Nutrition and disease course in inflammatory bowel disease

Impact paragraph

Inflammatory bowel disease (IBD) is a chronic, inflammatory disorder of the gastrointestinal tract, with Crohn's disease (CD) and ulcerative colitis (UC) as the two main entities. Both CD and UC are characterized by episodes of active inflammation (flares) alternated by periods of inactive disease (remission). The disease phenotype, for instance the disease localization, but also the occurrence of intestinal complications (like fistulas, abscesses, and strictures) and the disease course, such as the duration and frequency of episodes with flares and remission vary widely between patients.[1-3] This leads to extra challenges in identifying the right treatment as well as factors influencing disease outcome. IBD is mainly diagnosed at young adulthood and is a lifelong disease. Many patients require medications that suppress the immune system. These are costly, can lead to mild or severe side effects, and approximately one-third of the patients does not respond to specific drugs.[4-6] The disease has a huge impact on patients' general well-being and often leads to reduced work productivity and absenteeism. This increases the indirect healthcare costs.[7] Therefore, it is important to gain further insight in factors playing a role in IBD onset and disease course to improve disease outcome, quality of life, and costs.

The exact causes of IBD are not yet clear, though it has been shown that genetic susceptibility, a disturbed immune function and the intestinal microbiota play a role.[8,9] Because of the rising incidence of IBD in line with the adoption of a Western lifestyle, environmental factors are also thought to play an important role in the pathogenesis.[10] Environmental factors are of specific interest since many of them can be changed by lifestyle interventions. One of these environmental factors is diet, which is considered to be an important contributor to the development of disease flares by patients,[11-13] but which diets are associated with an increased risk of flares is still largely unclear. Therefore, in the first part of this thesis, we aimed to gain further insight into the habitual dietary intake of IBD patients and the association with disease course.

Patients often take the initiative to adjust their diet to reduce symptoms. This puts patients at increased risk for consuming an unhealthy diet, and thereby developing malnutrition. However, in the current literature, different subpopulations (CD and/or UC, in- and/or outpatients, active and/or remission disease status), definitions and assessment methods (with different cut-off points) were used to define malnutrition.[14-20] As a result, there is a wide variation in the reported prevalence of malnutrition in IBD patients, making it more difficult to define the impact on disease outcome and patient well-being. Therefore, in the second part of this thesis we addressed the assessment of malnutrition in patients with IBD and the association with disease course.

Summary of key findings in this thesis

In the first part of this thesis we focused on the habitual dietary intake and disease course in IBD. In an extensive review published in 2013, six studies on habitual dietary intake and relapse risk were identified. Some association with specific food items were found, but results were not always consistent between studies. Furthermore, none of these studies focused on dietary patterns (**chapter 2**). In **chapter 3**, we were able to identify three dietary patterns in two geographical distinctive IBD outpatient cohorts in the Netherlands. An association was found between one of these dietary patterns and the flare risk during two years of subsequent clinical follow-up.

In the second part of this thesis, we reported on the assessment of malnutrition by multiple parameters for nutritional status. A substantial proportion of the IBD outpatients (47%) was found to have at least one nutritional status parameter impaired (**chapter 4**). A combination of parameters is needed to identify most patients being at risk for malnutrition. Fat free mass index (FFMI), a proxy for muscle mass, was one of the parameters most often impaired. Muscle mass can be affected by fat infiltration, *i.e.,* myosteatosis, contributing to impaired muscle strength. Normally myosteatosis is determined on computed tomography images. However, in CD magnetic resonance imaging (MRI) is frequently used for the diagnostic work-up. The determination of skeletal muscle signal intensity on MRI, as a proxy for myosteatosis, was found to be reproducible and indicated potential clinical relevance, as it was associated with time to resection-free survival in an exploratory analysis (**chapter 5**). In **chapter 6,** we found the risk of an impaired nutritional status to be associated with an increased flare occurrence risk in the subsequent three months in a telemedicine cohort. This underscores the relevance of malnutrition as a risk factor for worse disease course and outcome.

Implications for research

So far, most studies on diet and disease course have focused on specific foods or nutrients, as discussed in **chapter 2.** However, further insight in the role of overall dietary patterns is relevant, since nutrients are ingested as part of a whole meal and are likely to interact. This is especially relevant since the microbiome can be affected by major dietary changes on one hand and is associated with disease onset and disease course on the other hand.[8,9,21,22] The observed association with a dietary pattern and flare risk during clinical follow-up (**chapter 3**) can not claim causality, but indicates the relevance of such patterns in relation to disease course. Dietary intake was only assessed at baseline using a food frequency questionnaire in this study. In future studies, dietary intake should be measured on regular time points during follow-up, in a longitudinal approach as intake can change over time, especially due to gastro-intestinal symptoms but also because of seasonal variation amongst others.

Digital approaches, for example using photos of meals and packaging, may enhance data accuracy and decrease the burden for patients.

In addition, the differences found in habitual dietary intake between the two geographical distinctive cohorts, emphasizes the need for considering geographical differences in intake in large cohorts. The three dietary patterns derived a-posteriori, showed partial similarities regarding the identified food groups. Further studies, in larger study populations and across geographical regions with potential differences in dietary intake are needed, to better identify the important food groups within these patterns. Most likely this will increase the differences between the dietary patterns. As a result, a tailored dietary advice for patients can be made. In subsequent mechanistic studies the observed associations can be studied in more detail. The impact on the intestinal microbiota composition and functional capacity as well on epigenetic changes and direct immune modulating effects can be addressed. Furthermore, the role of food additives, used to create durable and highly-palatable foods and found in processed foods as part of a Western diet, should be investigated.[23] Preliminary data suggest that food additives may directly affect immune function but may also disrupt the intestinal barrier function by affecting for example the intra-epithelial junctional complexes.[24-26] This will become an important research topic, as the consumption of ready-made meals increases, and studies on this topic are rare.

A substantial part of the IBD patients was found to have at least one nutritional status parameter impaired, but the majority was not identified by screening recommendations from current guidelines (**chapter 4**). Therefore, assessment of a combination of nutritional status parameters is needed in all patients, with special attention for the parameters most often impaired, like FFMI. There is still a need for better non-invasive, widely available and easy to apply malnutrition screening instruments in the outpatient clinic. Anthropometric measurements or handgrip strength are examples of proxies for muscle mass which can be considered. Additionally, a possible association was found between myosteatosis, affecting muscle quality, and time to resection-free survival in an explorative analysis (**chapter 5**). Therefore, better understanding of the disease course and association with muscle mass and quality is of interest. Before applying the determination of skeletal muscle signal intensity on MRI in daily clinical practice, future studies should address the differences between scanners and scan protocols first.

Implications for society

Further insight into the role of dietary intake in the pathophysiology of IBD will increase options for targeted preventive as well as therapeutic dietary strategies. This will decrease flare occurrence, the need for medication, is of great importance for

patients' overall well-being, and may improve work productivity and societal participation. This will be beneficial for both direct and indirect healthcare costs.

Additionally, further insight into dietary patterns, can lead to the development of beneficial meals for IBD patients. For example, meals in which specific food items and/or additives are replaced or adjusted. This approach can be taken up and developed by the food industry. These nutritional developments may also be relevant for other immune-mediated diseases, since aetiological factors of IBD and other immune-mediated diseases overlap. To guarantee timely development of these meals, the most recent scientific evidence has to be used and shared between researchers, healthcare professionals and the food industry.

Besides dietary intake, other psychosocial and lifestyle factors (*e.g.,* sleep quality, smoking, stress, and anxiety) are associated with the development of flares or patient well-being in IBD and they can interact with or add to the impact of diet.[27-29] These should be included in future analyses and may differ between patients. To monitor these prospectively in real life, good and trustable tools should be developed, and should be easy to use by patients and healthcare professionals. This requires a good cooperation between technical and healthcare employees. An example is the telemedicine tool 'myIBDcoach', specifically developed to monitor IBD patients. In addition to disease monitoring, questionnaires on quality of life, physiological problems, (work) disability, and screening for malnutrition are completed at regular intervals.[30] By using such tools, patients and physicians will become more aware of dietary quality and lifestyle factors and can refer patients for targeted interventions.

Implications for patients

More insight into the role of dietary patterns on flare occurrence and flare prediction will benefit the patients for a more, tailored, dietary advice and guidance.

Lifestyle factors, like psychosocial well-being and risk of malnutrition, can influence the disease course and are found to precede flares in longitudinal studies (**chapter 6**).[31] Telemedicine can be an important tool for patients to gain better insight in factors predicting disease flares, but also to monitor these factors for timely interventions and to provide feedback. By telemedicine, patients can also be informed actively on the latest developments relevant for their disease. By the implementation of e-learnings on beneficial lifestyle interventions (like dietary guidelines, physical exercise), patients can acquire and apply the knowledge at a convenient moment.

Patient education by e-learnings and dieticians on the relation between malnutrition and adverse outcome and the relations between functional complaints and specific dietary products, will help to prevent malnutrition and to improve disease outcome as well as patients' well-being. This will further be facilitated by a better identification of IBD outpatients with malnutrition when using a combination of measures.

Implications for healthcare professionals

For healthcare professionals (such as physicians, nurse practitioners and dieticians) more insight in the role of dietary patterns on disease course will be of benefit for dietary advice, disease management and guideline development. In turn, this will help the healthcare professionals to provide tailored advice on dietary intake and gastrointestinal symptoms or disease course in daily practice. In case of impairment of diet quality or nutritional status, tailored interventions by healthcare professionals can be applied, improving patients' disease outcome and overall well-being. For example, as the FFMI is often impaired (**chapter 4**), physiotherapist can play an important role in the guidance of physical exercise.

By use of a more holistic approach, addressing modifiable lifestyle factors by patient education and in collaborations between healthcare professionals like diet quality (by a dietician), physical exercise (by a physiotherapist), but also psychosocial factors (by a psychologist), will contribute to an individualised approach and increase patient empowerment. Especially, when future studies can confirm lifestyle factors as important flare predictors and modifiers of patient reported outcome measures. When monitored systematically, treating physicians can initiate timely interventions, provide referrals or learning modules when risk factors for flare development are present.

It is important that researchers publish and share their latest findings with healthcare professionals. A national network can be used to ensure that healthcare professionals specialized in IBD (like physicians, dieticians, physiotherapists, and psychologists) are regularly updated on the latest developments. In addition, patient associations can also play a role in these initiatives, and ensure that the latest developments reaches their target group.