Letter: disentangling the role of redox-active compounds in the development of inflammatory bowel diseases – moving towards causal associations

Geertsema, Sem; van Goor, Harry; Dijkstra, Gerard; Faber, Klaas Nico; Bourgonje, Arno R.

Published in:
Alimentary Pharmacology & Therapeutics

DOI:
10.1111/apt.17455

Received: 24 February 2023 | First decision: 24 February 2023 | Accepted: 24 February 2023

DOI: 10.1111/apt.17455

AP&T Alimentary Pharmacology & Therapeutics WILEY

LETTER TO THE EDITOR

Letter: disentangling the role of redox-active compounds in the development of inflammatory bowel diseases – moving towards causal associations

Editors,

We read with great interest the study by Chen et al,[1] in which the authors leveraged a Mendelian randomisation (MR) approach to systematically examine potentially causal associations of circulating levels of antioxidants, minerals and vitamins with the risk of inflammatory bowel disease (IBD). The authors generated evidence in support of causal associations for genetically predicted antioxidants like lycopene, retinol and ascorbate in relation to IBD risk. Interestingly, genetic predisposition to higher circulating calcium and magnesium was associated with elevated IBD risk. Ultimately, the presented data showing circulating levels of antioxidants, mineral and vitamins that may be causally linked to IBD development is promising and important, especially considering the inconclusive and scarce evidence currently available. We would like to highlight some suggestions to expand upon this work.

Although the analysis of vitamins and minerals is intriguing, performing MR on central regulators of the human redox system or truly integrative components driving oxidative stress in IBD would be a keystone concept for *personalised redox medicine*. Oxidative stress is often considered an early driver of IBD onset, although only limited available evidence supports this. Using genetic instruments to make inferences about potential causal relationships between key regulators of redox status and IBD development could improve our pathophysiological understanding. For example, free thiols are markers of whole-body redox status and have been closely associated with IBD activity.[2] However, subjecting the entire thiol redox metabolome[3] or integrative redox metabolomic signatures[4] to such genetic approaches would be very informative, thereby linking integrative biomarkers to IBD onset and progression. Furthermore, redox components could be further prioritised by performing downstream analyses like expression- and protein-quantitative trait loci (eQTL/pQTL) mapping. This has previously been employed in IBD and may complement on how genetic make-up influences gene and protein expression of antioxidant substances.[5] These approaches would help to characterise the needs of specific IBD patient groups in a patient-tailored fashion.

MR analyses connecting antioxidant substances to IBD risk stratified by primary disease location would also be particularly relevant in this regard. Although we acknowledge that statistical power may have been insufficient for this purpose, oxidative stress burden in IBD can be location-specific.[2] For example, patients with IBD having solely colonic disease seem to have a high oxidative stress burden alongside lower expression of antioxidants. Looking at known SNPs for known antioxidants and leveraging MR to pinpoint location-specific causal associations between antioxidants and IBD risk could be performed to personalise redox-targeted therapy (e.g. through colon-targeted release of antioxidant vitamins and minerals).[6,7]

The study by Chen et al provides valuable insights into potentially causal links between antioxidants, minerals and vitamins and IBD development. This work could be expanded upon by examining genetically predicted levels of integrative biomarkers central to human redox biology and incorporating MR and QTL mapping approaches. Furthermore, performing disease subtype-specific analyses may improve our understanding of the potentially causal involvement of oxidative stress in IBD and define specific patient groups benefiting most from nutritional or drug-based redox-modulating therapeutics, following the concept of personalised redox medicine.

AUTHOR CONTRIBUTIONS

Sem Geertsema: Conceptualization (lead); investigation (lead); methodology (lead); validation (lead); writing – original draft (lead); writing – review and editing (lead). **Harry van Goor:** Conceptualization (equal); investigation (equal); methodology (equal); project administration (equal); supervision (equal); validation (equal); writing – review and editing (equal). **Gerard Dijkstra:** Conceptualization (equal); investigation (equal); methodology (equal); project administration (equal); supervision (equal); validation (equal); writing – review and editing (equal). **Klaas Nico Faber:** Conceptualization (equal); investigation (equal); methodology (equal); project administration (equal); supervision (equal); validation (equal); writing – review and editing (equal). **Arno R. Bourgonje:** Conceptualization (lead); investigation (lead); methodology (lead); project administration (lead); supervision (lead); validation (lead); writing – original draft (equal); writing – review and editing (lead).

ACKNOWLEDGEMENTS

None.

AP&T correspondence columns are restricted to invited editorials and letters discussing papers that have been published in the journal. An invited editorial or letter must have a maximum of 500 words, may contain one table or figure, and should have no more than 10 references. It should be submitted electronically to the Editors via http://mc.manuscriptcentral.com/apt.

CONFLICT OF INTEREST STATEMENT

The authors received a research grant from Janssen Research and Development LLC, outside the submitted work.

LINKED CONTENT

This article is linked to Chen et al papers. To view these articles, visit https://doi.org/10.1111/apt.17392 and https://doi.org/10.1111/apt.17468

Sem Geertsema[1]
Harry van Goor[2]
Gerard Dijkstra[1]
Klaas Nico Faber[1]
Arno R. Bourgonje[1]

[1]*Department of Gastroenterology and Hepatology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands*
[2]*Department of Pathology and Medical Biology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands*

Correspondence
Arno R. Bourgonje, Department of Gastroenterology and Hepatology, University of Groningen, University Medical Center Groningen, Hanzeplein 1, 9713 GZ, Groningen, the Netherlands.
Email: a.r.bourgonje@umcg.nl

ORCID

Sem Geertsema https://orcid.org/0000-0002-0335-5347
Harry van Goor https://orcid.org/0000-0002-6670-1577
Gerard Dijkstra https://orcid.org/0000-0003-4563-7462
Klaas Nico Faber https://orcid.org/0000-0001-8893-3312
Arno R. Bourgonje https://orcid.org/0000-0001-5754-3821

REFERENCES

1. Chen J, Ruan X, Yuan S, Deng M, Zhang H, Sun J, et al. Antioxidants, minerals and vitamins in relation to Crohn's disease and ulcerative colitis: a mendelian randomization study. Aliment Pharmacol Ther. 2023;57(4):399–408. https://doi.org/10.1111/apt.17392
2. Bourgonje AR, Gabriëls RY, de Borst MH, Bulthuis MLC, Faber KN, van Goor H, et al. Serum free thiols are superior to fecal calprotectin in reflecting endoscopic disease activity in inflammatory bowel disease. Antioxidants (Basel). 2019;8(9):351. https://doi.org/10.3390/antiox8090351
3. Sutton TR, Minnion M, Barbarino F, Koster G, Fernandez BO, Cumpstey AF, et al. A robust and versatile mass spectrometry platform for comprehensive assessment of the thiol redox metabolome. Redox Biol. 2018;16:359–80. https://doi.org/10.1016/j.redox.2018.02.012
4. Bourgonje AR, Kloska D, Grochot-Przęczek A, Feelisch M, Cuadrado A, van Goor H. Personalized redox medicine in inflammatory bowel diseases: an emerging role for HIF-1α and NRF2 as therapeutic targets. Redox Biol. 2023;60:102603. https://doi.org/10.1016/j.redox.2023.102603
5. Hu S, Uniken Venema WT, Westra HJ, Vich Vila A, Barbieri R, Voskuil MD, et al. Inflammation status modulates the effect of host genetic variation on intestinal gene expression in inflammatory bowel disease. Nat Commun. 2021;12(1):1122. https://doi.org/10.1038/s41467-021-21458-z
6. Pham VT, Fehlbaum S, Seifert N, Richard N, Bruins MJ, Sybesma W, et al. Effects of colon-targeted vitamins on the composition and metabolic activity of the human gut microbiome- a pilot study. Gut Microbes. 2021;13(1):1–20.
7. Liu P, Gao C, Chen H, Vong CT, Wu X, Tang X, et al. Receptor-mediated targeted drug delivery systems for treatment of inflammatory bowel disease: opportunities and emerging strategies. Acta Pharm Sin B. 2021;11(9):2798–818. https://doi.org/10.1016/j.apsb.2020.11.003