Clinical, psychosocial and therapeutic aspects of irritable bowel syndrome: results of cohort studies and aprobiotic intervention trial

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VALORISATION ADDENDUM
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The gut is considered a gateway to many diseases and disorders not only within the gastrointestinal tract but also in other organs or at a systemic level. In the past decade more information has become available with respect to Irritable Bowel Syndrome (IBS). In this thesis, we have evaluated clinical characteristics and potential underlying pathophysiological mechanisms, such as psychosocial, central nervous system and intestinal factors, in patients with IBS in order to gain more insight in this heterogeneous condition.

IBS is a highly prevalent chronic disorder, which is increasingly found in Western countries. The condition is characterized by chronic, recurrent abdominal pain or discomfort associated with alterations in the pattern of defecation, in absence of an organic cause. IBS affects 15-20% of women and 5-20% of men in the Netherlands and it is assumed that at least 20% of the general population is affected at some time during life. Despite the high prevalence and the negative impact of the disorder on quality of life, only a limited number of effective therapeutic entities are available for IBS patients and subgroups of IBS. Previous studies have focused mainly on symptom improvement in IBS patients, but more recently, many studies have been performed to clarify the pathophysiology of IBS. When underlying pathophysiological mechanisms are better understood, this may open the way to new therapies and to optimize existing therapies. This is a challenging task due to the heterogeneity in presentation of IBS and its multifactorial etiology. Up to now, focusing on further insight in the pathophysiology has not yet led to major breakthroughs or novel therapeutic approaches. Gaining more insight in the pathophysiological mechanisms of IBS remains an important goal and may help to identify subgroups of IBS patients that could benefit from targeted interventions.

Due to the fact that IBS is a chronic disorder, the lack of effective therapies and the relatively high prevalence of IBS, direct healthcare related costs as well as indirect costs related to work-absenteeism are considerable. IBS patients more frequently utilize healthcare facilities compared to healthy subjects from the general population and they have a two to three fold higher consumption of medication compared to the general population. Furthermore, about one-third of the IBS patients also suffer from psychiatric comorbidity, requiring pharmacological and/or psychological interventions. An increased awareness for psychosocial context and co-morbidities is warranted, since almost two-third of all patients with self-reported depressive symptoms are not identified by the attending physician. Screening of patients for quality of life, anxiety, depression and dysfunctional cognitions can be performed rather easily through patient questionnaires and is the basis and justification for additional evidence based
therapeutic interventions.\textsuperscript{5-7} In this thesis we have pointed not only to a pronounced effect of dysfunctional cognitions on quality of life, but also of anxiety and depression, emphasizing the importance of screening for psychiatric complaints in IBS patients and treating them when present.

Patients with IBS actively seek for nutrients, medical of nutritional products and life style adjustments in order to be able to reduce symptoms and improve their quality of life. We have explored the role of a commercially available probiotic product on IBS symptoms in this thesis. No definite answer with respect to the role this of probiotic on IBS symptoms has been provided by us. Also in other studies, the efficacy of probiotics in IBS has been questioned. Based on our data several questions remain to be answered. First, the reason for the difference in response between males and females. Second the timing of the maximum response to the probiotic product. In our study an optimum was reached eight weeks after cessation of the product intake. Third, the mechanisms of action of the potentially beneficial probiotic product. So far, results of probiotic interventions in IBS have been rather disappointing. On the other hand, the role of gut microbiota and gut metabolism in pathogenesis of various gut and systemic disorders is of utmost relevance.

Since IBS has a clear female predominance and symptom scores may differ according to gender, we hypothesize that the phenotype differences in female versus male IBS patients relates to a different pathophysiological background. An important role has been claimed for dysregulations along the brain-gut axis in IBS pathophysiology. We have explored the role of serotonin (5-hydroxytryptamine, 5-HT) metabolism and observed a significant decrease in 5-HIAA concentrations and in 5-HIAA/5-HT ratio in IBS patients compared to healthy controls, with a possible role of gender in the 5-HIAA levels and serotonin metabolism. The question why female IBS patients have lower 5-HIAA plasma levels has not yet been found and warrants further research. We have also observed a significant decrease in short chain fatty acid (SCFA) concentrations in female IBS patients compared to male IBS patients. Based on our observations and findings we strongly recommend further gender specific investigation of the brain-gut-axis, SCFAs and microbiota, taking into account the dietary intake, BMI and the association with symptom severity.

The increasing knowledge about IBS contributes to a better understanding of the condition, not only for patients, but also for their treating physicians. Dissatisfaction of IBS patients regarding their treatment and the interaction with their treating physician is common and has a clear impact on disease outcome. This is to a large extent caused by lack of knowledge and lack of concept to explain to the patient what IBS is and how to manage IBS symptoms. Taking time to explain the complex multifactorial background of IBS to a patient, to acknowledge their symptoms and impact on daily life, and also to reassure patients that no life-threatening diseases is involved, is very important. Furthermore, general practitioners and gastroenterologists should provide patients
with tools for self-management, becoming more in control over their condition and their symptoms. Further research in IBS is needed before more targeted therapies can be provided. We consider the findings in this thesis as a step forward in a better understanding of IBS and the development of therapeutic strategies for all IBS patients.
REFERENCES