

# Irritable bowel syndrome : pathophysiology, symptoms and biomarkers

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## Valorisation addendum



## Valorisation addendum

With this thesis we aim to contribute to the true goal of medical research, that is to improve our understanding of human physiology and pathology, but also to find new approaches to improve and optimise healthcare. This thesis focused on a highly prevalent functional gastrointestinal (GI) disorder, *i.e.* Irritable Bowel Syndrome (IBS). IBS is associated with significant impact on patients' quality of life as well as on societal and health care costs. The studies we presented will add to further insight in the pathophysiology of IBS and provide tools to improve diagnosis and patient monitoring.

IBS is the most commonly diagnosed GI condition,<sup>1</sup> characterized by abdominal pain or discomfort and altered bowel habits. Other GI symptoms such as bloating, flatulence, nausea and belching, are also frequently reported by patients.<sup>2</sup> Although the prevalence of IBS varies geographically, a worldwide estimate of the prevalence is 11%, which is comparable to findings in the Dutch population.<sup>3</sup> Furthermore, IBS is more common in women than in man, with a 2:1 ratio. The exact reasons for this female predominance are not yet clear.<sup>4</sup>

Predominant symptoms and possible triggers vary between patients. Furthermore, in most patients, IBS is a chronic relapsing disorder in which symptoms may vary during the day as well as over time.<sup>5</sup> Symptom burden in IBS patients can be considerable, contributing to significant impairment of quality of life (QoL).<sup>6</sup> This is found not only when compared to the general population, but also in comparison with patients with other medical conditions, such as diabetes mellitus and even end-stage renal disease.<sup>7</sup> The high symptom burden and impact on QoL has a negative impact on work productivity. Therefore IBS is not only associated with significant healthcare costs but also with overall costs to society. The estimated annual healthcare costs per newly diagnosed IBS patient, for example, is up to 7.500 US dollar in the USA and ranges between 500 and 1.000 US dollar in Europe. Cost to industry in Europe through absenteeism and presenteeism related to IBS is estimated between 500 and 1000 US dollar per patient annually.<sup>8</sup>

Solving the riddle of IBS starts with understanding the mechanisms from which symptoms originate. The aetiology of IBS is complex, multifactorial and incompletely understood. Several possible aetiological factors are found to be associated with IBS, including intestinal (e.g. impaired intestinal barrier and altered microbiota composition and activity) and brain-derived factors (for example anxiety and depression) as well as the interaction between the brain and the gut.<sup>9</sup> Despite decades of scientific research and rapidly improving knowledge in the field of neurogastroenterology and motility, there is still much unclear with regard to the pathophysiology, the diagnostic process, standard therapeutics and prognosis of IBS or subgroups thereof.<sup>10</sup> The IBS patient population is very heterogeneous. It is a syndrome based on a cluster of symptoms and

generally divided in 4 subgroups based on predominant bowel habits (*i.e.* diarrhoea, constipating, a mix of both, or undefined). Therefore, it can be assumed that the main pathophysiological mechanisms may differ between IBS patients and the efficacy of therapies that target these mechanisms may differ per patient group. It is therefore of utmost importance to gain more insight in the underlying pathophysiological mechanism of IBS and to cluster patients in relevant subgroups. In the current thesis we investigated several potential pathophysiological mechanisms of IBS and focused on differences between groups of IBS patients.

As described in this thesis, the intestinal barrier function was found to be impaired resulting in increased intestinal permeability. However, this was influenced by a large number of host factors, such as use of medication. After adjustment for among others medication use the intestinal permeability was only found to be increased in the small bowel of the diarrhoea-predominant subtype (IBS-D). On one hand, these findings show that it is very important to take variations in host factors into account when performing mechanistic studies. On the other hand, this indicates that intestinal barrier function may contribute to symptom generation by increased permeation of toxic substances that may affect for example neuroendocrine and immune function, in IBS-D patients but not in other subtypes. A variety of agents have been demonstrated to improve and restore disturbed barrier function in experimental studies. Recently, faecal microbiota transplantation has been shown to re-establish mucosal barrier function in animal models,<sup>11</sup> pointing to a role of the intestinal microbiota in maintenance of stable barrier function. Furthermore, previous studies showed that the administration of living bacteria into the gut lumen of healthy subjects affected the rearrangement of tight junction proteins.<sup>12</sup> In line with these findings, we have demonstrated that potentially beneficial bacteria, *i.e.* different *L. plantarum* strains, may affect gene transcription related to intestinal barrier function as well as the mucosal and systemic immune system in healthy subjects in whom barrier function was disturbed by intake of non-steroidal anti-inflammatory drugs (NSAIDs). However, whether such interventions have potential clinical implication for IBS patients, especially in patients with IBS-D, still has to be investigated.

Furthermore, in this thesis we focused on other potentially affected biological processes in IBS patients such as the serotonin metabolism and visceral perception. Both are potential targets in future therapeutic interventions. The serotonin metabolism plays an important role in the physiology of the GI tract. It is involved in among others motility, secretion and sensitivity.<sup>13</sup> We found that fasting serotonin levels in blood plasma of IBS patients did not differ significantly when compared to healthy controls, but interestingly, the principle metabolite of serotonin, *i.e.* 5-HIAA, was decreased in plasma samples of IBS patients. This was particularly pronounced in the IBS subtype characterised by a mixed stool pattern (IBS-M). Our finding may point to the role of altered serotonin metabolism in this pathophysiology of this IBS subtype, but more research is needed to investigate the association. Recently it has been shown

that oral administration of 5-HTP, the precursor to serotonin, induced significant alterations in systemic serotonin metabolites that were accompanied by increased visceroperception of pain in hypersensitive IBS patients.<sup>14</sup> The presence of visceral hypersensitivity is a well-known phenomenon in IBS patients. However, in what way IBS patients with normal visceral perception differ from those with visceral hypersensitivity, was unknown. In this thesis we have shown that hypersensitive IBS patients, which comprise about 50% of the total IBS population, are younger when compared to the normosensitive patients, but that other demographic characteristic, and also the use of medication, life style factors and the level of psychological symptoms do not differ between these two groups. Furthermore, the groups did not differ with respect to faecal and plasma concentrations of several biomarkers. Since the IBS patient population is very heterogeneous, it is of utmost importance to select clinically relevant subgroups which can be treated by targeted interventions. However, our findings indicate that dividing IBS patients based on visceral sensitivity may be less relevant for daily clinical practice.

The diagnosis of IBS is symptom based using the Rome III criteria, in combination with the exclusion of other organic causes if indicated. In the second part of the thesis, we investigated tools to aid the diagnostic process and reliable symptom assessment in IBS. As abdominal pain is a key-symptom of IBS we provided a systematic overview of the currently available methods to measure abdominal pain in IBS patients, but also performed a pilot study to investigate an electronic momentary symptom (ESM) assessment method, which is rather novel in the field of neurogastroenterology and motility. Repeated symptom assessment at random moments during the day using a digital tool, was found to be feasible and to provide more accurate and detailed insight on symptoms scores and fluctuations during the day. Thereby, this tools may aid in identifying triggers of symptoms in individual patients, which will be of great value to implement more personalised treatment strategies. Based on our findings, the ESM tool is currently being optimised for application in IBS and will be validated in a large international multicentre study.

Finally, this thesis focused on the quest for new biomarkers in IBS. In two separate studies we developed and validated two biomarker panels with high sensitivity and specificity for the discrimination between IBS patients and healthy controls without GI symptoms. Both panels, a faecal and plasma biomarker panel and a panel consisting of volatile organic compounds in exhaled air, were based on a combination of markers reflecting several domains of gut health associated with the multifactorial aetiology of IBS. Both could accurately discriminate between IBS and healthy controls and furthermore did correlate with GI symptom scores. Such biomarker panels, if our results are replicated in future studies, could benefit the diagnostic process of IBS, but also provide more objective measures of treatment efficacy in intervention trials.

In summary, the current thesis contributed to the understanding of possible aetiological mechanisms of IBS, which may be useful for more clinically relevant subtyping of IBS patients and may lead to new targets for interventions. Furthermore, we have provided an overview and evaluated new methods to assess abdominal pain in IBS patients, which may lead to more uniform (therapeutic) outcome measures in future IBS studies. This is of utmost relevance when comparing results and data between studies. We have provided first clues for a potent alternative method of symptom assessment in IBS patients. The development and validation of this tool is currently ongoing. Finally, in this thesis we identified and validated new biomarker panels for IBS patients, which may add to diagnosis and follow-up of IBS. These findings contribute to our knowledge on IBS, provide new tools for evaluating effects in therapeutic trials in IBS and help to unravel and explore potential triggers and environmental factors contributing to symptom generation.

Although at this moment a 'cure' for IBS is only an utopic future perspective, our rapidly expanding knowledge in neurogastroenterology and motility will lead to better treatment options in the near future and thereby will reduce patient discomfort and economic burden of IBS for society.