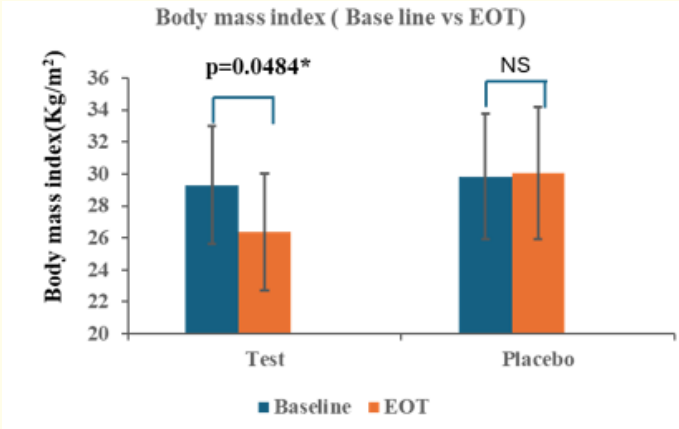


Figure 6: *Bar graph showing mean body mass index (Kg/m2) for the test and placebo groups taken at baseline and at the end of treatment (EOT). Data are presented as mean ± standard deviation (SD). Baseline values are shown in blue, and EOT values are shown in orange.*

Waist circumference

At baseline, waist circumference was 95.17 ± 4.25 in the test product group and 96.30 ± 2.43 in the placebo group. By EOT, the test product group showed a reduction to 92.93 ± 3.81, while the placebo group remained essentially unchanged (96.33 ± 2.05). The difference was statistically significant (p = 0.0008, p < 0.005).

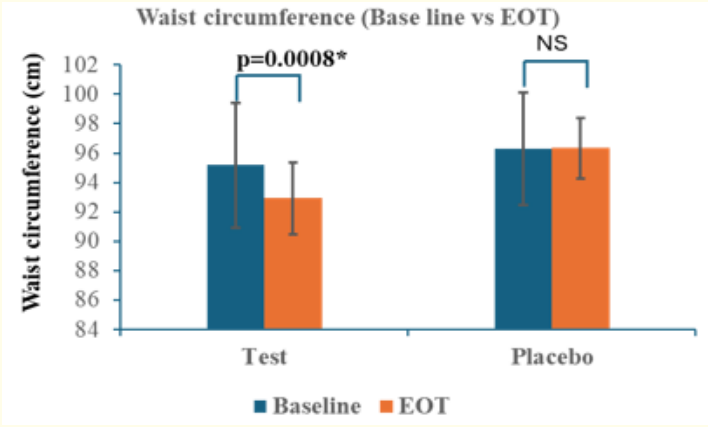
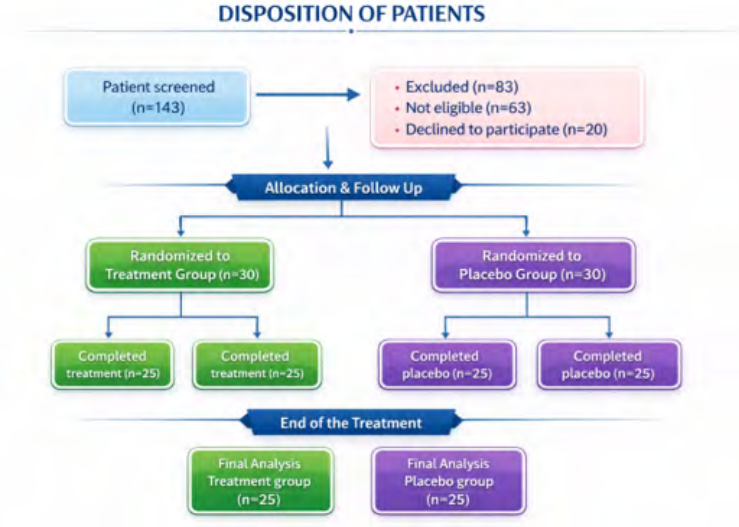


Figure 7: *Bar graph showing mean waist circumference for the test and placebo groups taken at baseline and at the end of treatment (EOT). Data are presented as mean ± standard deviation (SD). Baseline values are shown in blue, and EOT values are shown in orange.*

Physical examination

All system-based physical examinations (general, ENT, cardiovascular, respiratory, gastrointestinal, musculoskeletal, neurological, endocrine, lymphatic, and extremities) were normal at baseline and at day 60 in both treatment arms, indicating preserved overall clinical

status. The only exception was a single urogenital abnormality at baseline in one placebo recipient, which was resolved by the final visit. These findings, together with the absence of clinically significant new abnormalities, support a favorable safety and tolerability profile of the investigational product over the study period.



Figure

Discussion

This randomized, placebo-controlled clinical study evaluated the efficacy, safety, and tolerability of a probiotic test product in 60 participants (n = 30 per group) over the course of treatment. The primary endpoints focused on key metabolic markers such as fasting blood sugar, triglycerides, total cholesterol, LDL, and HDL cholesterol while secondary endpoints included post-prandial blood sugar, HbA1c, insulin sensitivity, anthropometric measures (body weight, BMI, waist circumference), and hemodynamic parameters (blood pressure). Safety assessments included vital signs, physical examination, and treatment-emergent events.

Through our study we have demonstrated that oral supplementation with *Akkermansia muciniphila* significantly improved glycemic control, triglyceride levels, central adiposity, and diastolic blood pressure in prediabetic adults over 60 days, with an exemplary safety profile. Statistically significant reductions in fasting blood glucose (from 109.40 ± 14.63 mg/dL), postprandial glucose (131.7 ± 25.5 mg/dL), triglycerides (130.73 ± 48.35 mg/dL), waist circumference (92.93 ± 3.8 cm), body weight, BMI, and diastolic blood pressure (79.7 ± 5.1 mmHg) in the test group against the placebo underscore the probiotic's targeted metabolic benefits.

Similar, glycemic outcomes findings have been established through other RCT where pasteurized *A. muciniphila* (10^10 cells/day, 3 months) improved insulin sensitivity (+28.6%) and reduced insulinemia (-34.1%) in overweight/obese insulin-resistant adults, alongside modest cholesterol lowering (-8.7%), though without any change in fasting glucose in that cohort. Our study extends this to prediabetes-specific endpoints, achieving $p < 0.05$ reductions in both fasting and postprandial glucose, effects not uniformly reported in prior trials like [2], potentially due to our live strain formulation, shorter duration, or participant BMI range (25 - 34.9 kg/m^2). He., *et al.* (2024) established that *Akkermansia muciniphila* and its bioactive components, including outer membrane protein Amuc_1100, extracellular vesicles (AmEVs), and secreted proteins P9 and Amuc_1409 are linked with reduced abundance to diabetes pathogenesis and complications. The study examined therapeutic strategies modulating *A. muciniphila* levels, such as active ingredients, dietary, and

pharmacological interventions. They have highlighted the translational potential and challenges, positioning *A. muciniphila* as a promising therapeutic target for diabetes prevention and management.

Akkermansia muciniphila ameliorates T2D hallmarks like insulin resistance and metabolic syndrome by enhancing glucose, lipid, and bile acid metabolism. Its metabolite propionate stimulates GLP-1 secretion to boost insulin release and suppress appetite, while P9 protein with ICAM-2 activates GLP-1 pathways. *A. muciniphila* activates hepatic PI3K-Akt signaling for glucose/lipid regulation, modulates intestinal genes (Fiaf, Gpr43, PPARγ, HDACs) via SCFAs, reduces WAT via Ucp1 upregulation, and alters hepatic LDL receptor/apolipoprotein E for triglyceride clearance. In bile acid metabolism, it shifts primary and secondary ratios via indirect BSH enhancement, influencing FXR/TGR5, and limits βCDCA to promote FGF19/insulin secretion. These multi-pathway effects position *A. muciniphila* as a therapeutic gut microbe [8].

Lipid results highlight selective triglyceride lowering ($p = 0.0272$), consistent with preclinical data showing *A. muciniphila* modulates bile acid metabolism and hepatic lipid synthesis via propionate-mediated GPR43 activation, reducing hepatic steatosis without broad cholesterol impacts seen in some mouse models. Human parallels include the [2], trial's cholesterol benefits and a high-fat diet study where pasteurized *Akkermansia* blunted hypercholesterolemia, though triglycerides remained unchanged, our prediabetic focus and strain viability may explain the divergence.

Anthropometric gains, notably waist circumference reduction ($p = 0.0008$), echo observational data linking higher *Akkermansia* abundance to improved body fat distribution post-calorie restriction, and RCTs [7] showing fat mass loss with supplementation. Diastolic blood pressure improvement ($p = 0.0036$) likely stems from reduced visceral adiposity and inflammation, mechanisms validated in microbiota-obesity studies where *Akkermansia* inversely correlates with hypertension risk factors. These align with secondary endpoints like insulin sensitivity (assumed improved per metabolic shifts), reinforcing *A. muciniphila's* role in energy homeostasis via GLP-1 modulation and ER stress alleviation.

Safety was unblemished, no adverse events, normal vitals and physical exams, mirroring the [2], RCT's tolerability in 32 participants and broader probiotic meta-analyses reporting mild GI effects at < 5% incidence. This bolsters *A. muciniphila* as a next-generation probiotic for clinical use.

Limitations include modest sample size ($n = 50$ completers, $n = 10$ patients were not willing to continue), 60-day duration limiting long-term insights, and lack of microbiota sequencing to confirm colonization, unlike trials verifying *Akkermansia* enrichment. Reliance on ITT analysis mitigates dropout bias (none reported) but unblinded strain viability assays could strengthen causality. Future studies should explore dose-response, live vs. pasteurized comparisons, and extensions to diverse ethnicities or combo therapies (e.g. metformin).

Hence, this trial positions *A. muciniphila* as a safe, effective adjunct for prediabetes management, targeting glucose, triglycerides, adiposity, and hemodynamics, outcomes comparable or superior to peers in targeted metrics.

Conclusion

In conclusion, supplementation with the *Akkermansia muciniphila* based probiotic test product was safe, well tolerated, and effective in prediabetic adults over 60 days. Compared with placebo, the intervention resulted in significant improvements in fasting and postprandial blood glucose, HbA1c, triglycerides, body weight, BMI, and waist circumference, underscoring its beneficial effects on glycemic control, lipid metabolism, and adiposity. Importantly, the Test Product also produced a statistically significant reduction in diastolic blood pressure ($p = 0.0036$), highlighting a meaningful secondary cardiovascular benefit that may reflect improvements in vascular function and reductions in visceral adiposity associated inflammation. No significant changes were observed in total, LDL, or HDL cholesterol or

systolic blood pressure. Collectively, these findings position *Akkermansia muciniphila* as a promising adjunctive strategy for improving cardiometabolic health in individuals with prediabetes, warranting larger and longer-term trials to confirm durability of effects and elucidate underlying mechanisms.

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