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The role of food in gastrointestinal symptoms

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Impact paragraph

The Western diet has been associated with an increased prevalence of gastrointestinal (GI) disorders.[1,2] Irritable bowel syndrome (IBS) is a disorder of gut-brain interaction (DGBI) that affects 5-10% of the Western population,[3] and is characterised by recurrent abdominal pain combined with altered stool patterns. Inflammatory bowel disease (IBD), a chronic inflammatory disease characterised by alternating sequences of active inflammation and remission, has a prevalence of 0.003% in Western countries.[4] About 35% of IBD patients in remission report IBS-like symptoms.[5] Food-related GI symptoms are common in these patients, with up to 90% of IBS patients, 56-68% of IBD patients with active disease, and 29-39% of IBD patients in remission indicating that GI symptoms like abdominal pain, bloating, and diarrhoea can be induced by meals and/or certain food products.[6,7] These symptoms severely impact patient's quality of life and are associated with substantial direct and indirect costs.[8,9] One of the common triggers, namely gluten-containing and/or wheat-based foods, has been indicated as the main culprit in non-coeliac gluten/wheat sensitivity (NCGS/NCWS). These individuals report symptoms despite the absence of coeliac disease and wheat allergy. NCGS/NCWS has an estimated prevalence of up to 15%.[10-12] The studies described in this thesis add to further insight into the role of potential trigger foods and food components, and their underlying mechanisms, thereby contributing to optimisation of (dietary) treatment of these patients.

Impact on research

Previous research focussed on the identification of trigger foods for GI symptom generation, but often lacked an extensive listing. The main challenge of understanding how these food products contribute to symptoms, is that they are generally not consumed in isolation, but as part of a whole diet. In this thesis, we investigated the effect of diet quality and dietary inflammatory potential as well as habitual consumption of individual potentially inflammatory components, *i.e.* dietary dicarbonyls and advanced glycation endproducts (AGEs), and food products on GI symptoms and intestinal inflammation in IBS and IBD patients (**Chapters 2-4**).

We highlighted the importance of investigating the effect of overall diet quality by showing its association with more intestinal inflammation in IBD and higher symptom levels in IBS. Furthermore, we noted a more pro-inflammatory diet was associated with higher abdominal pain scores in IBD (**Chapter 2**). Future studies on trigger foods and potential mechanisms should consider the matrix effects of the overall diet, because antagonistic as well as additive or synergistic effects will influence the *in vivo* effects of individual foods and compounds. Furthermore, inter-individual disease and host-related factors, such as the intestinal microbiome and host genetics, should be taken into account.

Not only overall diet composition, but also the processing of foods can impact health, such as 'browning' as part of the Maillard reaction during heating of food. We performed

the first study investigating the intake of dietary dicarbonyls and advanced glycation endproducts (AGEs) in IBS and IBD patients. Although these compounds are generally considered to be pro-inflammatory, we found no significant association with intestinal inflammation in these disorders (**Chapter 3**). As such, we concluded that the concentrations consumed seem insufficient to induce an inflammatory response. It should be noted that also other dicarbonyls and AGEs are present in food. Additionally, it is plausible that we found no inflammatory effects of dicarbonyls and AGEs because their effects may be counteracted by anti-inflammatory nutrients in the food matrix. Future studies should address the impact of the intestinal microbiota and the endogenous production of these compounds.
A lower diet quality may be the result of avoidance of culprit foods, without adequate replacement. Therefore, we added to the identification of known trigger foods and related food avoidance by evaluating 257 food items in patients with IBS. On one hand we found that reported sensitivity differed between foods within specific food groups (such as dairy and vegetables). On the other hand, we observed that many patients report a variety of food items that largely varied between patients. Based on these findings, it seems unlikely that just one underlying mechanism is involved. Finally, in our study population, food avoidance behaviour was associated with higher screening scores for somatisation and Avoidant/Restrictive Food Intake Disorder (ARFID), but not anxiety, depression, or type of symptoms (**Chapter 4**). Future studies should focus on an individualised approach and enter the field of precision nutrition, as well as including the impact of psychological factors.

A key culprit food, also among our top 25 of most frequently reported triggers in IBS patients, is wheat. The pathophysiological mechanism of individuals experiencing symptoms after consumption of wheat in general or gluten specifically (*i.e.* NCWS or NCGS), despite having ruled out wheat allergy and coeliac disease, is still under debate. This thesis includes the first study that actively investigated the nocebo effect in NCGS individuals and confirmed that it can play a substantial role in symptom generation. The nocebo effect was even more pronounced than the effect of actual gluten intake, and thereby suggests involvement of the gut-brain axis in this disorder (**Chapter 6**). Further research is needed to understand the role of the interaction between the gut and the brain in NCGS, and to understand whether it may be classified as a DGBI or possibly even a subtype of IBS.
Nevertheless, we also cannot rule out that specific wheat components, including gluten, trigger symptoms in NCGS/NCWS individuals. In **Chapter 6** we could not exclude an additive effect of gluten intake as highest symptom scores were found in the group that both expected and actually consumed gluten. Additionally, in **Chapter 5**, we showed that the majority of NCWS individuals responded with GI symptoms to at least one of the bread types (bread wheat, spelt, or emmer, made with either yeast- or sourdough fermentation) investigated. Based on our results, we were not able to identify which wheat component is the key culprit and whether symptoms are less

pronounced after consumption of bread from a specific grain type. Instead, we showed inter-individual differences in symptom response, suggesting that host factors, such as the gut microbiota, also play an important role. Future research should focus on better understanding of the mechanisms by which wheat (components) can induce GI symptoms, taking into account inter-individual variation, and aiming to identify biomarkers for the diagnosis of NCGS/NCWS.

The chapters of this thesis have been (or will soon be) published in international peer-reviewed scientific journals. Additionally, these results were presented to various audiences at multiple national and international conferences such as the Dutch Digestive Disease Days, the Digestive Disease Week, the United European Gastroenterology Week, the European Young Cereal Scientists and Technologists Workshop, and the International Gluten Workshop. Furthermore, we used the knowledge gained about NCGS/NCWS for education of dietitians from the Dutch gastroenterology network and the Dutch Coeliac Disease Association.

Impact on healthcare providers

The results from this thesis are relevant for healthcare providers involved in the care of patients with food-related symptoms, such as general practitioners, gastroenterologists, psychologists, and dietitians. One of the major challenges in treatment of these patients relates to the heterogeneity of food triggers and symptom responses.

This thesis has shown that treatment strategies for food-related symptoms in GI disorders require an individualised approach. The first step would be to identify which food products are mainly responsible for triggering symptoms. When eliminating these foods from the diet, also considering the lower diet quality found in IBS and IBD patients, referral to a dietitian is recommended. Dietitians can ensure adequate replacement of the eliminated food items/components and can monitor nutritional status. In NCGS/NCWS individuals, we found that a substantial group could tolerate at least one of the bread types tested. When coeliac disease and wheat allergy have been ruled out, it can therefore be advised to try different bread types to identify one(s) that can be tolerated.

Additionally, all healthcare providers should pay attention to psychological risk factors like excessive food avoidance behaviour, or coexistence of anxiety or depression. Elimination diets or excessive food avoidance are risk factors for eating disorders and worsening of psychological status. However, at the same time, concurrent psychological comorbidities may also impact symptoms occurrence.

Impact on patients and society

By increasing knowledge of the scientific community and healthcare providers, the research described in this thesis aims to improve treatment strategies for food-related GI symptoms in patients with IBS, IBD, and NCGS/NCWS. As media attention for negative effects of food is increasing, informing patients and society on the current evidence is of growing importance.

So far, a clear biological cause of NCGS/NCWS has not been identified. Also, potential causes for trigger foods may differ between various gastroenterology patients. Patients with a lot of food-related GI symptoms and therefore high food avoidance behaviour are at increased risk of nutritional deficiencies. Personal identification of the key trigger foods may already effectively relieve symptoms, making full elimination diets like the low-FODMAP (fermentable oligo-, di-, monosaccharides and polyols) or gluten-free diet unnecessary. Furthermore, a healthy relationship with food is important as it encompasses a complex interplay of biological, psychological, and social aspects. Food-induced symptoms and related anxiety can be an obstacle for a healthy diet as well as eating out and enjoying the social aspect of food. We showed the importance of paying attention to psychological factors, including an increased risk of eating disorders, which can go hand in hand with food-related GI symptoms. Adequate dietary treatment, if necessary combined with psychological intervention, can improve quality of life in these patients. The results from **Chapter 5** may contribute to dietary treatment by providing participants with further insight into which type(s) of bread they may tolerate best. Furthermore, findings of **Chapters 5 and 6** have been summarised and (will be) distributed among the participants.

Moreover, GI disorders are a major public health concern. Both IBS and IBD are associated with high direct and indirect costs.[8,9] For NCGS/NCWS this has not been studied yet, but gluten-free foods are expensive and because of the overlap with IBS we can hypothesise that costs may be similar. It has not been studied how much of these costs can be attributed to the role of food. Nevertheless, effectively managing food-related symptoms by adequate dietary and/or psychological therapy can reduce the socioeconomic impact.

Conclusion

The research described in this thesis has contributed to understanding the role of food in GI symptoms. We have evaluated the role of various food products and components, as well as the impact of psychological factors, in the common GI disorders IBS, IBD, and NCGS/NCWS. These results contribute to better understanding of food-related GI symptoms and add to optimisation of (dietary) treatment options for these patients.

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