

The role of food in gastrointestinal symptoms

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Summary

Various food products and components can trigger gastrointestinal (GI) symptoms in disorders like irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), and non-coeliac gluten/wheat sensitivity (NCGS/NCWS). These triggers can induce symptoms via different pathophysiological mechanisms, including immune responses and inflammation, intestinal barrier dysfunction, the gut microbiota, and/or the gut-brain axis. In this thesis, we further investigated overall diet, trigger foods and components, and their effect on GI symptoms and intestinal inflammation, as well as the role of psychological factors.

First, we studied the impact of the overall dietary pattern on intestinal inflammation and GI symptoms. In **Chapter 2**, we investigated the association of dietary indices with intestinal inflammation and GI symptoms in both IBD and IBS patients. Food frequency questionnaires (FFQ) from 238 IBD patients, 261 IBS patients, and 195 healthy controls (HC) were used to calculate the overall diet quality by the Dutch Healthy Diet index 2015 (DHD-2015) and its inflammatory potential by the Adapted Dietary Inflammatory Index (ADII). Intestinal inflammation was evaluated by faecal calprotectin and the Gastrointestinal Symptom Rating Scale was used to assess symptoms. We found that diet quality was significantly lower in IBD and IBS patients as compared to HC ($b=-4.009$; $p<0.001$). Lower diet quality was associated with more intestinal inflammation in IBD ($b=-0.016$; $p=0.006$) and more severe abdominal pain ($b=-0.012$, $p=0.023$) and reflux syndrome ($b=-0.016$, $p=0.004$) in IBS patients. Furthermore, although the dietary inflammatory potential was not significantly different between groups, in IBD patients a more pro-inflammatory diet was associated with higher abdominal pain scores ($b=0.194$, $p=0.004$). Longitudinal studies are needed to further investigate the role of dietary factors in the development of flares and predominant symptoms.

Besides the overall dietary composition, also the processing of the food consumed, such as the heat induced Maillard reaction, may impact intestinal health and thus disease. In **Chapter 3**, we investigated the intake of dietary dicarbonyls and advanced glycation endproducts (AGEs) as part of the habitual diet in IBD and IBS patients, and the association of these components with intestinal inflammation. The FFQ data from Chapter 2 were used to calculate the dietary intake of dicarbonyls methylglyoxal (MGO), glyoxal (GO), and 3-deoxyglucosone (3-DG), and of the AGEs N ϵ -(carboxymethyl)lysine (CML), N ϵ -(1-carboxyethyl)lysine (CEL), and methylglyoxal-derived hydroimidazolone-1 (MG-H1). We found that the absolute intake of dietary dicarbonyls and AGEs was lower in IBS as compared to IBD and HC (all $p<0.05$), but not after adjustment for energy intake. The intake of these components was not significantly associated with faecal calprotectin, as marker for intestinal inflammation, in IBD and IBS patients, apart from a potential protective effect as indicated by a higher

MGO intake in individuals with low as compared to moderate faecal calprotectin levels ($p=0.031$). Thus, the concentrations of dietary dicarbonyls and AGEs generally present in the diet of Dutch patients with IBD or IBS are not associated with intestinal inflammation, although potential harmful effects might be counteracted by anti-inflammatory components in the food matrix.

As IBS patients often report symptoms to be triggered by food intake, the role of specific food products in symptom generation was investigated. In **Chapter 4**, we evaluated the extent and nature of food intolerance and avoidance in IBS patients and their relation to GI symptoms and psychological comorbidities. Food intolerance and avoidance behaviour were evaluated in 124 IBS patients and 113 HC using a questionnaire with 257 food products of 13 food groups. IBS patients reported a higher number of food products with perceived intolerance than HC (median of 18.0 [25th-75th percentile 10.0-33.5] vs 1.0 [0.0-8.0], respectively, $p<0.001$). A wide variety of trigger foods was reported, with gas-producing foods and fatty/cream-based dairy products most frequently reported by both groups. The number of avoided food products was higher in IBS (15.0 [8.0-27.0] vs 1.0 [0.0-7.0], $p<0.001$). Food avoidance was not significantly related to symptom type, but was significantly associated with an IBS diagnosis, female sex, and higher screening scores for somatisation and Avoidant/Restrictive Food Intake Disorder (ARFID).

Subsequently, we focussed on one of the common trigger foods in GI disorders, namely wheat. In **Chapter 5**, we investigated the effects of six different types of bread on GI symptoms in individuals with self-reported NCWS in whom coeliac disease and wheat allergy were ruled out. Two parallel, randomised, double-blind, crossover, multicentre studies were performed to evaluate yeast fermented (study A, $n=20$) or sourdough fermented (study B, $n=20$) bread made of bread wheat, spelt, or emmer in a randomised order on three separate test days. Each test day was preceded by a run-in period of 3 days and separated by a wash-out period of at least 7 days. Participants followed a symptom-free diet throughout the study. GI symptoms were evaluated by change in symptom score (test day minus average of the 3-day run-in period) on a 0-100mm visual analogue scale (Δ VAS). Responders were defined as an increase in Δ VAS of at least 15mm for overall GI symptoms, abdominal discomfort, abdominal pain, bloating and/or flatulence. The overall change in GI symptoms did not differ significantly between breads of different grains (YF $p=0.267$; SF $p=0.144$). The number of responders was also comparable for both YF (6 to wheat, 5 to spelt, and 7 to emmer, $p=0.761$) and SF breads (9 to wheat, 7 to spelt, and 8 to emmer, $p=0.761$). The majority of NCWS individuals experienced some GI symptoms for at least one of the breads and could also tolerate at least one of the breads. On a group level, no differences were found between different grain types for either YF or SF breads. Therefore, personalised dietary guidance is warranted in NCWS.

In addition to potential biological mechanisms, food-related symptoms may be affected by negative expectancy. Therefore, in **Chapter 6**, we investigated the effects of expectancy versus actual gluten intake on symptoms in 83 individuals with self-reported NCGS in whom coeliac disease and wheat allergy were ruled out. In this randomised, double-blind, placebo-controlled, international multicentre study participants were randomised to one of four groups based on the expectation to consume “gluten-containing” (E+) or “gluten-free” (E-) oat bread for breakfast and lunch (two slices each), and actual intake of gluten-containing (G+) or gluten-free (G-) oat bread. Mean overall GI symptoms were significantly higher in E+G+ compared with E-G+ ($p=0.0010$) and E-G- ($p=0.0016$), but not E+G- ($p=0.28$), nor between E+G- versus E-G+ ($p=0.33$), E+G- versus E-G- ($p=0.47$), and E-G+ versus E-G- ($p>0.99$). We concluded that the combined effect of expectancy and actual gluten intake had the largest effect on GI symptoms, reflecting a nocebo effect, although an additional effect of gluten could not be ruled out. The results of this study necessitate further research into possible involvement of gut-brain interaction in NCGS.

Finally, in **Chapter 7**, we summarised and discussed the main findings of this thesis. We concluded that the association between food intake, psychological factors, and GI symptoms may be bidirectional or even three-dimensional, and future studies should aim to further elicit mechanisms underlying food-related GI symptoms, taking inter-individual variation into account. We highlighted that treatment of these food-related symptoms in GI disorders requires an individualised and multidisciplinary approach with close collaboration between gastroenterologists, dietitians, and psychologists.