Gastroenterology 2019;157:881–883

BRIEF COMMUNICATIONS

Gluten Does Not Induce Gastrointestinal Symptoms in Healthy Volunteers: A Double-Blind Randomized Placebo Trial

Iain David Croall,[1] Imran Aziz,[2] Nick Trott,[2] Paola Tosi,[3] Nigel Hoggard,[1] and David S. Sanders[2]

[1]Academic Unit of Radiology, University of Sheffield, Royal Hallamshire Hospital, Sheffield, United Kingdom; [2]Academic Unit of Gastroenterology, Royal Hallamshire Hospital, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, United Kingdom; and [3]University of Reading, School of Agriculture Policy and Development, Reading, United Kingdom

Keywords: Gluten Sensitivity; Randomized Control Trial; People Who Avoid Gluten; Lifestylers; Celiac Disease.

See editorial on page 607.

Although the gluten-free diet (GFD) is the best treatment for clinical gluten sensitivity (GS) (eg, celiac disease [CD], non-celiac gluten sensitivity [NCGS]), scientific opinion supports that gluten is safe for the general population.[1] However, celebrity/athletic endorsement of the GFD has cultivated an image of gluten as "unhealthy."[2]

"Lifestylers," "free from," or "people who avoid gluten" are individuals who avoid gluten as a lifestyle choice. American market research[3,4] found that 44% of people buy gluten-free food for reasons other than GS, and that 65% believe that a GFD is generally healthier. This trend has driven the worldwide gluten-free industry from values of $1.7 billion in 2011 to $3.5 billion in 2016, and it is forecast to reach $4.7 billion in 2020.[5]

The surge in gluten-free popularity has also encouraged an opposing belief that it is a "fad" diet.[2] This is unfortunate for people with CD/NCGS, who express that they are not taken seriously in restaurants, and even face dismissive attitudes from nonspecialist clinicians.[6] The drawing of a clear line between those who do and do not benefit from a GFD is needed to ground public and clinical perspective on these issues. For this reason, we undertook the first double-blind randomized controlled trial (DRCT) of gluten (via gluten-containing flour) in healthy controls, hypothesizing it would not cause any symptoms.

Methods

Participants

Participants (who received no financial incentives), recruited by advertising, were ≥18 years, had no diagnosed gluten-related disorders, and followed gluten-containing diets. The study aimed to recruit 30 subjects to divide into 2 groups; no previous data in healthy individuals are available, but NCGS DRCTs have reported gastrointestinal symptom changes induced by gluten, which would carry 89.2% power if observed within a group of n = 15.[7] Subjects were serologically tested to detect CD. The trial was supported by the personal research funds of Professor Sanders, and sought ethical approval from the Yorkshire and Humber Research Ethics Committee.

Trial Design

Participants attended 2 study sessions at a community venue. Subjects were educated by a dietitian about a GFD and asked (with support) to commence a GFD for 2 weeks (Biagi score[8] measured GFD adherence). Subjects completed Gastrointestinal Symptom Rating Scales[9] to measure baseline abdominal pain, reflux, indigestion, diarrhea, and constipation. A visual analogue scale measured "global fatigue."

Subjects were randomized by a study team member (double-blinded, parallel, 1:1 allocation in an "A-B-A-B" sequence) into 2 groups who received flour sachets labeled "A" or "B" to add to their diet twice daily for 2 weeks while otherwise continuing their GFD. Flours (provided by Dutch Organic International Trade, Barneveld, the Netherlands) contained either organic gluten (gluten group; 2 × 10 g vital gluten sachets, daily, providing 14 g gluten protein and 1.4 g starch carbohydrates), or a gluten-free blend (control group; rice, potato, tapioca, maize, and buckwheat flour blend, 2 × 10 g sachets daily). Finally, participants re-completed symptom measures and exited the DRCT.

Analysis

Variables were inspected for normality to determine appropriate analyses. Key variables were compared between randomized groups by frequency-based/groupwise testing to ensure baseline homogeneity. Primary/secondary outcomes examined change in symptom scores (follow-up minus baseline), compared between gluten and control groups by independent *t* test. The primary outcome was change in abdominal pain score. Post hoc analyses compared symptom scores within groups using paired *t* tests.

Results

Consecutive recruitment commenced in December 2015 and closed in January 2016. Forty-five people made contact

Abbreviations used in this paper: **CD, celiac disease; GFD, gluten-free diet; GS, gluten sensitivity; NCGS, non-celiac gluten sensitivity.**

Most current article

0016-5085/$36.00
https://doi.org/10.1053/j.gastro.2019.05.015

Table 1. Summaries of Key Variables and Analyses

Variable	Treatment group (n = 14)	Control group (n = 14)	*P* value	Partial ETA^2 (95% CI)
Sex, % female	78.6	71.4	Baseline comparison $P = .663$	-
Age, mean (SD)	38.79 (11.64)	37.57 (13.32)	Baseline comparison $P = .799$	-
Baseline (top) and follow-up abdominal pain GSRS, mean (SD)	2.50 (1.40) 2.14 (1.70)	2.36 (1.34) 2.07 (1.00)	Baseline comparison $P = .721$	-
Baseline (top) and follow-up reflux GSRS, mean (SD)	1.71 (1.14) 1.64 (1.15)	2.50 (2.24) 2.57 (1.95)	Baseline comparison $P = .667$	-
Baseline (top) and follow-up indigestion GSRS, mean (SD)	2.14 (1.35) 2.07 (1.33)	2.14 (1.35) 1.79 (0.98)	Baseline comparison $P = .946$	-
Baseline (top) and follow-up diarrhea GSRS, mean(SD)	2.71 (1.94) 1.64 (0.92)	1.85 (1.46) 1.64 (1.22)	Baseline comparison $P = .210$	-
Baseline (top) and follow-up constipation GSRS, mean (SD)	2.50 (1.83) 2.36 (1.78)	1.93 (1.54) 2.50 (1.65)	Baseline comparison $P = .454$	-
Baseline (top) and follow-up global fatigue, mean (SD)	6.64 (2.37) 6.64 (2.79)	6.57 (2.44) 5.57 (2.21)	Baseline comparison $P = .839$	-
Change in abdominal pain, mean (SD)	−0.36 (1.95)	−0.29 (1.49)	Symptom change $P = .914$	0.000 (−1.42 to 1.28)
Change in reflux, mean (SD)	−0.07 (0.73)	+0.07 (1.98)	Symptom change $P = .802$	0.002 (−1.30 to 1.02)
Change in indigestion, mean (SD)	−0.07 (1.69)	−0.36 (1.34)	Symptom change $P = .623$	0.009 (−0.90 to 1.47)
Change in diarrhea, mean (SD)	−1.07 (1.69)	−0.21 (0.89)	Symptom change $P = .105$	0.098 (−1.91 to 0.19)
Change in constipation, mean (SD)	−0.14 (2.45)	+0.57 (1.51)	Symptom change $P = .360$	0.032 (−2.29 to −0.86)
Change in fatigue, mean (SD)	0.00 (3.74)	−1.00 (3.60)	Symptom change $P = .477$	0.02 (−1.85 to 3.85)

NOTE. Tests above the bold line show Mann-Whitney *U*/ independent *t* test /χ^2 analyses that compare study groups for homogeneity on baseline characteristics. Primary and secondary analyses are shown below the bold line, which compare change in symptom scores between study groups using independent *t* tests. Partial ETA^2 and 95% confidence intervals (CIs) accompany these analyses to demonstrate effect size and precision.

before 30 were recruited. Reasons for not taking part included an unwillingness to commit to the dietary requirements/being unable to attend prespecified study meeting dates. Serological CD testing excluded 2 from the study. The remaining 28 subjects were randomized into the gluten (n = 14) and control (n = 14) groups and underwent the full trial, which ended in March 2016. No harms were reported.

The overall group had a mean age of 38 years (range = 19–63, SD = 12), and was 75% female (n = 21). Biagi score (which measured GFD adherence while participants otherwise consumed the study flours) was not different between groups (independent *t* test, $P = .834$), whereas χ^2 and independent *t* tests/Mann-Whitney *U* showed no significant differences in any baseline characteristic (Table 1).

Descriptively, mean symptom scores ubiquitously decreased in the gluten group (implying symptomatic improvement). Individually, only 1 gluten group participant reported a worsening of some symptoms without improvement in others. Independent *t* tests between randomized groups showed no significant differences in change of any symptom (abdominal pain: treatment/control mean (SD) = −0.36 (1.95)/−0.29 (1.49), $P = .914$, partial $ETA^2 = 0.000$, 95% confidence interval = −1.42 to 1.28). See Table 1 for full results.

Post hoc paired *t* tests examining change in Gastrointestinal Symptom Rating Scale scores within groups showed that the diarrhea score significantly reduced in the gluten group (baseline/follow-up mean (SD) = 2.71 (1.94)/1.64 (0.92), $P = .033$); this does not survive bonferroni correction. No other analyses were significant.

Discussion

This is the first DRCT to demonstrate that consumption of gluten-containing flour does not generate symptoms in healthy volunteers. The trial measured how daily ingestion of the flour (containing 14 g of gluten) affected a range of symptoms over 2 weeks, none of which significantly changed between groups. Within-group analyses similarly produced no significant findings, other than one indication that symptoms of diarrhea improved in the gluten group (likely anomalous and in any case does not support that the flour caused symptoms).

Our results support the view that gluten does not appear to cause symptoms in individuals who do not have a physiological susceptibility to it (ie, most of the population). As the GFD is not only thought to be no healthier than a "normal" diet, but has been suggested as overall suboptimal,[1] there is possibly clinical justification in actively discouraging people from starting it if they have no diagnosable sensitivity.

A potential study limitation is the relatively short duration of the trial, although other DRCTs in NCGS indicate onset of symptoms can begin after 1 week.[7] Another consideration is that the study topic may have unintentionally attracted participants with NCGS/irritable bowel syndrome; however, the presence of these would likely bias the study toward positive findings, so confidence in the null results should remain high.

Patients who self-report symptoms related to gluten must have CD and NCGS excluded, but on the basis of these new data perhaps the assertion by "lifestylers" that a GFD is beneficial can also be challenged.

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Received November 6, 2018. Accepted May 16, 2019.

Reprint requests
Address requests for reprints to: David Sanders, MBChB, MD, FACG, FRCP, Academic Unit of Gastroenterology, Room P39, P Floor, Royal Hallamshire Hospital, Glossop Road, S10 2JF, United Kingdom. e-mail: David.Sanders@sth.nhs.uk.

Acknowledgments
Additional contributors: A. Rej, Academic Unit of Gastroenterology, Royal Hallamshire Hospital, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, United Kingdom, and M. Hadjivassiliou, Department of Neurology, Royal Hallamshire Hospital, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, United Kingdom. I.D. Croall contributed to the analysis of the study and writing of the manuscript. I. Aziz, N. Trott, and P. Tosi contributed to the design and conduct of the study. N. Hoggard contributed to the analysis of the study and writing of the manuscript. D.S. Sanders conceived the study and contributed to the design, conduct, analysis of the study and writing of the manuscript. A. Rej and M. Hadjivassiliou M. contributed to the design and conduct of the study.

Conflicts of interest
The authors disclose no conflicts.

Funding
This study was supported by the personal research funds of David S. Sanders. It does not have any specific grant attached to it.