Samenvatting van het proefschrift
Zlatan Mujagic

"Irritable Bowel Syndrome: Pathophysiology, Symptoms and Biomarkers"

Promotiedatum: 21 december 2015
Universiteit: Universiteit Maastricht

Promotor:
Prof. dr. A.A.M. Masclee
Prof. dr. F.J. van Schooten

Co-promotor:
Dr. D.M.A.E. Jonkers

Irritable Bowel Syndrome is a prevalent functional gastrointestinal disorder, which often results in high symptom burden and significant impairment in quality of life of affected subjects. This thesis contained three parts, that focussed on i) the pathophysiology of IBS, ii) symptom assessment in IBS patients and iii) the development of new biomarker panels for IBS.

Pathophysiology: Intestinal permeability in IBS patients was studied. Small intestinal permeability was increased in diarrhoea predominant IBS patients (IBS-D) when compared to healthy controls. Gastro-duodenal, colonic and whole gut permeability were not altered when compared to controls after adjustment for confounding factors. These findings point to a different pathophysiological mechanism in the IBS-D subtype when compared to the other IBS subtypes. Furthermore, we investigated the effects of oral administration of three Lactobacillus plantarum strains on the intestinal barrier and mucosal and systemic immune function in healthy human subjects, after consumption of the NSAID indomethacin. Indomethacin induced an increase in small intestinal permeability, but which was not affected by any of the bacterial interventions. However, the interventions did induce strain-dependent effects on gene transcription in intestinal mucosal cells, with regard to mucosal gene transcription, with positive effects on repair processes in the compromised intestine and upregulated genes associated with maintenance of T and B-cell function and antigen presentation. These findings provide new insights for the interactions between intestinal barrier, immune system and bacteria present in the gut lumen. Thereafter we investigated differences in clinical characteristics and specific biomarkers in hyper- versus normosensitive IBS patients. Only younger age, female sex and the use of SSRI medication was significantly

Deze proefschriftsamenvatting is afkomstig van de website van
de Nederlandse Vereniging voor Gastroenterologie:
www.nvge.nl

1

associated with the presence of visceral hypersensitivity in IBS patients. Furthermore, the concentrations of several biomarkers related to gut and immune function did not differ significantly between normosensitive and hypersensitive IBS patients. These data raise the question whether the assessment of visceral sensitivity in IBS patients has relevant implications in daily clinical practice, since the differences the patient groups were moderate. Finally, we measured serotonin and 5-HIAA levels in plasma of IBS patients and controls. While no differences were detected in plasma serotonin between groups, 5-HIAA concentrations were significantly lower in IBS patients compared to controls, which was also true for 5 HIAA/serotonin ratio. This was particularly pronounced in IBS-M subtype.

Symptoms: Firstly the currently available instruments for assessing chronic abdominal pain in IBS patients have been evaluated in a systematic review. There was large variety in assessment tools used in the included studies, which hindered comparison between studies and pooling of data for a meta-analyses. Thereafter, we conducted a pilot study to investigate the potential of a momentary symptom assessment, i.e. ESM, in IBS patients. End-of-day diary abdominal pain scores were significantly higher compared to corresponding ESM mean-scores. The difference was even more pronounced for the end-of-week GSRS scores compared to ESM mean-scores. These findings indicate that subjects report peak pain rather than average pain scores in retrospective questionnaires.

Biomarkers: In the search for biomarkers for IBS, an 8-item biomarker panel consisting of IL-1β, IL-6, IL12p70, TNF-α, CgA, HBD2, calprotectin and caproate, was identified to discriminate IBS patients form healthy controls with high sensitivity (88%) and specificity (87%). When using the same 8-item biomarker panel to discriminate IBS subtypes from controls, comparable results were found. Furthermore, the biomarker panel correlated well with GI-symptom scores in a general population cohort. In the last study, a holistic approach was used to identify new biomarkers, i.e. volatile organic compounds (VOCs) in exhaled air. A set of 16 VOCs distinguished IBS patients from controls with a sensitivity of 89% and specificity of 73%. Although further research is needed to test the applicability of these biomarker panels in daily clinical practice, these findings are important steps towards biomarkers based diagnosis of IBS.

Deze proefschriftsamenvatting is afkomstig van de website van
de Nederlandse Vereniging voor Gastroenterologie:
www.nvge.nl

2