Nutritional Modulation of Gut Microbiota Alleviates Severe Gastrointestinal Symptoms in a Patient with Post-Acute COVID-19 Syndrome

RUTGERS
New Jersey Medical School

Ying Wang[1], Guojun Wu[1], Liping Zhao[1], Weizheng Wang[2]

2. Rutgers New Jersey Medical School, Newark, New Jersey, USA.

1. Rutgers School of Environmental and Biological Sciences, New Brunswick, NJ

BACKGROUND

- With the increase in total coronavirus disease 2019 (COVID-19) infection cases, post-acute COVID-19 syndrome, defined as experiencing ongoing health problems 4 or more weeks after the first severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, has become a new arising public health concern.
- As part of post-acute COVID-19 syndrome, gastrointestinal symptoms might be associated with dysbiosis of the gut microbiota, which has the potential to become a target for intervention.
- Our previous study showed that a high-fiber diet based on whole grains, traditional Chinese medicinal foods, and prebiotics recovered a healthier gut microbiota by selectively increasing a group of short-chain fatty acid (SCFA) producers and decreasing proinflammatory and/or endotoxin-producing bacteria in DM2
- We hypothesize that the ecological changes in the gut microbiota induced by this high-fiber formula might help alleviate the patient's post-acute COVID-19 syndrome

METHODS

- a patient with post-acute COVID-19 syndrome with long-lasting severe GI symptoms was provided 2-month expanded access to a high-fiber formula with investigational new drug (IND) status developed to alleviate COVID-19-related symptoms by modulating the gut microbiota.
- data collected on her daily symptoms and medication intake together with time series breath, blood and fecal samples
- Breath sample collection Breath samples were collected before and hourly after taking the high-fiber formula for 4 h on days 21, 28, 36, and 42.
- Fecal sample collection Fecal samples were collected at home using a collection kit
- 16S rRNA gene sequencing Hypervariable region V4 of the 16S rRNA gene was amplified using PCR with Ion Torrent barcode-tagged primers
- Gut microbiota analysis Primer and adapter removal, denoising, and quality filtration of the sequencing data were performed using QIIME 2 to obtain amplicon sequence variants (ASVs)
- Statistical analysis ASVs that significantly correlated with PC1 and PC2 scores were selected by Pearson correlation with the Benjamini-Hochberg correction method (adjustedP, 0.05). Pearson correlations between the severity of symptoms/dosage of medication and the duration of the intervention/consumption dosage of the high-fiber formula were calculated using the R stats package version4.1.0, and the general linear regression line and 95% confidence interval were plotted using the Rggplot2 package version 3.3.5

RESULTS

- Nutritional alleviation of post-acute COVID-19 syndrome

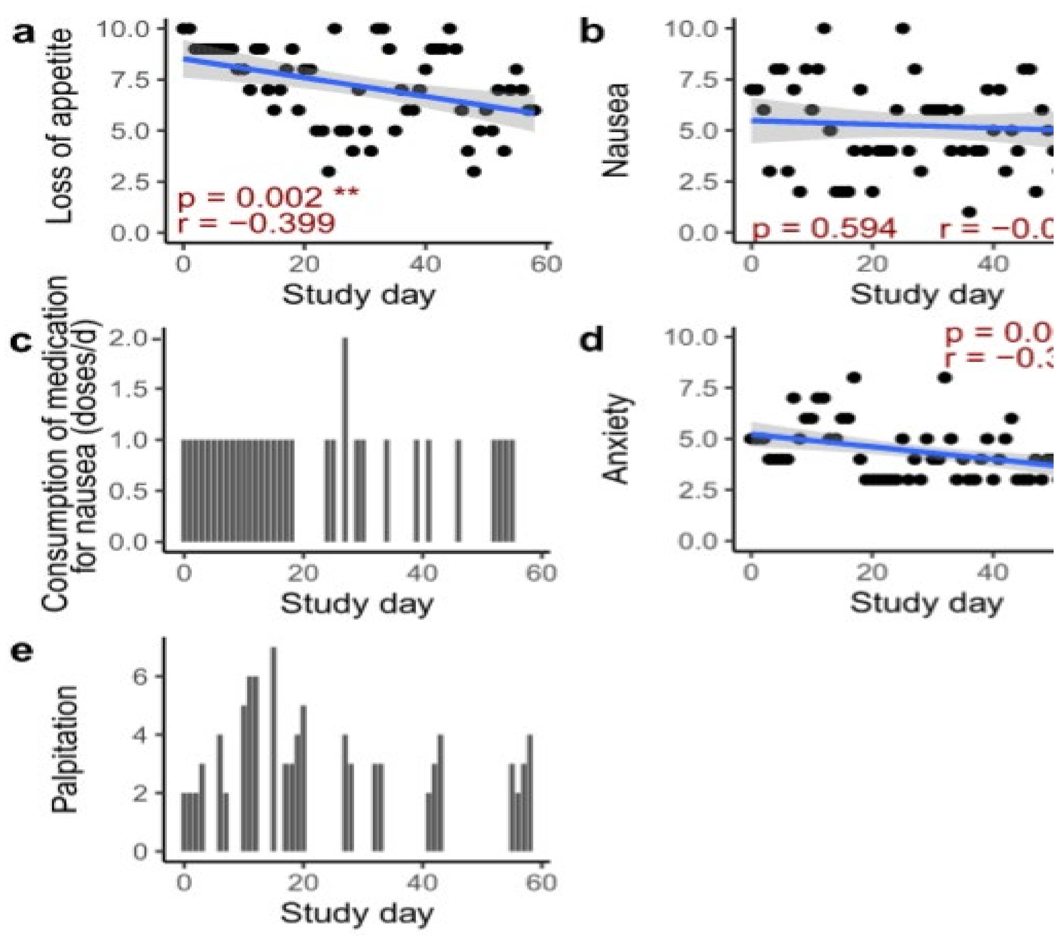

FIG 1 Severity of symptoms and medication intake decreased during the intervention. (Correlations between the severity of loss of appetite and nausea and days of intervention. (c showing that the frequency of medication intake for nausea decreased during the interve Correlations between the severity of anxiety and days of intervention. (e) Bar plot showing frequency of palpitation occurrence decreased during the intervention. Symptoms were eval a scale of 0 (none) to 10 (severe). The general linear regression line is shown as a blue line a, b, and d. The 95% confidence interval is shown as a gray area around the regression Pearson correlation was calculated, and the *P* value and *r* value are shown in dark red in ea Asterisks indicate significance (**, $P < 0.01$).

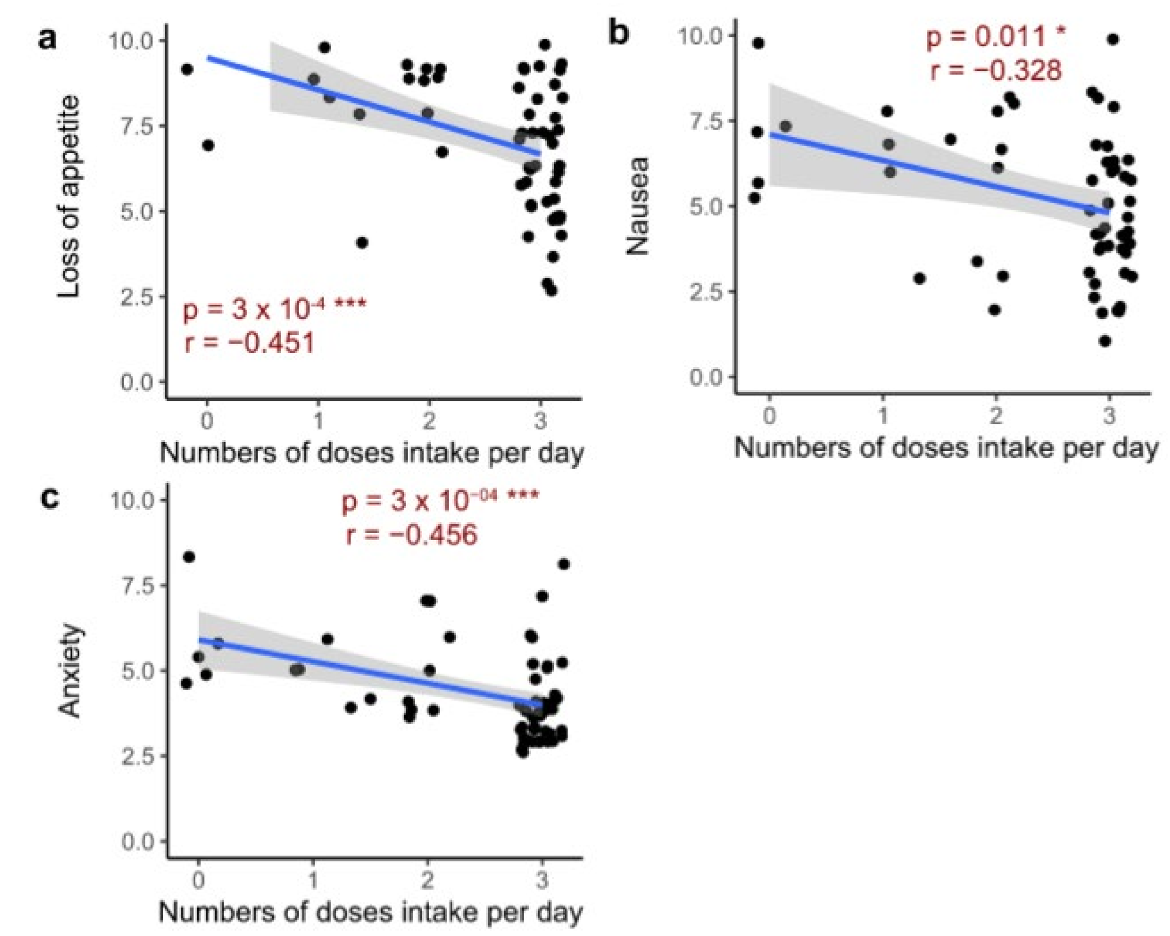

FIG 2 Severity of symptoms is alleviated with increased consumption of the fiber formula. Correlations between the severities of loss of appetite (a), nausea (b), and anxiety (c) and the consumption of the high-fiber formula were determined. Daily symptom severity and high-fiber formula consumption data collected from the 2-month intervention are plotted as points. Symptoms were evaluated on a scale of 0 (none) to 10 (severe). The general linear regression line is shown as a blue line. The 95% confidence interval is shown as a gray area around the regression line. The Pearson correlation was calculated, and the *P* value and *r* value are shown in each panel. Asterisks indicate significance (*, $P < 0.05$; ***, $P < 0.001$).

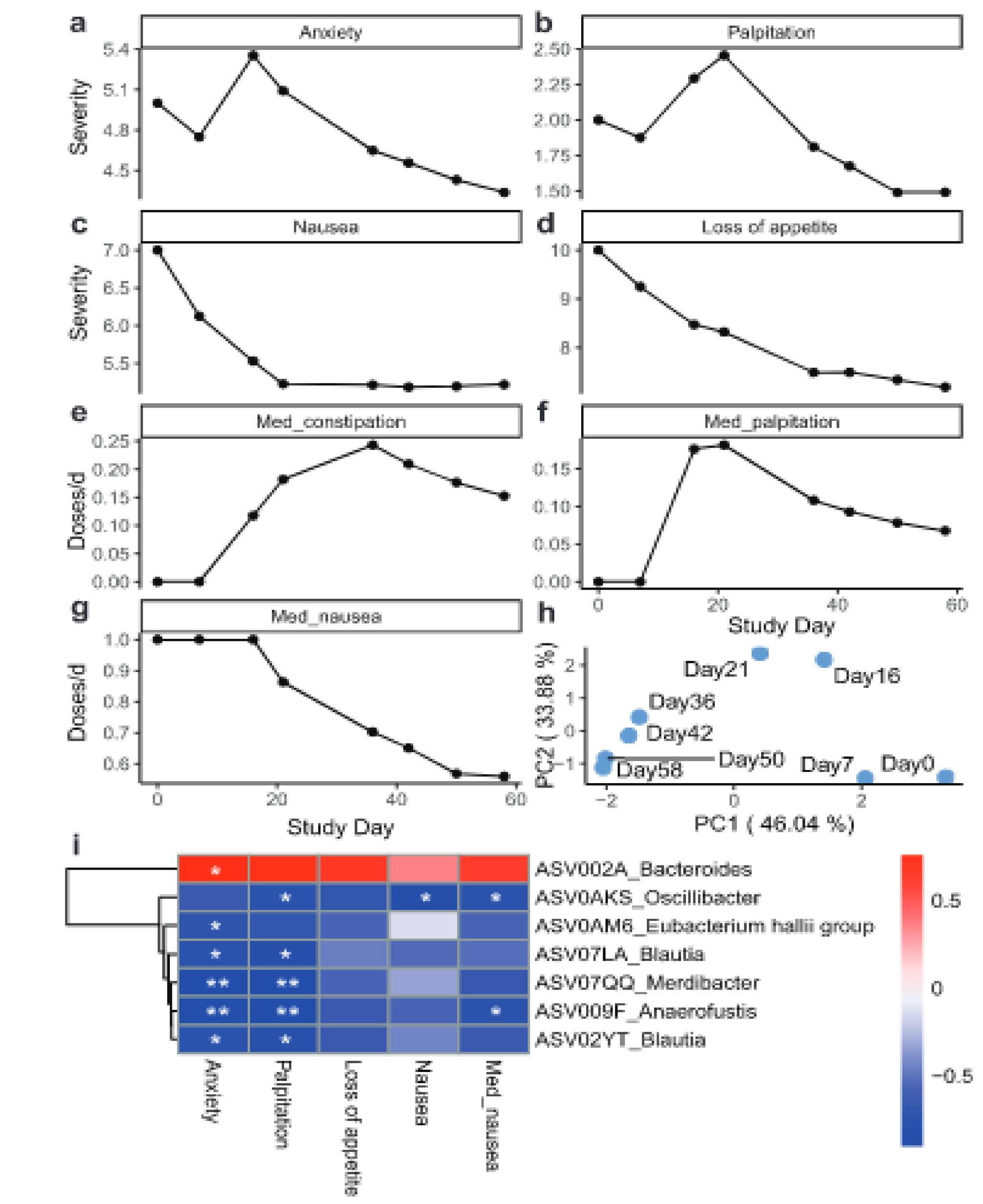

FIG 4 Changed microbial members were associated with the alleviation of symptoms. (a to g) The mean severity of symptoms and the need to take medication decreased by the end of the intervention. The mean severity of symptoms since the start of the intervention was calculated for days 0, 7, 16, 21, 36, 42, 50, and 59, corresponding to the days when the fecal samples were collected. (h) Principal-component analysis (PCA) was performed on the scaled mean severity of symptoms and dosage of medication during the 2-month intervention. Only the time that corresponded to the day of fecal sample collection is shown on the plot. (i) ASVs that were significantly correlated with the mean severity of symptoms. Spearman correlation coefficients are shown as colors in the heat map. Significance is indicated by asterisks (*, $P < 0.05$; **, $P < 0.01$). Med_constipation, dosage of medication for constipation; Med_palpitation, dosage of medication for palpitation; Med_nausea, dosage of medication for nausea.

TABLE 1 Blood-based clinical parameters before, during, and after the 2-month intervention[a]

	Value				
Parameter	Baseline (4 mo prior)	Day 9	Day 30	Day 58	Normal range
ALP (IU/L)	173 ↑	205 ↑	197 ↑	144	44–147
ALT (U/L)	15	14	15	12	7–55
AST (U/L)	27	29	30	23	8–45
Total bilirubin (mg/dL)	0.2	0.2	<0.2	0.3	<1.2
Total protein serum (g/dL)	7.1	7.2	7	6.8	6.0–8.3
Albumin/globulin ratio	1.7	1.8	1.9	1.7	1.1–2.5
Albumin (g/dL)	4.5	4.6	4.6	4.3	3.5–5.5
Total globulin (g/dL)	2.6	2.6	2.4	2.5	2.0–3.9
BUN (mg/dL)	11	9	11	14	6–24
BUN/creatinine ratio	11	10	12	13	10–20
EGFR	74	79	78	66	>60
Serum glucose (mg/dL)	92	91	92	88	<140
Insulin (μIU/mL)	NA	13.8	13.4	11.1	2.6–24.9
Serum leptin (ng/mL)	NA	121.2 ↑	113.1 ↑	91.7 ↑	9.1–50.4
Cholesterol (mg/dL)	NA	184	165	145	<200
HDL cholesterol (mg/dL)	NA	76	72	57 ↓	≥60
LDL cholesterol (mg/dL)	NA	86	74	70	<100
VLDL cholesterol (mg/dL)	NA	22	19	18	2–30
Triglycerides (mg/dL)	117	128	110	98	<150

[a]ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; BUN, blood urea nitrogen; EGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very-low-density lipoprotein; NA, not applicable. Upward-pointing arrow: higher than normal range. Down-pointing arrow: lower than normal range.

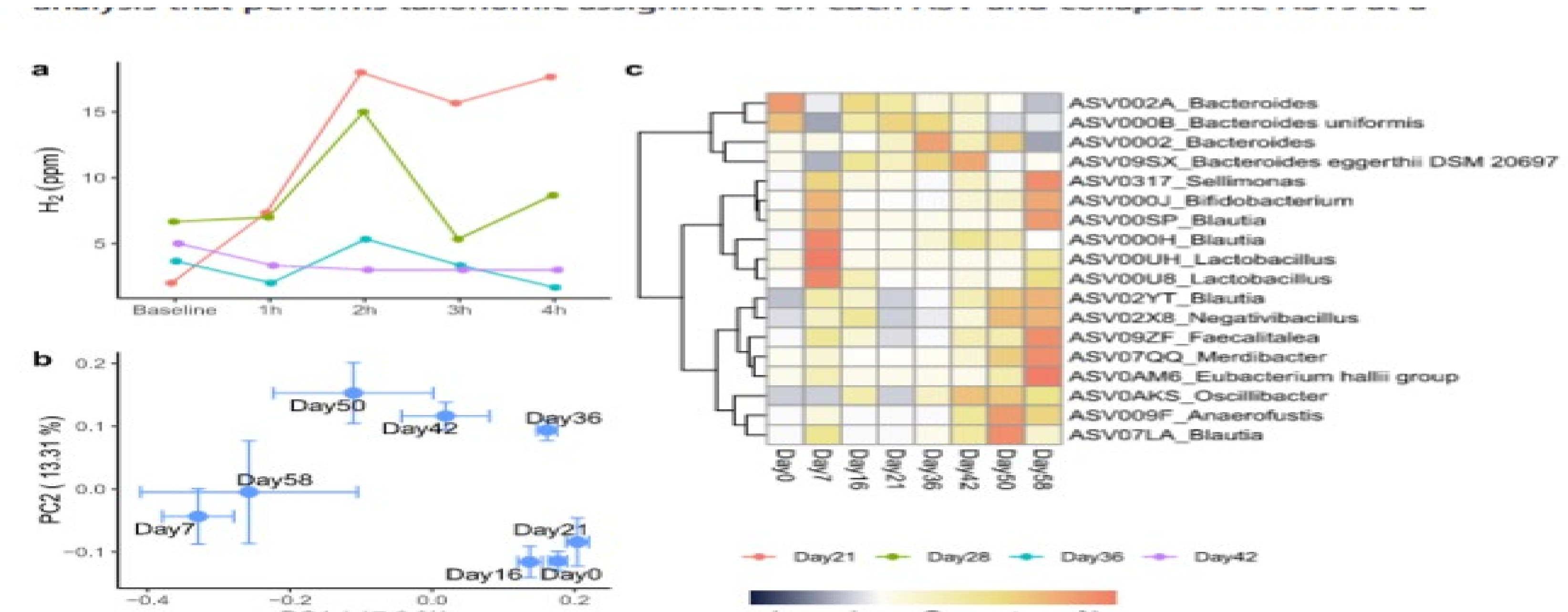

FIG 3 The high-fiber formula changed fermentation in the small intestine and the gut microbial structure. (a) Breath hydrogen levels were measured before and 4 h after taking NBT-NM108 in the morning. (b) Principal-coordinate analysis (PCoA) based on the Bray-Curtis distance was performed on stool samples during the 2-month intervention. Each data point represents the mean Principle coordinates (PC) score, and the error bar represents the standard error from triplicates. (c) Relative abundances of ASVs significantly correlated with PC1 and PC2 scores in panel b. The Pearson correlation was calculated with the *P* value adjusted by the Benjamini-Hochberg procedure (an adjusted *P* value of <0.05 is significant). The heat map shows the row-scaled relative abundance for each ASV. ASVs were clustered using Euclidean distance and the Ward.D2 method.

CONCLUSIONS

high intake of dietary fibers with diverse physicochemical structures significantly alleviated severe GI symptoms in a patient with post-acute COVID-19 syndrome.

The significant structural shifts in the patient's gut microbiota induced by the high-fiber formula, particularly the enrichment of SCFA-pro-ducing bacteria, might be associated with the alleviation of both GI and non-GI symp-toms such as anxiety and palpitation.

Prolonged high-fiber intake might also havereduced bacterial fermentation in the patient's small intestine. Reduced gut pressure from reduced gas production in the small intestine might work as a potential mechanism for the alleviation of GI symptoms such as nausea and loss of appetite.

This study indicates the feasibility of nutritional modulation of the gut microbiota for the alleviation of GI symptoms in patients with post-acute COVID-19 syndrome.

However, this single case showed only the feasibility of using high-fiber intervention for alleviating GI symptoms in post-acute COVID-19 syndrome. Randomized controlled trials are needed to establish the clinical efficacy and safety of the high-fiber formula as a potential intervention.