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A microbiome-targeting fibre-enriched nutritional formula is well tolerated and improves quality of life and haemoglobin A1c in type 2 diabetes: A double-blind, randomized, placebo-controlled trial

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Abstract

Aims: To investigate a prebiotic fibre-enriched nutritional formula on health-related quality of life and metabolic control in type 2 diabetes.

Materials and Methods: This was a 12-week, double-blind, placebo-controlled study with an unblinded dietary advice only comparator arm. Participants were randomized 2:1:1 to a prebiotic fibre-enriched nutritional formula (Active), a placebo fibre-absent nutritional formula (Placebo), or non-blinded dietary advice alone (Diet). Primary endpoint was change in core Type 2 Diabetes Distress Assessment System (cT2-DDAS) at week 12. Glycated haemoglobin (HbA1c) change was a key secondary endpoint.

Results: In total, 192 participants were randomized. Mean age was 54.3 years, HbA1c 7.8%, and body mass index 35.9 kg/m^2. At week 12, cT2-DDAS reduced significantly in Active versus Placebo (−0.4, $p = .03$), and HbA1c was reduced significantly in Active vs Placebo (−0.64%, $p = .01$). Gut microbiome sequencing revealed that the relative abundance of two species of butyrate-producing bacteria (*Roseburia faecis* and *Anaerostipes hadrus*) increased significantly in Active vs. Placebo.

Conclusions: A microbiome-targeting nutritional formula significantly improved cT2-DDAS and HbA1c, suggesting the potential for prebiotic fibre as a complement to lifestyle and/or pharmaceutical interventions for managing type 2 diabetes.

KEYWORDS
dietary intervention, randomized trial, type 2 diabetes, weight control

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1 | INTRODUCTION

The prevalence of type 2 diabetes (T2D) within the United States is estimated to range from 12% to 14%[1] costing the health care system over 300 billion dollars annually.[2] T2D disproportionately affects underserved and minority communities impacting 18.7% of African Americans, 16.1% of American Indians/Alaskan Natives, 11.8% of Hispanic/Latino Americans and 8.4% of Asian Americans/Native Hawaiians/Other Pacific Islanders ≥20 years of age.[3,4]

Health-related quality of life (HRQoL) in subjects with diabetes is an important measure of health that has been associated with improved self-care and metabolic outcomes.[5] A number of different validated assessment tools have been developed and used to evaluate HRQoL for both drug and dietary interventions in T2D.[6-8]

Despite decades of public health messaging about metabolically healthy diets, as well as new breakthrough incretin-based therapies for glycaemic control and weight loss, complementary approaches to traditional dietary guidance and pharmaceuticals may be necessary to help curb the ever-rising prevalence and related health care costs of metabolic diseases.

Epidemiological studies showed that there is a significant dietary fibre gap with only 5% of the population consuming their recommended fibre amount; and a correlation between low-fibre consumption and incidence of metabolic diseases.[9,10] Interventional studies support the benefit of high-fibre foods working through microbiome-dependent and independent mechanisms, to prevent and manage metabolic diseases.[11-13] Fibre supplements including but not limited to inulin, psyllium, oat beta glucan (OBG) and resistant starch (RS) have also been shown to improve glycaemic control and glycated haemoglobin (HbA1c).[14-17]

Dietary fibres such as OBG and RS have been shown to help manage postprandial hyperglycaemia in the upper intestine by blocking glucose transport (e.g. sodium–glucose cotransporter 1 and glucose transporter 2) and modulating duodenal K-cell-derived glucose-dependent insulinotropic polypeptide (GIP).[18,19] Butyrate as the end product of fibre processed by primary (*Bifidobacterium* ssp. and *Ruminococcus bromii*) and secondary degraders (*Clostridia* clusters IV and XIVa species) of the microbiome in the lower intestine is also believed to impact blood glucose through increased glucagon-like peptide 1 secretion from L-cells as well as systemic effects on mitochondrial genesis through epigenetic regulation by histone deacetylase inhibitors.[20-22]

Rationally designed fibre-based supplements and foods that are enjoyable and convenient may provide a well-tolerated and synergistic complement to lifestyle and pharmaceutical interventions, improving well-being and metabolic control in persons with T2D. This study fills a gap in the literature and is the first to our knowledge to evaluate a microbiome-targeting rationally designed fibre-enriched formula on cT2-DDAS in individuals with diabetes and overweight or obesity.

2 | MATERIALS AND METHODS

2.1 | Study design

This was a 12-week, double-blind, placebo-controlled trial with an unblinded dietary advice only comparator arm. It randomized individuals 2:1:1 to a fibre-enriched nutritional formula (Active), a fibre-absent, iso-caloric, iso-protein nutritional formula (Placebo) or dietary advice alone (Diet). The Active intervention contained a rationally designed blend of RS and OBG (Supplement, Formulation). This was a digital health-powered decentralized clinical trial with enrolment representing US geographic, ethnic and racial diversity.[23] The study communication was virtual and administered across the United States by a decentralized team.

The study protocol was approved by an independent ethics committee and conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. All subjects provided written informed consent before participation. The study was registered with ClinicalTrials.gov (NCT05110703).

2.2 | Study subjects and intervention

Eligible subjects had self-reported T2D for at least 90 days, self-reported HbA1c 7.5-10.5%, self-reported body mass index 27-50 kg/m^2, and were treated with diet and exercise alone or with a stable dose of antidiabetic medication (Supplement, Eligibility). Nutritional formulas were escalated over the course of 3 weeks to a maximally tolerated dose of two shake packets, with at least one replacing a meal, and continued for the duration of the study (Supplement, Formula Escalation). All subjects received general dietary recommendations including the CDC Living With Diabetes online resource (Supplement, Dietary Guidelines). Participants continued all baseline diabetes therapies throughout the study.

2.3 | Primary and secondary endpoints

After inclusion was determined by self-report, clinical measures including labs and anthropometrics were obtained at baseline and week 12 by Quest Labs. The primary endpoint was the change from baseline to week 12 in the core Type 2 Diabetes Distress Assessment System (cT2-DDAS), a validated measure of diabetes distress.[24] Key secondary endpoints included change from baseline to week 12 in HbA1c, fasting plasma glucose (FPG), body weight, systolic blood pressure and diastolic blood pressure. Other secondary endpoints included additional measures of HRQoL: World Health Organization Five Well-being Index (WHO-5),[25] Gastrointestinal Symptom Rating Scale (GSRS),[26] and an unvalidated Review of Systems Scale (ROSS) developed for this study to assess a spectrum of systemic health concerns (Supplement, HRQoL). Dietary fibre consumption was measured at baseline and endline using NutritionQuest's Fruit/Vegetable/Fibre Screener. A subset of participants underwent 14 days of continuous

glucose monitoring (CGM; Active, 16; Placebo, 12; Diet, 8; FreeStyle Libre Pro; Abbott Diabetes Care, Alameda, CA, USA) before randomization and during the final 2 weeks of the study.

Anthropometric measures were measured and fasting blood for clinical labs was drawn by a CLIA certified facility. Blood for short chain fatty acid analysis was drawn by a home phlebotomist 30-60 min postprandially, placed on a gel ice, and shipped overnight to a lab for processing and storage.

2.4 | Microbiome sequencing

Stool was collected using OMNIgene®•GUT stool collection kits (DNA Genotek, Kanata, ON, Canada). For metagenomic sequencing, nucleic acid extraction was carried out as per previously published protocols.[27] In brief, samples were purified using the MagMAX Microbiome Ultra Nucleic Acid Isolation Kit (Thermo Fisher Scientific, Waltham, MA, USA) and automated on KingFisher Flex robots (Thermo Fisher Scientific). Extraction controls and polymerase chain reaction controls were also prepared.

Metagenomic libraries were prepared using KAPA HyperPlus kits (Roche Diagnostics, Indianapolis, IN, USA) following manufacturer's instructions, and automated on EpMotion automated liquid handlers (Eppendorf, Hamburg, Germany). Sequencing was performed on the Illumina NovaSeq 6000 sequencing platform with paired-end 150 bp cycles.

Raw metagenomic reads were processed and filtered using the BBtools suite. The tools 'clumpify', 'bbduk' and 'bbmap' were used to mark exact duplicate reads, trim adapters and low-quality reads, and remove reads mapping to the human genome. Forward and reverse reads were merged using 'bbmerge' with the recommended settings.[28]

Processed reads were analysed using MetaPhlAn3 and HUMAnN3 from the BioBakery suite using default settings.[29] The list of primary and secondary RS degraders were based on Baxter et al.[30] Carbohydrate active enzyme (CAZyme) analysis was performed using dbCAN (v2.0.11).[31,32] Genes were called from merged reads using FragGeneScan.[33] Gene annotations were performed using both diamond and hotpep.[34,35] Total read counts per CAZyme were normalized based on reads per million for each CAZyme subfamily to account for variable sequencing depth. CAZyme analysis was restricted to glycoside hydrolases and polysaccharide lyases.

Microbiome alpha diversity was quantified as the Shannon diversity using the 'diversity' function from the 'vegan' package in R (version 2.6.2).[36] Beta diversity was calculated using the 'cmdscale' function from the 'stats' package in R (version 4.1.2) using the Bray-Curtis distance on arcsine transformation of species relative abundance. The adonis function (method = 'bray', permutations = 1000) in the 'vegan' package in R was used to determine if participant ID or treatment group explained a significant portion of variance.

For differential enrichment analysis, we focused on known primary and secondary degraders of RS.[30] The relative abundance of each species was determined by MetaPhlAn3. We then specified a linear model for each species using MaAsLin2.[37] We specified the centred log-ratio of relative abundance as the dependent variable, the treatment group and timepoint as fixed effects, the interaction between treatment group and time as an additional fixed effect, and participant ID as a random effect. Statistical analysis was restricted to participants who had metagenomic and metabolomic samples for both baseline and end timepoints. For metabolomic analysis of both stool and serum, we specified the same model as for the metagenomics analysis, except using log normalization of peak height as the dependent variable instead of the centred log-ratio of relative abundance.

2.5 | Short-chain fatty acid analysis

The OMNImet®•GUT collection kits produce a liquid supernatant from homogenized stool, which was used for sample preparation below. Plasma and stool samples underwent a liquid-liquid extraction using chilled (−20°C) acidified acetonitrile (0.1% HCl) containing internal standards at relevant biological concentrations (d3-acetate, d7-butyrate, d5-propionate). For the derivatization of short chain fatty acids, sample supernatant was combined with borate buffer, Pentafluorobenzyl bromide prepared in acetonitrile, and hexane. GC-MS was performed using an Agilent 7890B GC system coupled to an Agilent 5977B MSD operated in negative chemical ionization mode with methane as the reagent gas. A 5%-phenyl-methylpolysiloxane lined column (Agilent HP-5MS 30 m × 0.250 mm × 0.25 μM) (Agilent Technologies, Santa Clara, CA, USA) was used for the duration of the analysis. All compounds were chromatographically resolved, including known isomers. The MS was operated in scan mode with a mass range of 50-600 m/z, with a solvent delay of 4.2 min and electron multiplier voltage of 1500 V. Scan speed was 3125 μ/s [N = 1] with a frequency of 5.1 scans/s, cycle time of 197.35 ms and step size of 0.1 m/z. For GC-MS data, raw data were processed using Agilent MS quantitative analysis software (version 10.2) with the Agile2 automated integrator. All peaks were manually reviewed before peak heights were exported for further review.

2.6 | Statistical methods

Changes in clinical measures over 12 weeks were calculated by subtracting baseline values from endpoint values. Difference in change among treatment groups was tested with ANOVA and pairwise t-tests in the statistical programs, R and Prism. For comparison of changes in GIP and HbA1c, values were normalized by dividing endpoint by baseline and correlation was evaluated with linear regression in R.

Sample size was determined via a difference in differences model. Assuming a difference in the mean cT2-DDAS change at 12 weeks based on a Cohen's D-value of 0.67 (which reflects a medium effect size in this metric, that is, two-thirds of a standard deviation), with 80% power (and a two-sided 2.5% significance level to allow for multiple comparisons with the Active group) and a 10% dropout rate, 73 participants in the Active arm and 37 participants in the other two arms were required.

The efficacy data analysis was performed on the intent-to-treat population, including all subjects randomized regardless of study

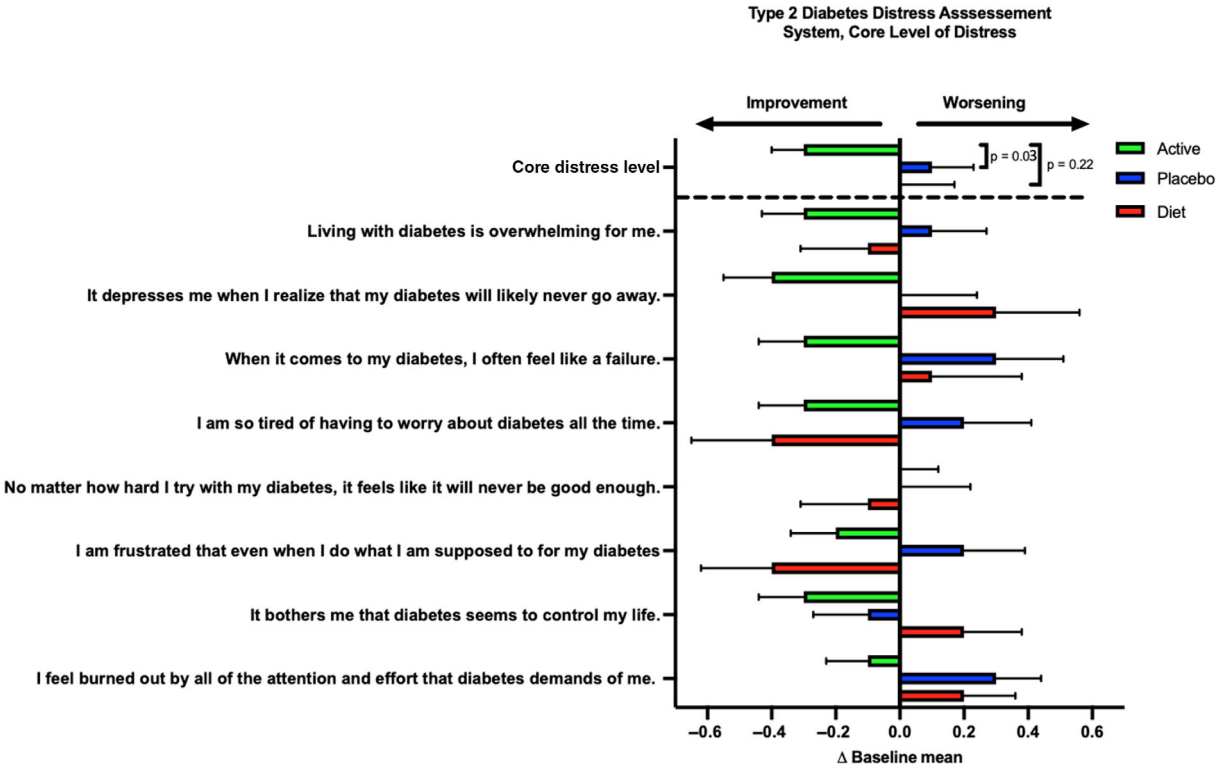

FIGURE 1 Change from baseline at week 12 in the core type 2 diabetes distress assessment system for the Active (green), Placebo (blue) and Diet (red) study arms. Standard errors and *p*-values are shown. A positive mean change from baseline >0.25 (5% improvement) in the core distress level is considered clinically meaningful

completion. A repeated measures linear model was used that allowed for incomplete results from dropouts. Secondary endpoints such as HbA1c were evaluated similarly. Chi-squared analyses were used for categorical data.

3 | RESULTS

The study was conducted between 20 October 2021 and 16 May 2022. Overall, 192 participants were randomized (Active, 95; Placebo, 48; Diet, 49) with additional subjects beyond sample size calculations enrolled to account for higher than anticipated dropout rate (Active, 19%; Placebo, 28%; Diet, 27%).

Demographics and clinical characteristics were not statistically different across arms. Overall mean ± SD age 54.3 ± 9.7 years, duration of diabetes 8.6 ± 6.1 years, HbA1c 7.80 ± 1.62% (62 ± 13 mmol/mol), FPG 160 ± 64 mg/dl (8.89 ± 3.56 mmol/L), body weight 104.6 ± 19.5 kg and body mass index 35.9 ± 5.8 kg/m^2. The majority of participants were female (62.0%); 62.5% were white, 19.3% black, 3.6% other and 14.6% were Hispanic/Latino.

3.1 | Primary endpoint

The cT2-DDAS change from baseline was reduced significantly in Active versus Placebo arm at week 12 ($p = .03$) (Figure 1). In the Active arm, cT2-DDAS declined from a mean ± SD of 3.1 ± 0.9 at baseline to 2.8 ± 0.9 at week 12. The cT2-DDAS in the Placebo arm increased from 3.0 ± 1.0 to 3.1 ± 0.9 and the Diet arm remained unchanged from a baseline value of 3.1 ± 0.9. In the Active arm, there was improvement in seven of the eight cT2-DDAS questions (Figure 1).

3.2 | Secondary endpoints

At 12 weeks, the mean ± SD change from baseline in HbA1c was −0.36 ± 1.23%, +0.30 ± 1.49% and −0.17 ± 1.26% for Active, Placebo and Diet arms, respectively (Figure 2A). The mean difference between the change in HbA1c in the Active and Placebo arms was −0.66% ($p = .01$). In participants with a baseline HbA1c of ≥7.0%, the mean change in HbA1c at week 12 was −0.53 ± 1.49%, +0.04 ± 1.40% and +0.05 ± 1.66% for Active, Placebo and Diet arms, respectively. In the subset of participants with CGM results at baseline and study end (Active, 16; Placebo, 12; Diet, 8), the change from baseline in mean glucose (−12.7 ± 46.4, 4.7 ± 75.4, −3.1 ± 30.7 mg/dl), glucose management index (−0.28 ± 1.13, 0.14 ± 1.84, −0.09 ± 0.75%) and time-in-range 70-180 mg/dl (3.9-10.0 mmol) (5.2 ± 21.2, −1.0 ± 38.3, −6.5 ± 23.2%) were all consistent with HbA1c results, favouring the Active arm.

In the three study arms, FPG at week 12 did not change significantly from baseline and there was no difference in the change

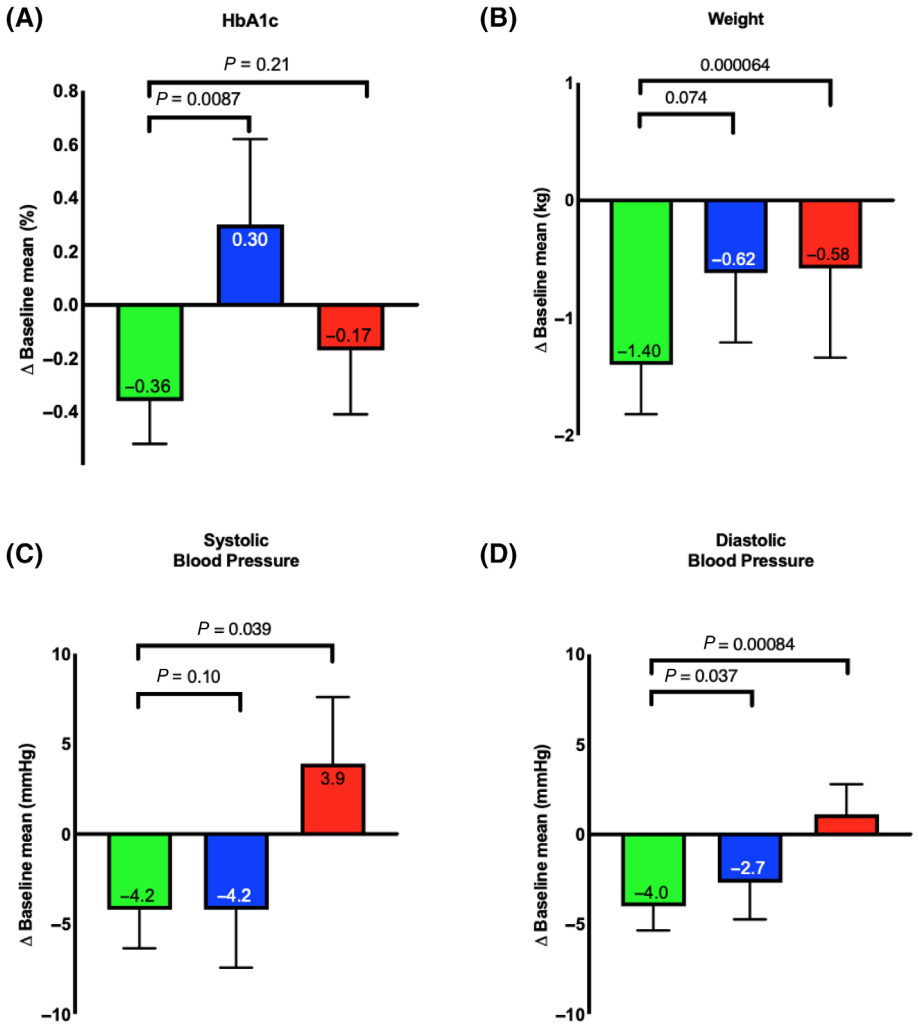

FIGURE 2 Change from baseline at week 12 in mean: A, HbA1c, B, body weight, C, systolic blood pressure and D, diastolic blood pressure, for the Active (green), Placebo (blue) and Diet (red) study arms. Standard errors and *p*-values are shown

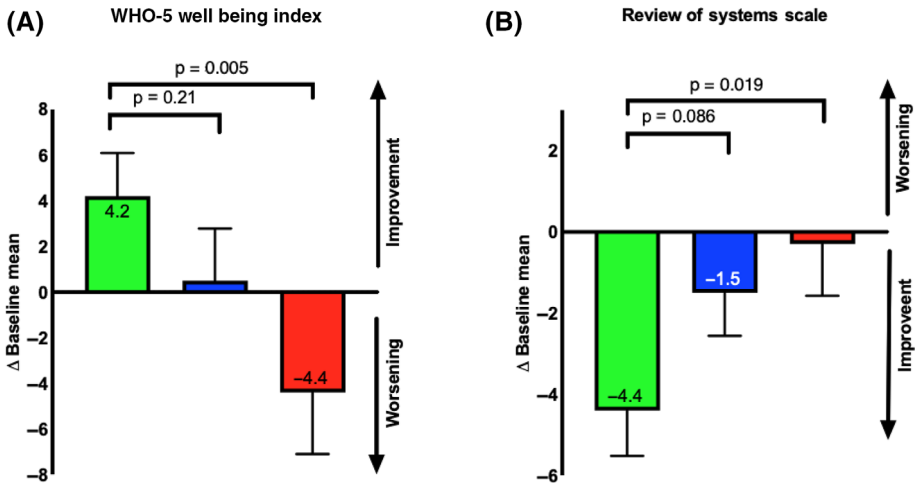

FIGURE 3 Change from baseline at week 12 in mean A, WHO-5 Well-being Index, B, review of systems scale and C, gastrointestinal rating scale, Placebo (blue) and Diet (red) study arms. Standard errors and *p*-values are shown

between arms. At week 12 the change in body weight from baseline was −1.36 ± 3.26 kg for Active arm, −0.64 ± 2.73 kg for Placebo arm and −0.54 ± 3.93 kg for Diet arm (Figure 2B). The Active arm showed significantly greater weight reduction compared with Diet arm ($p = .000006$). Other metabolic (systolic blood pressure and diastolic blood pressure) and HRQoL (WHO-5 and ROSS) measures improved significantly in Active arm relative to Diet arm (Figures 2C,D and 3A,B; Supplement, Results Details, Figures S1 and S2). There was no change from baseline in non-formula based dietary fibre consumption in any of the study arms (data not shown).

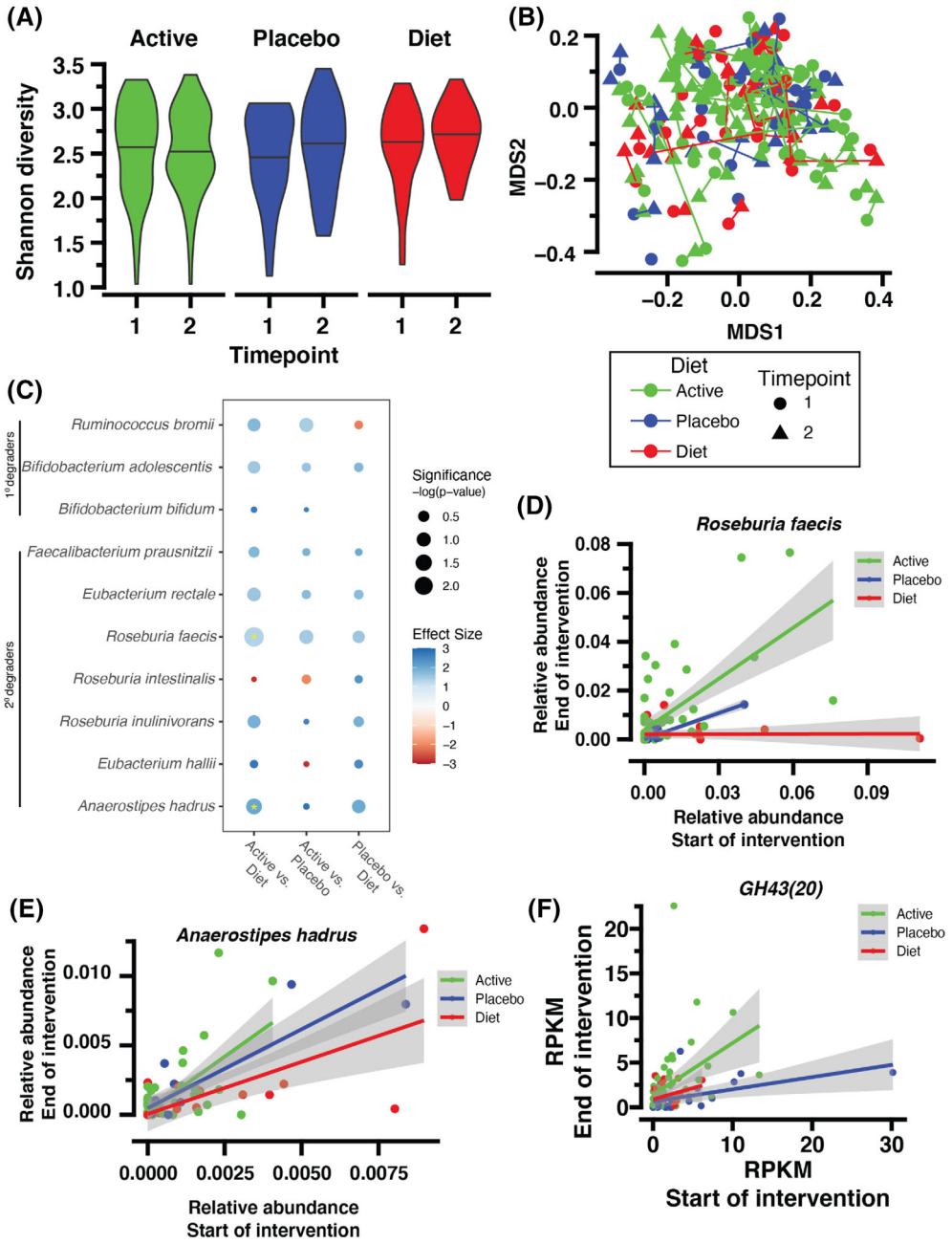

FIGURE 4 Gut microbiome analysis. A, Shannon diversity at each timepoint for each diet (timepoint 1 = week 0, timepoint 2 = week 12). B, Multidimensional scaling analysis for each timepoint and diet using the Bray-Curtis between each microbiome sample (relative abundances transformed with the arcsine transformation). Treatment arm explains a significant portion of microbiome variation ($R^2 = 0.012$, $p < .001$, Adonis test). C, Change in abundance from baseline to end of intervention for known primary and secondary resistant starch degraders. Colour scale indicates effect size of the interaction between timepoint and diet. Size of dot indicates significance of effect. *Roseburia faecis* and *Anaerostipes hadrus* had statistically significant interaction effects comparing the Active to Diet arms ($p = .0037$ and $p = .043$, respectively). D, Scatter plot showing the baseline and end of intervention relative abundances for *R. faecis* for each diet. E, Scatter plot showing the baseline and end of intervention relative abundances for *A. hadrus* for each diet. F, Scatter plot showing the baseline and end of intervention reads per kilobase-million (RPKM) for the glycoside hydrolase 43, subfamily 20, which showed a statistically significant interaction between timepoint and diet ($p < .00001$, linear mixed effects model)

3.3 | Microbiome results

No significant changes in alpha diversity were observed from baseline to end of intervention for any treatment group (Figure 4A). A small but significant portion of variance in beta diversity was observed in the Active arm relative to the control arms ($R^2 = .012$, $p < .001$, adonis test) (Figure 4B). RS primary degraders (*Roseburia bromii* and *Bifidobacterium* spp.) were found in 72% of subjects in the Active arm at baseline (compared with 83% in the Placebo arm and 80% in the Diet arm). The relative abundance of these primary degraders increased in the Active arm versus the Diet arm, albeit not significantly ($p = .16$ and $p = .19$ for *R. bromii* and *Bifidobacterium adolescentis*, respectively; linear mixed effects model) (Figure 4C). The relative abundance of butyrate-producing secondary degraders *Roseburia faecis* and *Anaerostipes hadrus* increased significantly from baseline to end of intervention in the Active arm relative to the Diet arm ($p = .0037$ and $p = .043$, respectively) (Figure 4D,E). Analysis of all species in the gut microbiota (beyond just primary and secondary degraders of RS) did not reveal any other species with significant changes in relative abundance. Functional analysis of microbial genes and pathways revealed a significant increase in the relative abundance of glycoside hydrolase 43 subfamily 20 in the Active arm ($p < .00001$, linear mixed effects model) (Figure 4F); no substrate specificity of this subfamily has been reported. We did detect this gene in the genomes of several secondary degraders, including *R. faecis*, meaning this gene may function as a marker for bacteria that are enriched in the Active arm. No significant

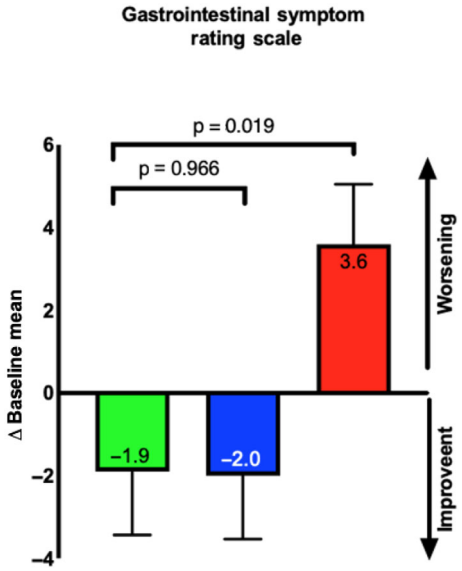

FIGURE 5 Change from baseline at week 12 in mean gastrointestinal rating scale. Placebo (blue) and Diet (red) study arms. Standard errors and *p*-values are shown

differences in short-chain fatty acids and organic acids were detected in stool or serum samples with mass spectrometry.

3.4 | Safety and tolerability

There were no severe or serious adverse events and no symptomatic hypoglycaemia reported. The Active and Placebo formulas were both well tolerated with improvement in GSRS seen in both study arms (Figure 5; Figure S3 in Appendix S1). No subjects discontinued because of gastrointestinal (GI) intolerance, and there was no statistical difference in discontinuation between the Active and Placebo arms. One participant in each of the Active and Placebo groups discontinued the study because of taste intolerance. Subjects consumed an average of 63% of the maximum recommended shakes in both the Active and the Placebo arms.

4 | DISCUSSION

In this randomized controlled trial, a microbiome-targeting fibre-enriched nutritional formula resulted in improved measures of HRQoL and metabolic health in persons with T2D. The microbiome of participants in the Active group showed significant increases relative to placebo in butyrate-producing species belonging to *Clostridium* clusters IV and XIVa.

The primary endpoint, cT2-DDAS change from baseline at week 12, improved significantly in Active vs. Placebo and Diet arms, exceeding the minimal clinically important difference of 0.25 recently reported by Fisher et al.[38] Importantly, seven of eight questions contributing to the Core Level improved in the Active group. Consistent with these findings, significant improvements in other HRQoL questionnaires (WHO-5, ROSS) were also seen in the Active arm relative to Diet arm. Mental parameters of sleep, energy and mood all contributed to improvement in ROSS (Supplement). Although assessment of mechanisms responsible for these were beyond the scope of the present trial, these improvements may have resulted from subjects' optimism around improved metabolic health metrics. In addition, model systems suggest that microbiome-derived metabolites, including short chain fatty acids and neurotransmitter precursors may regulate the gut-brain axis through GI (gut permeability, inflammation, vagal stimulation) and direct central nervous system effects (blood-brain barrier permeability, neuroinflammation and neuronal signalling) with impact on diverse neurocognitive outcomes including mood, energy and sleep.[39-41]

Consistent numeric improvements from baseline in metabolic health parameters, including HbA1c, CGM time in range, weight and blood pressure were also seen in the Active arm. The HbA1c reduction was probably because of improvement in postprandial glucose, as no change was seen in plasma fasting glucose. Given the modest reduction in body weight (<2%), it is probable that factors in addition to weight loss played a role in improving glycaemic control, suggesting other mechanisms. RS and OBG related-slowing of glucose absorption because of viscosity and/or a direct effect on glucose transport via sodium–glucose cotransporter 1 and glucose transporter 2 inhibition and GIP regulation in the small intestine are possible mechanisms.[18,19] Lastly, it is possible that the sugar substitutes in the shakes could have contributed to the blood glucose effects. Allulose may have contributed to the decrease in HbA1C in the Active arm,[42] while sucralose or maltodextrin may have contributed to the increase in HbA1C in the Placebo arm.[43]

Improvements in metabolic parameters are also thought to result from RS and OBG's impact on increased production of the microbiome-derived short chain fatty acid butyrate. Indeed, butyrate-producing bacteria that secondarily degrade RS and OBG (*Roseburia faecalis* and *A. hadrus*) were shown to be significantly elevated. Despite this, we did not observe significant differences in butyrate levels in stool or serum (data not shown), which could be explained by colonic absorption of butyrate and metabolism by colon-resident cells (e.g. colonocytes). It is also possible that the preparation and shipping conditions were not sufficient to preserve butyrate levels. Butyrate directly regulates blood glucose systemically via histone deacetylase inhibitors, which has been shown to promote β-cell differentiation, proliferation, function and improve insulin resistance.[44,45] Butyrate also stimulates glucagon-like peptide-1 release from intestinal L-cells, enhancing insulin secretion, modulating gastric emptying and, via central mechanisms, reducing appetite.[46,47] Recent epidemiological and interventional trials have also suggested RS and butyrate reduce blood pressure via proposed anti-inflammatory and vagal nerve-mediated mechanisms.[48-50] Other differences in the Active and Placebo formulas (e.g. sweetener, fat content and micronutrient profile) may have also impacted outcomes.

The fibre-enriched nutritional formula was well tolerated and improved GSRS with decreased upper GI symptoms (heartburn,

burping, bloating and nausea) as well as lower symptoms (improved sensation of not emptying) as notable drivers of improvement (Supplement). This may be explained in part by regulation of incretin hormones and their impact on nausea.[51] Indeed it is intriguing to hypothesize that fermentable fibres such as the type 2 RS and OBG used in this study could be a complement to dual-agonist therapy in helping mitigate upper GI side effects. The improvement in GI symptoms might also partly be explained by the RS and OBG low FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides and polyols) designation with limited small intestine fermentability.[52] A handful of subjects experienced mild time-limited GI symptoms that were mitigated by pausing or slowing the dose escalation. There were no reported dropouts because of GI intolerance and dropout rate was lowest in the Active arm. Most subjects discontinued for 'personal reasons', including inability to comply with study procedures.

To our knowledge, this is the first double-blind, randomized controlled trial assessing a microbiome-targeted formula enriched for a blend of RS and OBG on HRQoL and metabolic outcomes in T2D. The decentralized trial design was an important strength, enabling geographical and racial diversity. Notably, almost 20% of participants were black. The decentralized trial design may also have been a limitation, as it probably contributed to the higher than anticipated dropout rate. The complexity of the biospecimen collection protocol may have also contributed to the dropout rate. Only one subject in each arm dropped out of the study because they did not tolerate the taste of the shake. Both arms had similar compliance, with one or more shakes consumed daily. In addition, the study was of relatively short duration and conducted during US Thanksgiving, Christmas and Hanukkah, potentially adversely impacting metabolic outcomes. The COVID-19 pandemic did not appear to impact outcomes. Given that inclusion criteria were self-reported, some participants had lower than anticipated HbA1c levels, but were still included in the intent-to-treat analysis. The study was not powered to assess differences in metabolic parameters.

In summary, the present study showed that a rationally designed fibre-enriched formula containing RS and OBG improved measures of HRQoL and metabolic health, suggesting that it may serve as a complement to lifestyle and/or pharmaceutical interventions for improving quality of life in people with T2D. Future studies powered for metabolic outcomes such as HbA1c will be necessary to confirm these findings.

AUTHOR CONTRIBUTIONS

CJD, JPF, MEW, MLL and R-HL contributed to study design. JPF provided study oversight as principal investigator. ERE, MMC and JLS performed statistical analysis of microbiome and incretin data. MLL performed statistical analysis. R-HL provided guidance on use of Active and Placebo nutritional formulas. LR provided compilation and analysis of continuous glucose monitoring data. CJD, JPF, MLL, ERE and MMC drafted the manuscript. CJD, JPF, MLL, MEW, ERE, MMC and JLS edited the manuscript. CJD is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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CONFLICT OF INTEREST

CJD, MEW, LR and R-HL are employees of Supergut. CJD consults for Evolve Biosystems, BCD Biosciences and Reference Capital. MLL consults for Supergut. JPF receives research support from Akero, AstraZeneca, Boehringer Ingelheim, BMS, 89bio, Eli Lilly, Intercept, IONIS, Janssen, Madrigal, Metacrine, Merck, NorthSea Therapeutics, Novartis, Novo Nordisk, Oramed, Pfizer, Poxel, Sanofi and Supergut; is a consultant for Akero, Altimmune, Axcella Health, Becton Dickinson, Boehringer Ingelheim, Carmot Therapeutics, Echosens, 89bio, Eli Lilly, Gilead, Intercept, LifeScan, Metacrine, Merck, Novo Nordisk, Pfizer, Sanofi and Supergut; is on speakers' bureaus for Eli Lilly and Sanofi.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/dom.14967.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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