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Original Article

The Need for Fiber Addition in Symptomatic Heart Failure (FEAST-HF): A Randomized Controlled Pilot Trial

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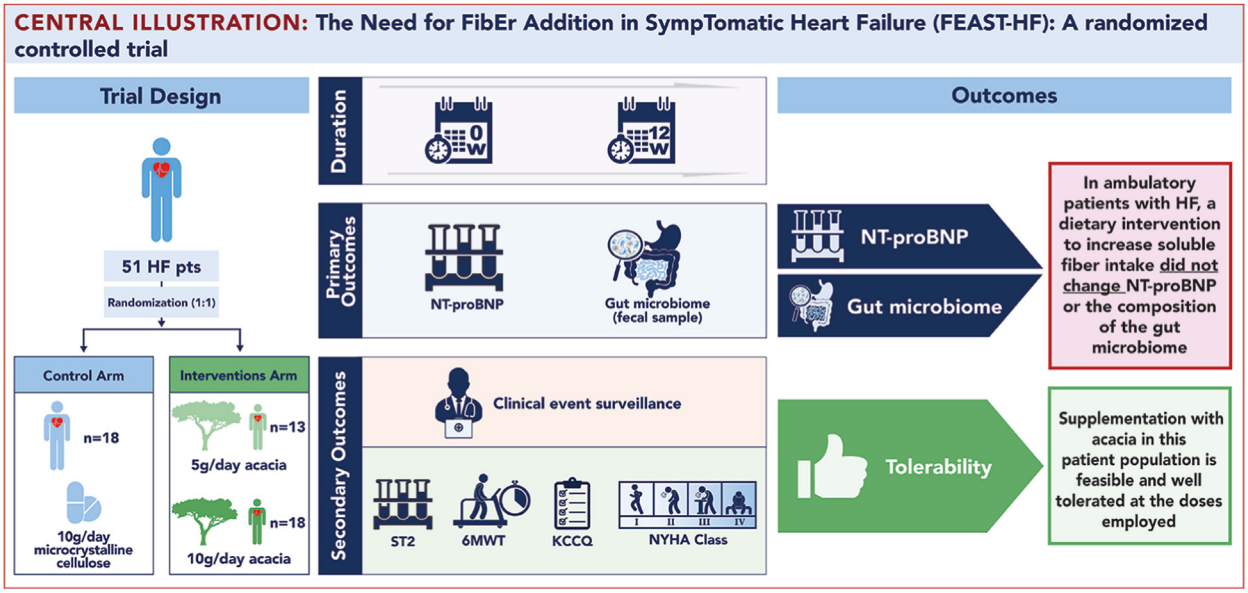

ABSTRACT

Background: Preclinical and observational studies suggest that the gut microbiome plays a role in the pathogenesis of heart failure (HF); the gut microbiome may be modified by fermentable dietary fibre (FDF). The Need for Fiber Addition in Symptomatic Heart Failure (FEAST-HF) trial evaluated feasibility of recruitment and supplementation with FDF in HF and whether FDF (acacia), compared to control, reduced the level of N-terminal pro–b-type natriuretic peptide (NT-proBNP) and growth stimulation

RÉSUMÉ

Contexte : Des études précliniques et observationnelles donnent à penser que le microbiome intestinal joue un rôle dans la pathogenèse de l'insuffisance cardiaque (IC). Or, ce microbiome pourrait être modifié par la consommation de fibres alimentaires fermentescibles (FAF). L'essai pilote contrôlé avec répartition aléatoire FEAST-HF (pour *The Need for Fiber Addition in Symptomatic Heart Failure*) visait à évaluer la possibilité d'administrer un supplément de FAF (l'acacia) et à déterminer si celui-ci entraîne une réduction du taux du propeptide

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expressed gene 2 (ST2), and produced changes in the gut microbiome.

Methods: Participants were randomly allocated 1:1:1 to either of the intervention arms (5 g/d or 10 g/d acacia) or to the control arm (10 g/d microcrystalline cellulose (MCC; nonfermentable active control). Adherence and tolerance were assessed, and clinical events were monitored for safety. All outcomes (NT-proBNP, ST2, New York Heart Association class, Kansas City Cardiomyopathy Questionnaire scores, 6-minute walk test score, gut microbiome) were measured at baseline, and at 6 and 12 weeks.

Results: Between September 13, 2018 and December 16, 2021, 51 patients were randomly allocated to either MCC (n = 18), acacia 5 g daily (n = 13), or acacia 10 g daily (n = 18). No differences occurred between either dose of acacia and MCC in NT-proBNP level, ST2, New York Heart Association class, or questionnaire scores over 12 weeks. Dietary treatment arms had a negligible impact on microbial communities. No safety, tolerability, or adherence issues were observed.

Conclusions: Dietary supplementation with acacia gum was both safe and well tolerated in ambulatory patients with HF; however, it did not change NT-proBNP level, ST2, or the composition of the gut microbiome.

ClinicalTrials.gov: NCT03409926

natriurétique de type B N-terminal (NT-proBNP) et du récepteur ST2 (*growth stimulation expressed gene 2*) ou une modification du microbiome intestinal comparativement au placebo.

Méthodologie : Les participants ont été répartis de façon aléatoire selon un rapport 1:1:1 dans l'un des groupes d'intervention (recevant 5 g/jour ou 10 g/jour d'acacia) ou dans le groupe témoin (recevant 10 g/jour de cellulose microcristalline [CMC], une fibre de référence non fermentescible). La tolérance et l'observance du traitement ont été évaluées, et les événements cliniques ont été surveillés pour évaluer l'innocuité. Tous les indicateurs (NT-proBNP, ST2, classe d'IC selon l'échelle de la New York Heart Association, score au questionnaire de cardiomyopathie de Kansas City, score à un test de marche de 6 minutes et microbiome intestinal) ont été évalués au début de l'étude, à la semaine 6 et à la semaine 12.

Résultats : Entre le 13 septembre 2018 et le 16 décembre 2021, 51 patients ont pris, après répartition aléatoire, de la CMC (n = 18), 5 g d'acacia par jour (n = 13) ou 10 g d'acacia par jour (n = 18). Aucune différence n'a été observée quant au taux de NT-proBNP ou de ST2, à la classe d'IC selon la New York Heart Association ou aux scores au questionnaire entre les groupes prenant l'une ou l'autre des doses d'acacia et le groupe prenant la CMC au cours d'une période de 12 semaines. L'effet sur la flore microbienne était négligeable dans les groupes de traitement alimentaire. Par ailleurs, aucun problème lié à l'innocuité, à la tolérabilité ou à l'observance du traitement n'a été observé.

Conclusions : Les suppléments alimentaires d'acacia (gomme arabique) sont sûrs et bien tolérés; toutefois, ces suppléments n'ont pas entraîné de changement dans les taux de NT-proBNP ou de ST2, ni dans la composition du microbiome intestinal.

ClinicalTrials.gov : NCT03409926

Evidence-based care of patients with heart failure (HF) has evolved substantially and includes pharmacologic, device, self-care, and other aspects endorsed by guidelines and thought to improve clinical outcomes.[1,2] An increasing amount of evidence suggests that the gut microbiome plays a significant role in the pathogenesis of HF.[3] Gut-wall permeability is increased in HF, due to gut edema and hypoperfusion of the bowel, which increases the risk of translocation of bacteria, or bacterial products such as lipopolysaccharides and trimethylamine (TMA), through the gut epithelial barrier.[4,5] TMA is a microbial metabolite derived from dietary choline and carnitine that, after absorption, is transformed to TMA-N-oxide (TMAO). Recent studies of the microbiome in patients with HF have identified reductions in inter-individual microbiome diversity,[6] in short-chain fatty acid (SCFA)-producing genera,[6,7] and elevation of genes involved in lipopolysaccharide and TMAO synthesis.[7] Overgrowths of pathogenic genera in patients with HF, correlated with more-severe symptoms, also have been observed.[8]

Treatments that modify the composition and function of the microbiome in patients with HF are a promising target for novel therapies. In an animal model of HF, mice fed a high-fibre diet had decreased levels of gut dysbiosis, which correlated with decreased blood pressure, cardiac fibrosis, and left ventricular hypertrophy.[9] An additional animal model study assessing the effect of dietary fibre supplementation found that the microbiome was modulated by fibre supplementation, with increases in SCFA production, and a reduction in circulating TMAO levels demonstrating downstream effects on the host.[10] No adequately controlled studies have tested the impact of fermentable dietary fibre (FDF) in patients with HF.

The Need for **F**ib**e**r **A**ddition in **S**ymp**t**omatic **H**eart **F**ailure (FEAST-HF) trial was designed to evaluate the feasibility of recruitment and supplementation with FDF in patients with HF (assessing safety, tolerability, and adherence). Also, the trial was designed to pilot test the clinical effects of a dietary supplementation with FDF acacia gum through the following 2 study objectives: (i) primary—to investigate whether dietary supplementation reduces the level of the HF-related biomarkers N-terminal pro—b-type natriuretic peptide (NT-proBNP) and growth stimulation expressed gene 2 (ST2), compared to placebo, and to determine how the gut microbiome responds to dietary supplementation with acacia gum; and (ii) secondary—to evaluate the impact of dietary supplementation with acacia gum, compared to placebo, on health-related quality of life, New York Heart Association

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(NYHA) class, and exercise capacity, as well as clinical outcomes at 12 weeks.

Methods

Trial design and oversight

FEAST-HF was a pilot randomized double-blind trial. The trial design and operations were led by the Canadian VIGOUR Centre (CVC) at the University of Alberta (Edmonton, Canada). The full trial protocol was approved by the appropriate regulatory authorities, and by individual institutional review boards or ethics committees at the participating sites. The CVC conducted oversight of site monitoring, data management, and all analyses related to the trial. The first author had unrestricted access to the data and drafted the initial version of the manuscript, which was reviewed and edited by all the authors. All the authors confirm the accuracy and completeness of the data.

Participants

Eligible participants were at least 18 years of age, had chronic HF (NYHA class 2-3), and were on optimally tolerated medical therapy. The diagnosis of chronic HF was established by the primary treatment team, who had experience and expertise in HF. Participants were recruited from 3 heart function clinics in Alberta, Canada. All patients provided written informed consent. No ejection fraction or natriuretic peptide inclusion or exclusion criteria were applied. A full list of exclusion criteria is provided in Supplemental Appendix S1.

Randomization and masking

Participants were randomly allocated 1:1:1 to either of the intervention arms (5 g or 10 g per day of acacia gum) or the control arm. Randomization lists were generated by a statistician at the data-coordinating centre (CVC, Edmonton, Canada) using a standard random number generator. Randomization and data collection were done centrally in Research Electronic Data Capture (REDCap). Allocation was concealed using a secure web-based randomization system. Investigators, participants, treating clinicians, and outcome assessors were not aware of the assigned treatment strategy.

Procedures

After providing informed consent, patients were randomly allocated to 1 of the 3 following groups: (i) 10 g/d microcrystalline cellulose (MCC; nonfermentable active control); (ii) 5 g/d acacia gum; (iii) 10 g/d acacia gum. MCC (Microcel MC-12, Blanver Farmoquimica, Boca Raton, FL), which is a nonfermentable fibre and has little effect on the microbiome, tolerance, or health, was chosen as an active control. Acacia gum was obtained as Pre-Hydrated Gum Arabic Spray Dry Powder (TIC Gums, Inc., Belcamp, MD). The MCC and acacia gum are off-white odorless powders repackaged into identical packaging to maintain the masking, and they have similar texture and taste. Patients were instructed on methods for adding MCC/acacia gum to their diet (ie, dissolving in drinking water, sprinkling on and/or mixing into food and/or adding to recipes, such as for baked goods). No run-in period was used, nor was any specific fluid restriction or dietary supplementation recommended. After randomization, patients were followed every 3 weeks with either a phone or in-person visit for a total of 12 weeks.

Dietary intake was assessed using 3-day food records (including 1 weekend day) at baseline, 6, and 12 weeks in all groups. Food records were analyzed by trained personnel in a core lab, using a nutrient software program (ESHA Food Processor SQL version 10.11; ESHA Research, Salem, OR).

Clinical outcomes

All outcomes were measured at baseline, 6, and 12 weeks. The primary clinical outcome was the change in NT-proBNP over 12 weeks. Blood samples were collected by standard methods and were frozen at -20°C prior to analysis with the NT-proBNP assay (Roche Diagnostics, Mannheim, Germany), with total coefficients of variation of $< 3\%$. Secondary endpoints included the ST2 determined via the ELISA-based Presage ST2 Assay (Critical Diagnostics, San Diego, CA), with a coefficient of variation of 4.0%. Quality of life was measured via the Kansas City Cardiomyopathy Questionnaire (KCCQ[11]) as change in score from baseline to 6 and 12 weeks. A 6-minute walk test (6MWT) was performed at baseline and at 12 weeks and was assessed as change in score from baseline to 12 weeks. Stool collection occurred at baseline and at 12 weeks. The collecting process and microbiome analysis are outlined in Supplemental Appendix S1.

Safety, tolerability, and adherence

Clinical events (all-cause mortality, cardiovascular-related hospitalizations, and cardiovascular-related emergency department visits were monitored during follow-up for safety purposes. A clinical events committee adjudicated outcome events, based on data provided, blinded to group allocation, and using standardized definitions.

We used the following questions to assess tolerability to dietary supplementation: (Q1) Have you experienced any stomach aches and pains recently? If so how would you rate the severity?; (Q2) How would you rate the abdominal distension or bloating experienced over the past week?; and (Q3) Have you experienced any flatulence or gas recently? If so how often and to what extent? Answer options ranged from 1 = normal/no symptoms to 5 = severe. A mean score from the 3 questions was obtained.

Adherence was recorded during each study visit by asking the study participants how many days between visits they did not consume the dietary supplement. Also, participants were asked to report the overall product daily amount consumed each day. Additional recommendations to incorporate dietary supplementation into the daily food preparations were provided when needed.

Statistical analysis

As this was a pilot study, feasibility of recruitment and a supplementation with FDF were main outcomes; however, we estimated sample size for hypothesis testing for a relatively definitive trial. When the trial was initially designed, NT-proBNP and ST2 were co-primary endpoints, and the sample size was based on the detection of between-treatment group differences from baseline to 12 weeks. After logistical

and operational re-evaluation in light of the impact of the COVID-19 pandemic on recruitment and monitoring, the primary outcome was altered to NT-proBNP level alone. This modification occurred before the data were analyzed, after considering the impact of COVID-19 on ability to conduct the trial, and the difficulty in collecting blood samples for ST2 (at baseline and in follow-up). When designing the trial, we estimated a baseline NT-proBNP level (on log-scale) of 6.5 pg/mL and a log-transformed standard deviation of 1.42; we calculated that ~69 patients (23 per group) would be needed to be able to detect a 20% reduction in the primary outcome of NT-proBNP level by each of the intervention arms (2 and 3), compared to the control (MCC) arm, with a 2-sided alpha of 0.05, power = 0.80. Given that the 2 experimental arms were to be compared against a common control, a multiple-testing correction with the Bonferroni method was considered; that is, each pair comparison is tested at a significance level (α) = 0.025 to maintain an overall 2-sided significance level of 0.05. Further, assuming a 20% loss to follow-up or dropout rate, the trial planned to enroll 87 patients (29 patients per arm).

The primary endpoint was analyzed in the intention-to-treat population, including all randomized patients who had the NT-proBNP measured at both baseline and week 12. Data on NT-proBNP were log-transformed to normalize the distribution, and each experimental arm vs control arm comparison was performed using analysis of covariance. This method evaluated between-treatment-group (the 2 intervention arms vs the common control arm) differences in NT-proBNP level at 12 weeks, controlling for the respective baseline levels. Other patient characteristics, including sodium intake at baseline, were examined for their influence on the estimate of the study treatment effect using multivariable regression. A similar analysis of covariance approach was used to assess the change in ST2 level at 12 weeks. We analyzed changes in the scores on the KCCQ and the 6MWT using linear mixed-effects models consisting of the baseline score, treatment group, time (6 or 12 weeks), and the interaction effect as the fixed-effect component and a random-intercept component, to account for the correlation of within-patient scores. We estimated the mean changes from baseline at 6 and 12 weeks from the fitted model and tested whether the changes in each of the 2 intervention arms were different from those in the MCC control arm. NYHA class was analyzed via a proportional odds logistic regression for ordinal scores to determine whether the change over time in the intervention arms was significantly different, compared to that in the control arm. Missing data in the primary outcome of NT-proBNP level, and the other outcomes, including ST2, KCCQ scores, 6MWT score, and NYHA functional class were not imputed. Furthermore, changes in dietary-intake parameters that include sodium, energy, and fibre intake were evaluated and compared between groups using the linear mixed-effects model.

Very few clinical events were observed over the follow-up period, and no formal analysis using the proportional Cox regression model was performed. We present all patient characteristics as median (interquartile range [IQR]) for continuous variables, and as counts and proportions for categorical variables. All tests involving paired comparisons of the 2 interventions against the control were conducted at an alpha level of 0.025 to maintain an overall 2-sided level of 0.05. The analyses were performed with SAS software, version 9.4 (SAS Institute, Cary, NC).

Role of the funding source

The funders of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Participants

Between September 13, 2018, and December 16, 2021, a total of 51 patients were enrolled at 3 sites and were randomly allocated to either MCC (n = 18), acacia 5 g daily (n = 13), or acacia 10 g daily (n = 18); 2 patients were misrandomized and were excluded from further analyses (Supplemental Fig. S1). Baseline characteristics were balanced between groups (Table 1). The median age was 66 years (IQR: 61, 74), and 22.4% were women. With regard to HF-related factors, 79.6% had HF for > 1 year, 26.5% had a HF hospitalization in the prior 12 months, and they were well treated with current guideline-directed medical therapy (89.8% on renin-angiotensin-aldosterone system inhibitors, 93.9% on beta-blockers, and 63.3% on mineralocorticoid receptor antagonists). In the 45 patients with a natriuretic peptide measurement at randomization, the median NT-proBNP level was 438 pg/mL (IQR: 125, 1437).

Dietary intake

Overall, dietary intake at baseline was similar between groups, including energy, macronutrients, and micronutrients. Median dietary fibre intake was 15 g/d (IQR: 12, 26) for all groups, whereas sodium intake tended to be lower in the control group (Supplemental Table S1) with no significant differences between groups. Dietary intake did not change over the course of the study (data not shown).

Follow-up and trial outcomes

Of 49 patients, 35 and 30 patients had NT-proBNP and ST2 assessments at baseline and 12 weeks. None of the treatment groups showed a significant change over time as compared to the MCC group (Fig. 1, A and B). Results were similar after considering the effect of sodium intake at baseline (data not shown).

Overall, only 4 clinical events (n = 2 in the 10 g acacia gum group; n = 2 in the 5-g acacia gum group) had occurred at 12 weeks. Three of these events were emergency department visits, and 1 was a noncardiovascular event. Due to the low rate of events, no formal time-to-event analysis was conducted.

Health-related quality of life as measured by the KCCQ (Fig. 2, A-C) and NYHA class (Supplemental Fig. S2) remained the same between each intervention arm, compared to the control group, over time. The mean change in the

Table 1. Baseline patient characteristics

Characteristic	10-g group (n = 18)	5-g group (n = 13)	MCC group (n = 18)
Age, y	67 (64, 77)	62 (57, 65)	69 (61, 75)
Women	5 (27.8)	2 (15.4)	4 (22.2)
HF diagnosis ≥ 1 y	16 (88.9)	9 (69.2)	14 (77.8)
HF hospitalization in last 1 y	5 (27.8)	4 (30.8)	4 (22.2)
NYHA class			
I	4 (22.2)	5 (38.5)	1 (5.6)
II	13 (72.2)	7 (53.8)	16 (88.9)
III	1 (5.6)	1 (7.7)	1 (5.6)
KCCQ scores			
PLS	83 (58, 92)	83 (79, 94)	79 (71, 92)
CSS	83 (66, 90)	88 (77, 92)	80 (69, 94)
OSS	70 (57, 85)	79 (69, 92)	74 (69, 88)
Six-minute walking distance, m	388 (354, 463)	428 (378, 490)	400 (325, 455)
Medical history			
Hypertension	10 (55.6)	7 (53.8)	12 (66.7)
Coronary artery disease	6 (33.3)	6 (46.2)	8 (44.4)
Peripheral arterial disease	1 (5.6)	0 (0.0)	0 (0.0)
Cerebrovascular disease (ie, TIA or stroke)	2 (11.1)	0 (0.0)	1 (5.6)
Atrial fibrillation/flutter	7 (38.9)	4 (30.8)	7 (38.9)
Diabetes (type 1 or 2)	10 (55.6)	4 (30.8)	7 (38.9)
COPD	2 (11.1)	1 (7.7)	5 (27.8)
Dyslipidemia	11 (61.1)	7 (53.8)	10 (55.6)
Vital signs and physical findings			
BMI, kg/m^2	31 (28, 34)	33 (28, 35)	30 (26, 34)
Weight, kg	94 (82, 98)	95 (87, 111)	88 (83, 101)
Heart rate, bpm	68 (64, 74)	68 (64, 72)	63 (61, 69)
Systolic BP, mm Hg	114 (106, 134)	120 (109, 126)	111 (98, 125)
Diastolic BP, mm Hg	69 (64, 72)	76 (69, 81)	70 (61, 74)
Biomarkers			
NT-proBNP, pg/mL	484 (267, 2201)	419 (148, 962)	723 (117, 1664)
ST2, ng/mL	26 (21, 29)	29 (25, 36)	31 (23, 38)
Medical and device therapy			
Any RAAS inhibitor (ACEi/ARB/ARNI)	16 (88.9)	12 (92.3)	16 (88.9)
Beta-blocker	18 (100.0)	12 (92.3)	16 (88.9)
ACEi/ARB	10 (55.6)	7 (53.8)	7 (38.9)
ARNI	8 (44.4)	5 (38.5)	10 (55.6)
Mineralocorticoid receptor antagonist	10 (55.6)	10 (76.9)	11 (61.1)
Calcium-channel blocker	2 (11.1)	1 (7.7)	0 (0.0)
Anticoagulant	7 (38.9)	5 (38.5)	10 (55.6)
Antiplatelet	3 (17.6)	5 (38.5)	4 (22.2)
Statin	14 (77.8)	8 (61.5)	13 (72.2)
Other lipid-lowering medication	3 (16.7)	1 (7.7)	1 (5.6)
ICD	7 (38.9)	3 (23.1)	8 (44.4)
Pacemaker	4 (22.2)	0 (0.0)	2 (11.1)
CRT	1 (5.6)	1 (7.7)	5 (27.8)
Diuretic	8 (44.4)	7 (53.8)	11 (61.1)
Amiodarone	0 (0.0)	0 (0.0)	3 (16.7)
Digoxin	1 (5.6)	0 (0.0)	2 (11.1)
Sotalol	0 (0.0)	0 (0.0)	1 (5.6)
Dietary supplement use			
Omega-3	2 (11.1)	4 (30.8)	4 (22.2)
Calcium	3 (16.7)	0 (0.0)	4 (22.2)
Vitamin D	7 (38.9)	1 (7.7)	14 (77.8)
Multivitamin	4 (22.2)	2 (15.4)	5 (27.8)

Values are n (%) or median (interquartile range).

ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor blocker neprilysin inhibitor; BMI, body mass index; BP, blood pressure; bpm, beats per minute; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; CSS, clinical summary score; HF, heart failure; ICD, implantable cardioverter-defibrillator; KCCQ, Kansas City Cardiomyopathy Questionnaire; MCC, microcrystalline cellulose; NT-proBNP, N-terminal b-type natriuretic peptide; NYHA, New York Heart Association; OSS, overall summary score; PLS, physical limitation score; RAAS, renin-angiotensin-aldosterone system; ST2, growth stimulation expressed gene 2; TIA, transient ischemic attack.

6MWT score from baseline to 12 months was similar in the 5-g acacia gum group (-19.1 [95% CI, -58.4, 20.18], $P = 0.329$) and the 10-g acacia gum group (2.87 [95% CI, -31.9, 37.63], $P = 0.868$), compared to that in the MCC control arm. The changes in KCCQ and 6MWT were not influenced by baseline sodium-intake level (data not shown).

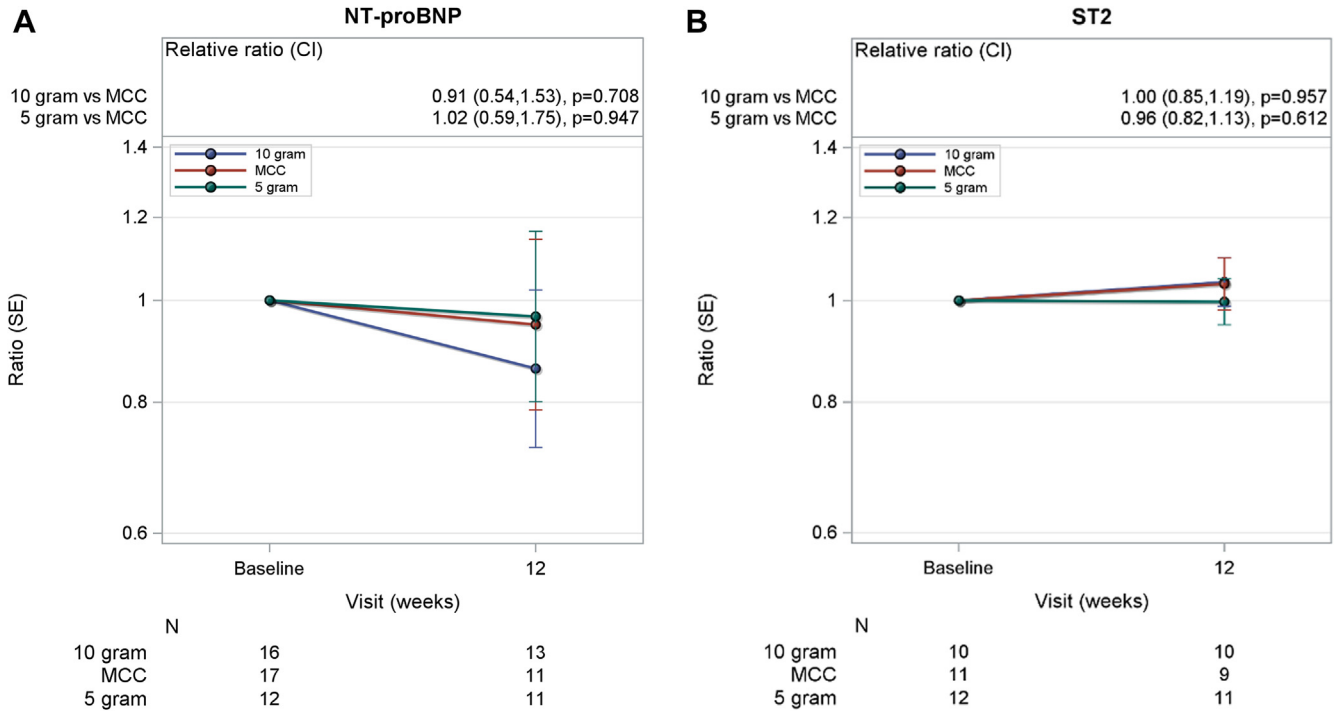

Figure 1. Primary and secondary outcomes. Relative changes at 12 weeks (baseline adjusted ratio [± standard error {SE}]) by treatment arm for (**A**) N-terminal pro—b-type natriuretic peptide (NT-proBNP) and (**B**) growth stimulation expressed gene 2 (ST2). The table at the top is for comparison of the relative changes in each intervention arm to that in the microcrystalline cellulose (MCC) arm. CI, confidence interval.

Gut microbiome outcomes

Dietary treatment arms had a negligible impact on microbial communities, with a slight variation attributed to baseline starting microbial differences between participant treatment groups (Figs. 3 and 4; Supplemental Figs. S3-S5). At baseline, microbial profiles of the 5-g acacia gum group revealed a difference in unweighted but not weighted UniFrac ($P = 0.02$; Fig. 3A), with reduced richness as described by the Chao1 alpha diversity metric, compared to the acacia gum 10 g group and the MCC group ($P = 0.02$ and $P = 0.02$, respectively; Fig. 4B). The difference in microbial communities for the 5-g group participants can be attributed to a reduced abundance of members from the Firmicute populations, such as *Christensenellaceae* R7 group and *Ruminococcus bicirculans* (Fig. 3C). Similar changes were found at 12 weeks of treatment with 5 g acacia gum, with unweighted UniFrac analysis indicating a more pronounced change in microbial community, compared with that in the 10-g group and the MCC group ($P = 0.03$ and $P = 0.04$, respectively; Fig. 4A). From baseline to week 12 of treatment, no appreciable difference in alpha- and beta-diversity could be determined in any of the treatment arms (Fig. 4, B and C; Supplemental Figs. S3-S5).

Safety, tolerability, and adherence

No safety events attributable to the acacia gum or MCC were reported. The 4 clinical events reported at 12 weeks (2 in each intervention arm) were not attributed to acacia gum. Data on adherence to the dietary supplementations were available for a total of 38 patients. At each study visit, 83% or more of study participants reported consuming 100% of a dietary supplement or placebo. Regarding tolerability, the 10-g group reported a lower mean gastrointestinal tolerability score at 6 weeks, compared to that in the MCC group (relative difference [95% confidence interval]: -0.57 [-1.10, -0.05], $P = 0.033$). No additional differences between groups over time were observed (Supplemental Table S3).

Discussion

Results of this trial showed that supplementation with acacia gum in this patient population is both feasible and well tolerated at the doses employed. The primary finding of FEAST-HF is that in ambulatory patients with HF, a strategy of supplementing FDF did not appreciably alter the HF biomarkers NT-proBNP and ST2, although, as this was a pilot study, our sample size was insufficient to detect significant differences in NT-proBNP level with acacia gum treatment. Secondary outcomes, such as health-related quality of life, exercise capacity, and NYHA class were not affected by the dietary supplementation, and additionally, the gut microbiome did not change significantly. The FDF chosen was both safe and well tolerated, but it was not efficacious in modifying the tested biomarkers or microbiome.

Several key findings deserve consideration in interpreting these results. First, dietary supplementation with acacia gum did not alter the gut microbial communities. Our study is the first to explore the effects of FDF in humans with HF. A study of 14 patients with HF (left ventricular ejection fraction < 50%) utilizing probiotic therapy (using *Saccharomyces boulardii* vs placebo) demonstrated a reduction in left atrial

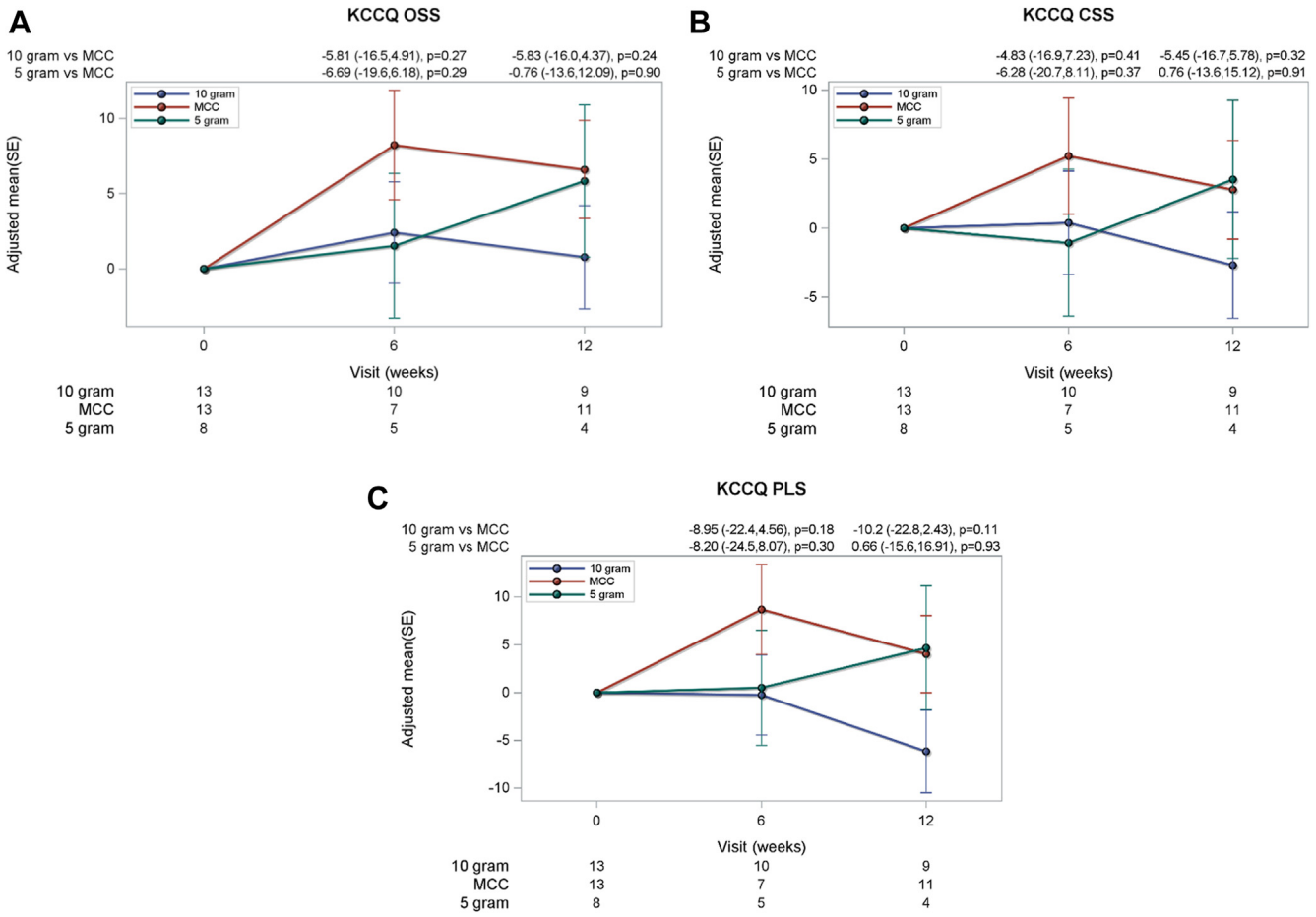

Figure 2. Kansas City Cardiomyopathy Questionnaire (KCCQ) quality-of-life outcomes. (**A**) Overall summary score (OSS); (**B**) clinical summary score (CSS); (**C**) physical limitation score (PLS). Means are adjusted for the respective score at baseline. MCC, microcrystalline cellulose; SE, standard error.

diameter and uric acid after 3 months of therapy.[12] In our study, patients' diets were supplemented with an FDF at 2 different doses, 5 g and 10 g per day, for 12 weeks. One possibility is that the duration of treatment was insufficient to induce changes in the microbiome. In addition, an important point to take into consideration is that the colonic microbiota is part of a complex ecosystem, in which substantial cross-feeding occurs; in other words, metabolites produced by one bacterium are used as a substrate by another one, and specific species or strains are required to degrade a substrate. Thus, an improvement in host health has been postulated to be more likely to occur when a variety of substrates are used.[13,14] Therefore, a mixture of fibres rather than a single fibre may be better at altering the gut microbiome in this patient population.

We postulated that gut microbiome configurations (composition, diversity), stability, and function (gene content) would be significantly altered in patients in response to acacia gum, and that acacia gum-induced changes in the microbiome would correlate with a reduction in the HF biomarkers NT-proBNP and ST2. ST2, a member of the interleukin-1 receptor family, is linked to HF severity and clinical outcomes.[15,16] Two of its key mechanistic relationships are with mechanical overload and inflammation. ST2 also is linked to binding with macrophages in response to bacterial lipopolysaccharide[15] and other immunomodulatory pathways. In this study, microbiome was not altered by the intervention with acacia gum; thus, we were unable to detect changes in the studied biomarkers related to the postulated changes in the microbiome configuration. Further and larger studies may need to consider an extended follow-up and a higher dose of FDF or a different mix of FDF.

Limitations

Several other design-related issues deserve consideration. First, adherence to dietary supplementation was good, and no safety issues were reported in any of the study groups. This level of adherence points out the feasibility of testing a dietary supplementation with an FDF at the studied doses in a larger population. However, an important point to note is that the dose of FDF employed in this study may not have been high enough to provide the postulated benefits. Indeed, the baseline median dietary fibre intake was around 15 g/d in all groups, which means that after supplementation, total overall dietary fibre was 20 g and 25 g/d in the 5-g/d and 10-g/d groups, respectively. The dietary fibre intake recommendation for the Canadian population is 25 g/d for women

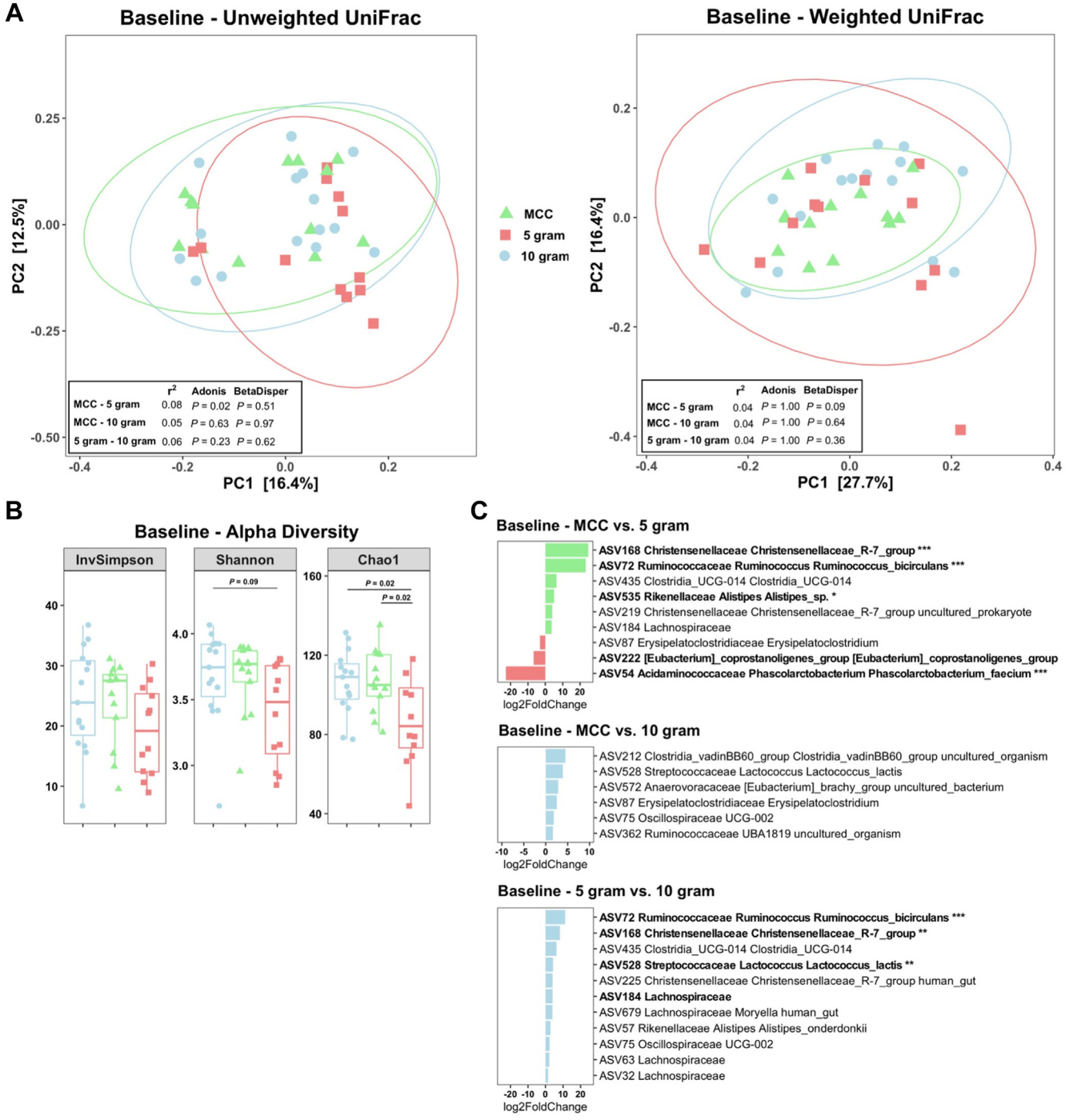

Figure 3. Baseline microbial community analysis between 10-mg group, microcrystalline cellulose (MCC) group, and 5-mg group. (**A**) Principal coordinate analysis (PCoA) plots of unweighted and weighted UniFrac distance indices for beta-diversity comparison. (**B**) Boxplot of inverse Simpson, Shannon, and Chao1 alpha-diversity metrics. (**C**) Plot of significant asymptotic variances (ASVs; unadjusted $P < 0.05$) from DEseq2 analyses between the 3 treatment groups. Bolded ASVs signifying the significant adjusted *P*-value < 0.10, < 0.05 (*), < 0.01 (**), and < 0.001 (***). PC1, principal component 1; PC2, principal component 2.

and 38 g/d for men.[17] Future studies may need to consider FDF supplementation at a higher dose in this patient population. Second, we captured but did not intentionally alter either caloric or fluid intake, diuretics, or other dietary supplements. Third, this pilot trial is aimed at testing feasibility and generating hypotheses; thus, these data should not be treated as definitive, as the small sample size may have increased the risk of type 2 error. Fourth, due to the COVID-19 pandemic, recruitment of study participants was affected, and the trial needed to stop before the sample size

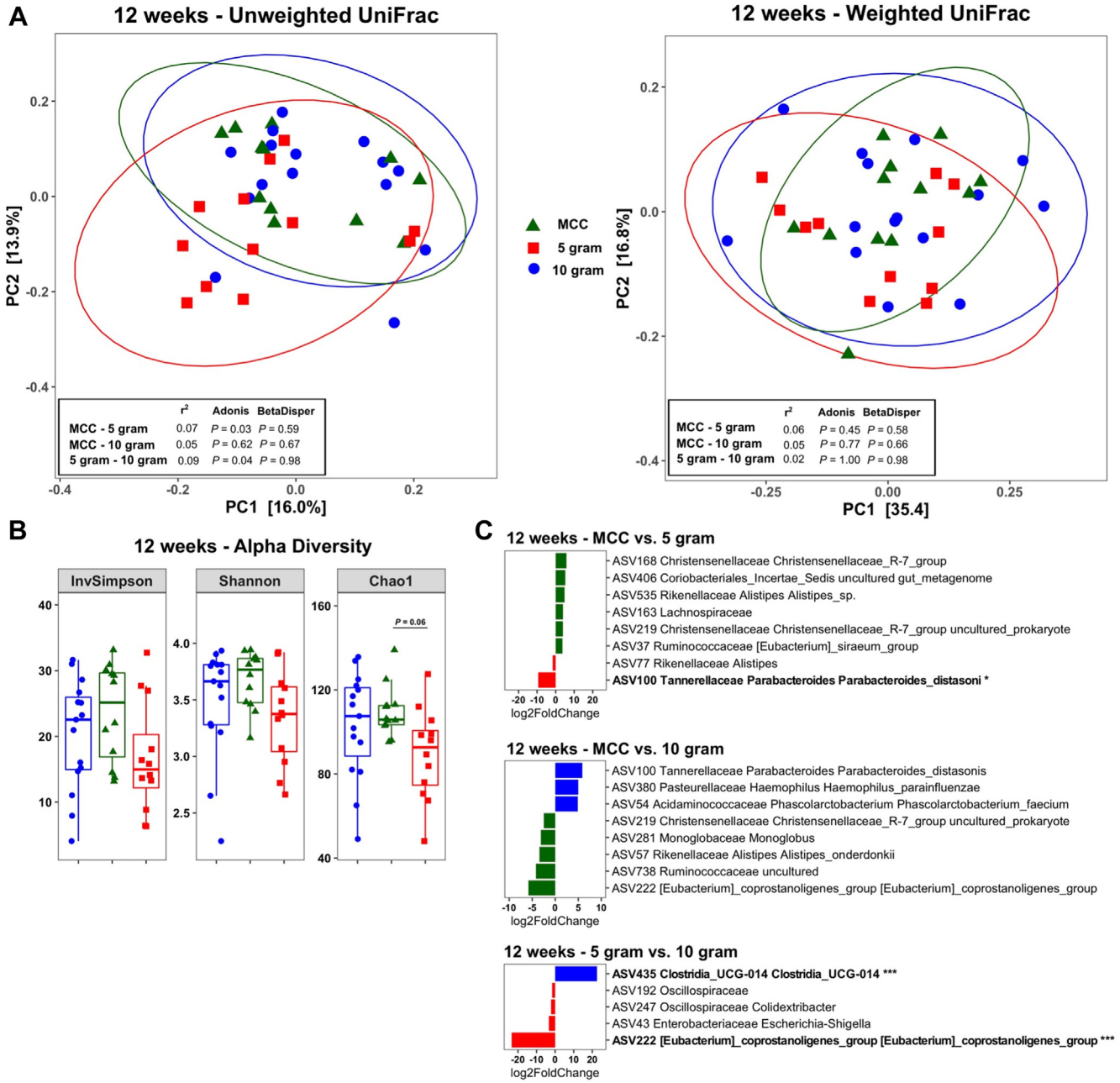

Figure 4. Microbial community analysis of GroupA, GroupB, and GroupC after 12 weeks of treatment. (**A**) Principal coordinate analysis (PcoA) plots of unweighted and weighted UniFrac distance indices for beta-diversity comparison. (**B**) Boxplot of inverse Simpson, Shannon, and Chao1 alpha-diversity metrics. (**C**) Plot of significant asymptotic variances (ASVs; unadjusted $P < 0.05$) from DEseq2 analyses between the 3 treatment groups. Bolded ASVs signifying the significant adjusted *P*-value < 0.10, < 0.05 (*), < 0.01 (**), and < 0.001 (***). MCC, microcrystalline cellulose; PC2, principal component 2.

was achieved and therefore is potentially at risk of generating inaccurate effect estimates.[18] Fifth, our results are applicable to those patients enrolled who were, generally, in NYHA class 2; different results might occur if patients were more or less symptomatic. Finally, additional operational issues regarding the collection and storage of blood samples were noted but could not be altered.

Conclusions

The dietary intervention in this pilot study was safe, feasible to administer, and well tolerated, but it did not alter the gut microbiome, NT-proBNP or ST2 levels, or quality of life in ambulatory patients with HF. The lack of effect of acacia gum observed in this study may be related to the small sample size leading to a type 2 error. Effects of an FDF on

clinical outcome in HF should be tested in future large and definitive trials. In addition, further research should identify soluble fibres that can deliver SCFA effectively to the myocardium to improve myocardial function and patient outcomes.

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Ethics Statement

The full trial protocol was approved by the appropriate regulatory authorities, and by individual institutional review boards or ethics committees at the participating sites. All patients provided written informed consent.

Patient Consent

The authors confirm that a patient consent form has been obtained for all participants in FEAST-HF.

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Supplementary Material

To access the supplementary material accompanying this article, visit *CJC Open* at https://www.cjcopen.ca/ and at https://doi.org/10.1016/j.cjco.2023.07.005.