GA-map® | **Dysbiosis Test**

PUBLICATION LIST

A comprehensive list of peer-reviewed articles and clinical studies using the GA-map® Dysbiosis Test.

Revision 4

GA Genetic Analysis

Genetic Analysis AS
www.genetic-analysis.com

Address: Kabelgaten 8 | 0580 OSLO | Norway
Phone: +47 48 32 16 10
E-mail: info@genetic-analysis.com

Decreasing the time from gut microbiota analysis to publication

An increasing number of researchers have discovered the efficiency and simplicity of performing gut microbiota analysis using the GA-map® Dysbiosis Test, a CE-marked In-Vitro Diagnostic (IVD) test.

The technology uses single nucleotide differences in the 16S rRNA gene to measure the abundance of species and groups of bacteria in a fecal sample. All pre-processing of the data is done by the GA-map® Analyzer software, hence no bioinformatician resources needed. Reports for microbiota profiles are automatically generated containing information on the dysbiosis index a measure of bacteria profile changes calculated based on the deviation from a reference population.

Merging the rapidness, preciseness, and robustness of RT-PCR approaches with the comprehensiveness of next generation sequencing, the GA-map® technology drastically reduces the time from analysis to publication. Below, a selection of publications performed by using the GA-map® Dysbiosis Test is presented.

The GA-map® technology has been until now reported in the fields of gastroenterology (IBS and IBD) and metabolic disorders (Diabetes and Obesity). Genetic Analysis has the potential to develop In-Vitro Diagnostic (IVD) tests for all diseases and conditions where the microbiota is involved.

Number of publications: **40**

Update: March 2022

GA-map® Dysbiosis Test is not available for clinical use in the US. In the US; for research use only

2022

El-Salhy M, Mazzawi T, Hausken T, Hatlebakk JG. Irritable bowel syndrome patients who are not likely to respond to fecal microbiota transplantation. Neurogastroenterol Motil. 2022 Mar 18:e14353. doi: 10.1111/nmo.14353. Epub ahead of print. PMID: 35302268.

Rej A, Sanders DS, Shaw CC, Buckle R, Trott N, Agrawal A, Aziz I. Efficacy and Acceptability of Dietary Therapies in Non-Constipated Irritable Bowel Syndrome: A Randomized Trial of Traditional Dietary Advice, the Low FODMAP Diet and the Gluten-Free Diet. Clin Gastroenterol Hepatol. 2022 Feb 28:S1542-3565(22)00202-6. doi: 10.1016/j.cgh.2022.02.045. Epub ahead of print. PMID: 35240330.

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2021

Vasapolli R, Schulz C, Schweden M, Casèn C, Kirubakaran GT, Kirste KH, Macke L, Link A, Schütte K, Malfertheiner P. Gut Microbiota Profiles and the Role of Anti-CdtB and Anti-vinculin Antibodies in Patients with FGID. Eur J Clin Invest. 2021 Aug 14:e13666. doi: 10.1111/eci.13666. Epub ahead of print. PMID: 34390492.

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Mazzawi T, El-Salhy M, Lied GA, Hausken T. The Effects of Fecal Microbiota Transplantation on the Symptoms and the Duodenal Neurogenin 3, Musashi 1, and Enteroendocrine Cells in Patients With Diarrhea-Predominant Irritable Bowel Syndrome. Front Cell Infect Microbiol. 2021 May 12;11:524851. doi: 10.3389/fcimb.2021.524851. PMID: 34055657; PMCID: PMC8149964.

Öhman L, Lasson A, Strömbeck A, Isaksson S, Hesselmar M, Simrén M, Strid H, Magnusson MK. Fecal microbiota dynamics during disease activity and remission in newly diagnosed and established ulcerative colitis. Sci Rep. 2021 Apr 21;11(1):8641. doi: 10.1038/s41598-021-87973-7. PMID: 33883600; PMCID: PMC8060394.

Wei S, Bahl MI, Baunwall SMD, Hvas CL, Licht TR. Determining Gut Microbial Dysbiosis - A review of applied indexes for assessment of intestinal microbiota imbalances. Appl Environ Microbiol. 2021 Mar 19:AEM.00395-21. doi: 10.1128/AEM.00395-21. Epub ahead of print. PMID: 33741632.

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Andréasson K, Neringer K, Wuttge DM, Henrohn D, Marsal J, Hesselstrand R. Mycophenolate mofetil for systemic sclerosis: drug exposure exhibits considerable inter-individual variation-a prospective, observational study. Arthritis Res Ther. 2020 Oct 6;22(1):230. doi: 10.1186/s13075-020-02323-8. PMID: 33023643; PMCID: PMC7539387.

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Mazzawi T, Eikrem Ø, Lied GA, Hausken T. Abnormal Uroguanylin Immunoreactive Cells Density in the Duodenum of Patients with Diarrhea-Predominant Irritable Bowel Syndrome Changes following Fecal Microbiota Transplantation. Gastroenterol Res Pract. 2020;2020:3520686. Published 2020 Feb 4.

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El-Salhy M, Hatlebakk JG, Gilja OH, Bråthen Kristoffersen A, Hausken T. Efficacy of faecal microbiota transplantation for patients with irritable bowel syndrome in a randomised, double-blind, placebo-controlled study. Gut. 2020;69(5):859-867.

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PUBLICATIONS

2022

El-Salhy M. et al, Neurogastroenterol Motil (March 2022);
Irritable bowel syndrome patients who are not likely to respond to fecal microbiota transplantation.

Background:
Fecal microbiota transplantation (FMT) interventions have recently been advocated to not succeed in every irritable bowel syndrome (IBS) patient, since the outcome of FMT varies with the IBS subset. This study investigated the factors potentially affecting FMT response using the same patient cohort used in our previous study.
Method:
This study included 109 patients who received allogenic FMT. Patients completed five questionnaires that assessed their symptoms and quality of life at baseline and at 2 weeks, 1 month, and 3 months after FMT. Patients also provided fecal samples at baseline and 1 month after FMT. The fecal bacterial profile and dysbiosis index (DI) were determined using 16S rRNA gene PCR DNA amplification covering variable genes V3-V9. Response to FMT was defined as a decrease of ≥50 points in the total IBS-SSS score after FMT.
Results:
An IBS patient's response or nonresponse to FMT was not determined by age, IBS duration, IBS subtype, IBS symptoms, fatigue, quality of life, or DI. There were more male nonresponders than responders, and the fluorescence signals of Alistipes were lower in nonresponders than in responders.
Conclusions:
We concluded that IBS patients who are male and/or have low fecal Alistipes levels are most likely to not respond to FMT treatment. Whether low fecal Alistipes levels could be used as a marker for predicting the outcome of FMT remains to be determined.

Rej A. et al, Clin Gastroenterol Hepatol (February 2022);
Efficacy and Acceptability of Dietary Therapies in Non-Constipated Irritable Bowel Syndrome: A Randomized Trial of Traditional Dietary Advice, the Low FODMAP Diet and the Gluten-Free Diet.

Background:
Various diets are proposed as first-line therapies for non-constipated irritable bowel syndrome (IBS) despite insufficient or low-quality evidence. We performed a randomized trial comparing traditional dietary advice (TDA) against the low FODMAP diet (LFD) and gluten-free diet (GFD).
Method:
Patients with Rome IV-defined non-constipated IBS were randomized to TDA, LFD, or a GFD (the latter allowing for minute gluten cross-contamination). The primary endpoint was clinical response after 4 weeks of dietary intervention, as defined by ≥50-point reduction in IBS symptom severity score (IBS-SSS). Secondary endpoints included i) changes in individual IBS-SSS items within clinical responders, ii) acceptability and food-related quality of life with dietary therapy, iii) changes in nutritional intake, iv) alterations in stool dysbiosis index, and v) baseline factors associated with clinical response.
Results:
The primary endpoint of ≥50-point reduction in IBS-SSS was met by 42% (n=14/33) undertaking TDA, 55% (n=18/33) for LFD, and 58% (n=19/33) for GFD; p=0.43. Responders had similar improvements in IBS-SSS items regardless of their allocated diet. Individuals found TDA cheaper (p<0.01), less time-consuming to shop (p<0.01), and easier to follow when eating out (p=0.03) than the GFD and LFD. TDA was also easier to incorporate into daily life than the LFD (p=0.02). Overall reductions in micro- and macro- nutrient intake did not significantly differ across the diets. However, the LFD group had the greatest reduction in total FODMAP content (27.7g/day pre-intervention to 7.6g/day at week 4) compared with the GFD (27.4/g/day to 22.4g/day) and TDA (24.9g/day to 15.2g/day); p<0.01. Alterations in stool dysbiosis index were similar across the diets, with 22-29% showing reduced dysbiosis, 35-39% no change, and 35-40% increased dysbiosis; p=0.99. Baseline clinical characteristics and stool dysbiosis index did not predict response to dietary therapy.
Conclusions:
TDA, LFD and GFD are effective approaches in non-constipated IBS, but TDA is the most patient-friendly in terms of cost and convenience. We recommend TDA as the first-choice dietary therapy in non-constipated IBS, with a LFD and GFD reserved according to specific patient preferences and specialist dietetic input.

Sagard J. et al, Arthritis Res Ther. (February 2022);
Gut dysbiosis associated with worse disease activity and physical function in axial spondyloarthritis

Background:
Based on clinical and genetic associations, axial spondyloarthritis (axSpA) and inflammatory bowel disease (IBD) are suspected to have a linked pathogenesis. Gut dysbiosis, intrinsic to IBD, has also been observed in axSpA. It is, however, not established to what degree gut dysbiosis is associated with axSpA disease severity. The objective of this study was to compare gut dysbiosis frequency between controls, non-radiographic axial spondyloarthritis (nr-axSpA), and ankylosing spondylitis (AS) patients and investigate whether gut dysbiosis is cross-sectionally associated with axSpA disease activity, physical function, mobility, or pain.
Method:
Gut dysbiosis was assessed by 16SrRNA analysis of feces from 44/88 nr-axSpA/AS patients (ASAS/mNY criteria) without inflammatory bowel disease (IBD) and 46 controls without IBD or rheumatic disease. The GA-map™ Dysbiosis Test was used,

grading gut microbiota aberrations on a 1-5 scale, where ≥3 denotes dysbiosis. Proportions with dysbiosis were compared between the groups. Furthermore, standard axSpA measures of disease activity, function, mobility, and pain were compared between patients (nr-axSpA and AS combined) with and without dysbiosis, univariately, and adjusted for relevant confounders (ANCOVA).

Results:

Gut dysbiosis was more frequent in AS than controls (36% versus 17%, p=0.023), while nr-axSpA (25% dysbiosis) did not differ significantly from either AS or controls. Univariately, most axSpA measures were significantly worse in patients with dysbiosis versus those without: ASDAS-CRP between-group difference 0.6 (95% CI 0.2-0.9); BASDAI 1.6 (0.8-2.4); evaluator's global disease activity assessment (Likert scale 0-4) 0.3 (0.1-0.5), BASFI 1.5 (0.6-2.4), and VAS pain (cm) 1.3 (0.4-2.2). Differences remained significant after adjustment for demographics, lifestyle factors, treatments, gut inflammation (fecal calprotectin ≥50 mg/kg), and gut symptoms, except for VAS pain. BASMI and CRP were not associated with dysbiosis.

Conclusions:

Gut dysbiosis, more frequent in AS patients than controls, is associated with worse axSpA disease activity and physical function, seemingly irrespective of both gut inflammation and treatments. This provides further evidence for an important link between disturbances in gastrointestinal homeostasis and axSpA.

2021

Vasapolli R. et al, Eur J Clin Invest (August 2021);

Gut Microbiota Profiles and the Role of Anti-CdtB and Anti-vinculin Antibodies in Patients with FGID.

Background:

Distinct fecal microbiota profiles are reported to be associated with various subtypes of IBS. Circulating antibodies to cytolethal-distending-toxin B (CdtB) and vinculin are proposed as biomarkers to identify post-infectious IBS. The aim of our study was to analyze serum levels of anti-CdtB and anti-vinculin antibodies in patients with different Functional Gastrointestinal Disorders (FGID) and their correlation with the composition of fecal microbiome.

Method:

The study cohort comprised 65 prospectively recruited individuals: 15 with Diarrhea-type-IBS (IBS-D), 13 with Constipation-type-IBS (IBS-C), 15 with functional dyspepsia (FD) and 22 healthy controls. FGID subgroups were defined according to Rome III criteria. Serum levels of anti-CdtB and anti-vinculin antibodies were measured by ELISA. Fecal microbiome composition analysis and assessment of dysbiosis were performed by GA-map®-Dysbiosis Test.

Results:

Positivity rate either for anti-CdtB or anti-vinculin antibodies was higher in the IBS-C group (76.9%) compared to IBS-D (40.0%), FD (60%) and healthy (63.6%) groups. Dysbiosis was more frequent in subjects positive for anti-CdtB antibodies and in IBS-C patients, who showed an increased amount of opportunistic/pro-inflammatory bacteria and reduced gut protective bacteria. IBS-C patients showed a high inter-individual variation of bacterial communities compared to other FGID subgroups and healthy individuals, whereas microbial profiles of patients with IBS-D and FD were overlapping with those of healthy controls. No bacteria markers showed significant differences between FGID subgroups and healthy controls.

Conclusions:

Neither anti-CdtB/anti-vinculin antibodies nor fecal microbial profiles allowed to discriminate between specific FGID subgroups. Dysbiosis was more frequent in patients presenting with anti-CdtB antibodies and in IBS-C patients.

El-Salhy M. et al, Neurogastroenterol Motil. (June 2021);

Long-term effects of fecal microbiota transplantation (FMT) in patients with irritable bowel syndrome.

Background:

We recently found fecal microbiota transplantation (FMT) in irritable bowel syndrome (IBS) patients to be an effective and safe treatment after 3 months. The present follow-up study investigated the efficacy and safety of FMT at 1 year after treatment.

Method:

This study included 77 of the 91 IBS patients who had responded to FMT in our previous study. Patients provided a fecal sample and completed five questionnaires to assess their symptoms and quality of life at 1 year after FMT. The dysbiosis index (DI) and fecal bacterial profile were analyzed using a 16S rRNA gene-based DNA probe hybridization. The levels of fecal short-chain fatty acids (SCFAs) were determined by gas chromatography.

Results:

There was a persistent response to FMT at 1 year after treatment in 32 (86.5%) and 35 (87.5%) patients who received 30-g and 60-g FMT, respectively. In the 30-g FMT group, 12 (32.4%) and 8 (21.6%) patients showed complete remission at 1 year and 3 months, respectively; the corresponding numbers in the 60-g FMT group were 18 (45%) and 11 (27.5%), respectively. Abdominal symptoms and the quality of life were improved at 1 year compared with after 3 months. These findings were accompanied by comprehensive changes in the fecal bacterial profile and SCFAs.

Conclusions:

Most of the IBS patients maintained a response at 1 year after FMT. Moreover, the improvements in symptoms and quality of life increased over time. Changes in DI, fecal bacterial profile and SCFAs were more comprehensive at 1 year than after 3 months. www.clinicaltrials.gov (NCT03822299).

Ahluwalia B. et al, Cells. (June 2021);

A Distinct Faecal Microbiota and Metabolite Profile Linked to Bowel Habits in Patients with Irritable Bowel Syndrome

Abstract:

Patients with irritable bowel syndrome (IBS) are suggested to have an altered intestinal microenvironment. We therefore aimed to determine the intestinal microenvironment profile, based on faecal microbiota and metabolites, and the potential link to symptoms in IBS patients. The faecal microbiota was evaluated by the GA-map™ dysbiosis test, and tandem mass spectrometry (GC-MS/MS) was used for faecal metabolomic profiling in patients with IBS and healthy subjects. Symptom severity was assessed using the IBS Severity Scoring System and anxiety and depression were assessed using the Hospital Anxiety and Depression Scale. A principal component analysis based on faecal microbiota (n = 54) and metabolites (n = 155) showed a clear separation between IBS patients (n = 40) and healthy subjects (n = 18). Metabolites were the main driver of this separation. Additionally, the intestinal microenvironment profile differed between IBS patients with constipation (n = 15) and diarrhoea (n = 11), while no clustering was detected in subgroups of patients according to symptom severity or anxiety. Furthermore, ingenuity pathway analysis predicted amino acid metabolism and several cellular and molecular functions to be altered in IBS patients. Patients with IBS have a distinct faecal microbiota and metabolite profile linked to bowel habits. Intestinal microenvironment profiling, based on faecal microbiota and metabolites, may be considered as a future non-invasive diagnostic tool, alongside providing valuable insights into the pathophysiology of IBS.

El-Salhy M. et al, World J Gastroenterol. (May 2021);

Responses to faecal microbiota transplantation in female and male patients with irritable bowel syndrome

Background:

Faecal microbiota transplantation (FMT) seems to be a promising treatment for irritable bowel syndrome (IBS) patients. In Western countries (United States and Europe), there is a female predominance in IBS. A sex difference in the response to FMT has been reported recently in IBS patients.

Aim:

To investigate whether there was a sex difference in the response to FMT in the IBS patients who were included in our previous randomized controlled trial of the efficacy of FMT.

Method:

The study included 164 IBS patients who participated in our previous randomized controlled trial. These patients had moderate-to-severe IBS symptoms belonging to the IBS-D (diarrhoea-predominant), IBS-C (constipation-predominant) and IBS-M (mixed) subtypes, and had not responded to the National Institute for Health and Care Excellence (NICE)-modified diet. They belonged in three groups: placebo (own faeces), and active treated group (30-g or 60-g superdonor faeces). The patients completed the IBS severity scoring system (IBS-SSS), Fatigue Assessment Scale (FAS) and the IBS quality of life scale (IBS-QoL) questionnaires at the baseline and 2 wk, 1 mo and 3 mo after FMT. They also provided faecal samples at the baseline and 1 mo after FMT. The faecal bacteria profile and dysbiosis were determined using the 16S rRNA gene polymerase chain reaction DNA amplification covering V3-V9; probe labelling by single nucleotide extension and signal detection. The levels of short-chain fatty acids (SCFAs) were determined by gas chromatography and flame ionization.

Results:

There was no sex difference in the response to FMT either in the placebo group or active treated group. There was no difference between females and males in either the placebo group or actively treated groups in the total score on the IBS-SSS, FAS or IBS-QoL, in dysbiosis, or in the faecal bacteria or SCFA level. However, the response rate was significantly higher in females with diarrhoea-predominant (IBS-D) than that of males at 1 mo, and 3 mo after FMT. Moreover, IBS-SSS total score was significantly lower in female patients with IBS-D than that of male patients both 1 mo and 3 mo after FMT.

Conclusion:

There was no sex difference in the response to FMT among IBS patients with moderate-to-severe symptoms who had previously not responded to NICE-modified diet. However, female patients with IBS-D respond better and have higher reduction of symptoms than males after FMT.

Core tip:

A sex difference in the response to faecal microbiota transplantation (FMT) was previous reported for a subgroup of refractory irritable bowel syndrome (IBS) patients with severe bloating who had not responded to at least three conventional therapies for IBS. This subgroup only contained patients with diarrhoea-predominant (IBS-D) or mixed (IBS-M) IBS. The present study found no sex difference in the response to FMT among IBS patients with moderate-to-severe symptoms of IBS-D, constipation-predominant (IBS-C) and IBS-M. However, female patients with IBS-D respond better and have higher reduction of symptoms than males after FMT.

Mazzawi T. et al, Front Cell Infect Microbiol. (May 2021);

The Effects of Fecal Microbiota Transplantation on the Symptoms and the Duodenal Neurogenin 3, Musashi 1, and Enteroendocrine Cells in Patients with Diarrhea-Predominant Irritable Bowel Syndrome.

Introduction:

Interactions between the gut microbiota and enteroendocrine cells play important role in irritable bowel syndrome (IBS). Reduced stem cell densities and their differentiation into enteroendocrine cells may cause abnormal densities of the duodenal enteroendocrine cells in IBS patients.

Materials and methods:

We aimed to investigate the effects of fecal microbiota transplantation (FMT) on stem cell differentiation into enteroendocrine cells as detected by neurogenin 3, stem cells

as detected by Musashi 1, and the enteroendocrine cells in the duodenum of IBS patients. The study included 16 IBS patients according to Rome III criteria. Four patients were excluded. The remaining patients (n = 12, four females and eight males) were divided according to the cause of IBS into post-infectious (n = 6) and idiopathic (n = 6) IBS. They completed the following questionnaires before and 3 weeks after FMT: IBS-Symptom Severity Scoring system (IBS-SSS) and IBS-Symptom Questionnaire (IBS-SQ). Feces donated by healthy relatives of the patients were transplanted via gastroscope. Biopsies were taken from the descending part of the duodenum at baseline and 3 weeks after FMT. They were immunostained for neurogenin 3, Musashi 1, and all types of duodenal enteroendocrine cells and quantified by computerized image analysis. Microbiota analyses of feces collected just before and 3 weeks after FMT were performed using GA-map™ Dysbiosis test (Genetic Analysis AS, Oslo, Norway).

Results:

The total scores for IBS-SSS and IBS-SQ were significantly improved 3 weeks after receiving FMT, P = 0.0009 and <0.0001, respectively. The stem cell densities of neurogenin 3 increased significantly following FMT (P = 0.0006) but not for Musashi 1 (P = 0.42). The cell densities of chromogranin A, cholecystokinin, gastric inhibitory peptide, serotonin, and somatostatin, but not for secretin, have significantly changed in both IBS groups after 3 weeks from receiving FMT.

Conclusion:

More than two-thirds of IBS patients experienced improvement in their symptoms parallel to changes in the enteroendocrine cells densities 3 weeks after FMT. The changes in the enteroendocrine cell densities do not appear to be caused by changes in the stem cells or their early progenitors rather by changes in the differentiation progeny as detected by neurogenin 3. The study was retrospectively registered at ClinicalTrials.gov (ID: NCT03333291).

Öhman L. et al, Sci Rep. (April 2021);

Fecal microbiota dynamics during disease activity and remission in newly diagnosed and established ulcerative colitis.

Abstract:

Patients with ulcerative colitis (UC) have an altered gut microbiota composition, but the microbial relationship to disease activity needs to be further elucidated. Therefore, temporal dynamics of the fecal microbial community during remission and flare was determined. Fecal samples were collected at 2-6 time-points from UC patients during established disease (cohort EST) and at diagnosis (cohort NEW). Sampling range for cohort EST was 3-10 months and for cohort NEW 36 months. Relapses were monitored for an additional three years for cohort EST. Microbial composition was assessed by Genetic Analysis GA-map Dysbiosis Test, targeting ≥ 300 bacteria. Eighteen patients in cohort EST (8 with maintained remission and 10 experiencing a flare), provided 71 fecal samples. In cohort NEW, 13 patients provided 49 fecal samples. The microbial composition showed no clustering related to disease activity in any cohort. Microbial dissimilarity was higher between than within patients for both cohorts, irrespective of presence of a flare. Microbial stability within patients was constant over time with no major shift in overall composition nor modification in the abundance of any specific species. Microbial composition was not affected by intensified medical treatment or linked to future disease course. Thus in UC, the gut microbiota is highly stable irrespective of disease stage, disease activity or treatment escalation. This suggests that prolonged dietary interventions or repeated fecal transplantations are needed to be able to induce permanent alterations of the gut microbiota.

Wei S. et al, Appl Environ Microbiol. (March 2021);

Determining Gut Microbial Dysbiosis - A review of applied indexes for assessment of intestinal microbiota imbalances

Abstract:

Assessing "dysbiosis" in intestinal microbial communities is increasingly considered a routine analysis in microbiota studies and has added relevant information to the prediction and characterization of diseases and other adverse conditions. However, dysbiosis is not a well-defined condition. A variety of different dysbiosis indexes have been suggested and applied, but their underlying methodology, as well as the cohorts and conditions for which they have been developed, differ considerably. To date, no comprehensive overview and comparison of all the different methodologies and applications of such indexes is available. Here, we list all types of dysbiosis indexes identified in the literature, introduce their methodology, group them into categories, and discuss their potential descriptive and clinical applications as well as their limitations. Our focus is thus not on the implications of dysbiosis for disease, but on the methodological approaches available to determine and quantify this condition.

2020

Bratlie M. et al, Eur J Nutr. (October 2020);

Effects of high intake of cod or salmon on gut microbiota profile, faecal output and serum concentrations of lipids and bile acids in overweight adults: a randomised clinical trial

Purpose:

To explore whether high intake of cod or salmon would affect gut microbiota profile, faecal output and serum concentrations of lipids and bile acids.

Methods:

Seventy-six adults with overweight/obesity with no reported gastrointestinal disease were randomly assigned to consume 750 g/week of either cod or salmon, or to avoid fish intake (Control group) for 8 weeks. Fifteen participants from each group were randomly selected for 72 h faeces collection at baseline and end point for gut microbiota profile analyses

using 54 bacterial DNA probes. Food intake was registered, and fasting serum and morning urine were collected at baseline and end point.

Results:

Sixty-five participants were included in serum and urine analyses, and gut microbiota profile was analysed for 33 participants. Principal component analysis of gut microbiota showed an almost complete separation of the Salmon group from the Control group, with lower counts for bacteria in the Bacteroidetes phylum and the Clostridiales order of the Firmicutes phyla, and higher counts for bacteria in the Selenomonadales order of the Firmicutes phylum. The Cod group showed greater similarity to the Salmon group than to the Control group. Intake of fibres, proteins, fats and carbohydrates, faecal daily mass and output of fat, cholesterol and total bile acids, and serum concentrations of cholesterol, triacylglycerols, non-esterified fatty acids and total bile acids were not altered in the experimental groups.

Conclusion:

A high intake of cod or salmon fillet modulated gut microbiota but did not affect faecal output or serum concentrations of lipids and total bile acids.

Andréasson K. et al, Arthritis Res Ther. (October 2020);

Mycophenolate mofetil for systemic sclerosis: drug exposure exhibits considerable inter-individual variation-a prospective, observational study

Objectives:

Mycophenolate mofetil (MMF) is an established therapy for systemic sclerosis (SSc), but its pharmacokinetics in this disease remains unexplored. We have investigated drug exposure in MMF-treated patients with SSc in relation to clinical features of the disease and common concomitant drugs.

Methods:

This study was predefined to include 35 MMF-treated SSc patients who were using MMF at a fixed dose of 0.5, 1.0 or 1.5 g twice daily since at least 3 months. The 12-h drug exposure of the active MMF metabolite mycophenolic acid (MPA) was estimated by repeated analysis of plasma MPA over a 6-h period. This 12-h drug exposure was dose normalised to a daily intake of 3 g MMF (MPA_AUC3g) in order to compare subjects using MMF at different doses. Drug exposure was analysed in reference to the clinical characteristics including body weight, renal function, autoantibodies, intestinal dysbiosis, intestinal inflammation assessed by faecal (F)-calprotectin, intestinal symptoms assessed by the University of California Los Angeles Scleroderma Trial Consortium Gastrointestinal Tract Instrument 2.0 and concomitant drug usage including proton-pump inhibitors (PPI)

Results:

Thirty-four out of 35 study participants completed the study. The mean daily MMF dose was 2.1 g. Drug exposure expressed as MPA_AUC3g varied up to 8-fold between patients (median 115, range 27-226 mg h/L). MPA_AUC3g was inversely related to body weight ($rs = -0.58$, $p < 0.001$) and renal function ($rs = -0.34$, $p = 0.054$). Anti-topoisomerase-1 antibodies and male sex were associated with lower MPA_AUC3g (87 vs 123 and 71 vs 141; $p = 0.008$ and $p = 0.015$, respectively). MPA_AUC3g was inversely related to the intestinal abundance of lactobacilli and to F-calprotectin ($rs = -0.54$, $p = 0.004$; $rs = -0.36$, $p = 0.034$), but not to gastrointestinal symptoms. MPA_AUC3g was inversely related to PPI usage ($rs = -0.45$, $p = 0.007$). We found no association between MPA_AUC3g and disease subtype, disease duration or disease activity.

Conclusion:

MMF-treated SSc patients exhibit considerable inter-individual variation in drug exposure, and lower MPA levels were primarily found in PPI users with poor prognostic factors. Body weight, renal function, sex, serology, gastrointestinal manifestations and/or measuring individual MPA exposure should be considered when using MMF for SSc.

Vatn S. et al, Scand J Gastroenterol. (August 2020);

Faecal microbiota signatures of IBD and their relation to diagnosis, disease phenotype, inflammation, treatment escalation and anti-TNF response in a European Multicentre Study (IBD-Character)

Methods:

We examined faecal samples, using the GA-map™ Dysbiosis Test, to associate gut microbiota composition with Crohn's disease (CD) and ulcerative colitis (UC) and to identify markers for future biomarker identification. We conducted a prospective case-control study (EU-ref. no. 305676) in an inception cohort of 324 individuals (64 CD, 84 UC, 116 symptomatic non-IBD controls and 44 healthy controls) across five European centres and examined 54 predetermined bacterial markers. We categorized patients according to the Montreal Classification and calculated the dysbiosis index (DI). Non-parametric tests were used to compare groups and the Bonferroni correction to adjust for multiple comparisons.

Results:

The fluorescent signals (FSSs) for *Firmicutes* and *Eubacterium hallii* were lower in inflammatory bowel disease (IBD) vs. symptomatic controls ($p<.05$). FSS for Firmicutes, *Lachnospiraceae*, *Eubacterium hallii* and *Ruminococcus albus / bromii* were lower, whereas the signal for Bacteroides Fragilis was higher in UC vs. symptomatic controls ($p<.05$). FSS was higher for *Bifidobacterium spp.*, *Eubacterium hallii*, Actinobacteria and Firmicutes among patients with ulcerative proctitis, compared to extensive colitis ($p<.05$). In CD, we observed no association with disease location. The DI correlated with faecal calprotectin in both CD and in UC ($p<.001$). In terms of treatment escalation and anti-TNF response, differences were observed for some bacterial markers, but none of these associations were statistically significant.

Conclusion:

Our data reveal that the GA-map™ Dysbiosis Test holds the potential to characterize the faecal microbiota composition and to assess the degree of dysbiosis in new-onset IBD. On the other hand, our results cannot demonstrate any proven

diagnostic or predictive value of this method to support clinical decision making.

Berentsen B. et al, Medicine (Baltimore). (September 2020);

Study protocol of the Bergen brain-gut-microbiota-axis study: A prospective case-report characterization and dietary intervention study to evaluate the effects of microbiota alterations on cognition and anatomical and functional brain connectivity in patients with irritable bowel syndrome.

Abstract:

Irritable bowel syndrome (IBS) is a common clinical label for medically unexplained gastrointestinal (GI) symptoms, recently described as a disturbance of the brain-gut-microbiota (BGM) axis. To gain a better understanding of the mechanisms underlying the poorly understood etiology of IBS, we have designed a multifaceted study that aim to stratify the complex interaction and dysfunction between the brain, the gut, and the microbiota in patients with IBS.

Methods:

Deep phenotyping data from patients with IBS (n = 100) and healthy age- (between 18 and 65) and gender-matched controls (n = 40) will be collected between May 2019 and December 2021. Psychometric tests, questionnaires, human biological tissue/samples (blood, faeces, saliva, and GI biopsies from antrum, duodenum, and sigmoid colon), assessment of gastric accommodation and emptying using transabdominal ultrasound, vagal activity, and functional and structural magnetic resonance imaging (MRI) of the brain, are included in the investigation of each participant. A subgroup of 60 patients with IBS-D will be further included in a 12-week low FODMAP dietary intervention-study to determine short and long-term effects of diet on GI symptoms, microbiota composition and functions, molecular GI signatures, cognitive, emotional and social functions, and structural and functional brain signatures. Deep machine learning, prediction tools, and big data analyses will be used for multivariate analyses allowing disease stratification and diagnostic biomarker detection.

Discussion:

To our knowledge, this is the first study to employ unsupervised machine learning techniques and incorporate systems-based interactions between the central and the peripheral components of the brain-gut-microbiota axis at the levels of the multiomics, microbiota profiles, and brain connectome of a cohort of 100 patients with IBS and matched controls; study long-term safety and efficacy of the low-FODMAP diet on changes in nutritional status, gut microbiota composition, and metabolites; and to investigate changes in the brain and gut connectome after 12 weeks strict low-FODMAP-diet in patients with IBS. However, there are also limitations to the study. As a restrictive diet, the low-FODMAP diet carries risks of nutritional inadequacy and may foster disordered eating patterns. Strict FODMAP restriction induces a potentially unfavourable gut microbiota, although the health effects are unknown.

Trial registration number:

NCT04296552 (ClinicalTrials.gov).

Aasbrenn M. et al, BMC Endocr Disord. (July 2020);

Changes in serum zonulin in individuals with morbid obesity after weight-loss interventions: a prospective cohort study

Background:

Zonulin is a biomarker of impaired intestinal permeability, which has been associated with various disorders. The primary aim was to study serum zonulin (s-zonulin) in individuals with morbid obesity before and after a conservative weight loss intervention followed by bariatric surgery. The secondary aims were to explore predictors of s-zonulin, and the associations between the changes of the predictors and changes in s-zonulin, and to compare the associations in the two treatment periods.

Methods:

Individuals with morbid obesity were included. Data before any weight loss interventions, after a 6 months' conservative weight loss intervention, and 6 months after bariatric surgery were used. S-zonulin was measured with an ELISA method from Immundiagnostik AB, Bensheim, Germany. Data were analysed with mixed models.

Results:

The mean body mass index was 42.1 kg/m2 (SD 3.8) at inclusion and was reduced to 38.7 kg/m2 (SD 3.8) and 29.8 kg/m2 (SD 3.8) after the conservative treatment and bariatric surgery respectively. S-zonulin was 63 ng/mL (SD 32) at inclusion and was reduced with 19 ng/ml (95% CI 12 to 26, p < 0.001) after conservative treatment and 11 ng/ml (95% CI 0 to 21, p = 0.04) after bariatric surgery. At inclusion, s-zonulin was significantly associated with factors including p-glucose (B = 2.21, 95% CI 1.09 to 3.33, p < 0.001), c-reactive protein (B = 1.02, 95% CI 0.45 to 1.58, p < 0.001) and the intake of proteins (B = 0.23, 95% CI 0.08 to 0.38, p = 0.003) and non-nutritive sweeteners (B = 0.68, 95% CI 0.19 to 1.17, p = 0.007). The reduction in s-zonulin after the conservative weight loss intervention was significantly associated with improvement in diarrhoea (B = 6.6, 95% CI 1.3 to 11.8, p = 0.02), HbA1c (B = 9.7, 95% CI 1.1 to 18.3, p = 0.03), p-glucose (B = 3.5, 95% CI 1.2 to 5.9, p = 0.004) and gamma-GT (B = 0.28, 95% CI 0.09 to 0.47, p = 0.004), but not associated with the change in body mass index (B = 0.9, 95% CI - 1.5 to 3.3, p = 0.46).

Conclusion:

S-zonulin was markedly reduced after the conservative weight loss intervention, and further reduced after bariatric surgery. The reduction in s-zonulin was associated with improvement of diarrhoea, markers of glucose intolerance and liver disease, but not associated with the change in body mass index.

Ganda Mall J.P. et al, Nutrients (June 2020);

Effects of Dietary Fibres on Acute Indomethacin-Induced Intestinal Hyperpermeability in the Elderly: A Randomised Placebo Controlled Parallel Clinical Trial

Abstract:

The effect of dietary fibres on intestinal barrier function has not been well studied, especially in the elderly. We aimed to investigate the potential of the dietary fibres oat β-glucan and wheat arabinoxylan to strengthen the intestinal barrier function and counteract acute non-steroid anti-inflammatory drug (indomethacin)-induced hyperpermeability in the elderly. A general population of elderly subjects (≥65 years, n = 49) was randomised to a daily supplementation (12g/day) of oat β-glucan, arabinoxylan or placebo (maltodextrin) for six weeks. The primary outcome was change in acute indomethacin-induced intestinal permeability from baseline, assessed by an in vivo multi-sugar permeability test. Secondary outcomes were changes from baseline in: gut microbiota composition, systemic inflammatory status and self-reported health. Despite a majority of the study population (85%) showing a habitual fibre intake below the recommendation, no significant effects on acute indomethacin-induced intestinal hyperpermeability in vivo or gut microbiota composition were observed after six weeks intervention with either dietary fibre, compared to placebo.

Iribarren C. et al, Neurogastroenterol Motil. (June 2020);

Human Milk Oligosaccharide Supplementation in Irritable Bowel Syndrome Patients: A Parallel, Randomized, Double-Blind, Placebo-Controlled Study

Objectives:
Human milk oligosaccharides safely and beneficially impact bifidobacteria abundance in healthy adults, while their effects in patients with irritable bowel syndrome (IBS) are unknown. Hence, we aimed to determine the dose of 4:1 mix of 2'-O-fucosyllactose and Lacto-N-neotetraose (2'FL/LNnT) that increases fecal bifidobacteria abundance without aggravating overall gastrointestinal symptoms in IBS patients in a randomized, double-blind, controlled study. Additionally, the impact of 2'FL/LNnT on the fecal bacterial profile was assessed.
Methods:
Irritable bowel syndrome patients diagnosed according to the Rome IV criteria received placebo (glucose), or 5 g or 10 g 2'FL/LNnT for 4 weeks followed by a four-week follow-up period. Gastrointestinal Symptom Rating Scale-IBS was used to assess gastrointestinal symptom severity; fecal microbiota composition was evaluated by GA-map™ Dysbiosis Test.
Results:
Of the included 60 patients, two (one placebo and one 10 g) discontinued prematurely. Fecal bifidobacteria abundance was increased at week 4, but not at week 8, in the 10 g group compared to the other groups. Severity of overall or individual gastrointestinal symptoms did not differ between the groups at week 4 or 8, and no symptom deterioration was seen in any of the groups. The 10 g dose influenced overall fecal microbiota composition, and responders-defined as bifidobacteria increase ≥50%-could be discriminated from non-responders based on fecal microbiota modulation.
Conclusion:
The 10 g dose of 2'FL/LNnT induced an increase in the beneficial Bifidobacterium spp. without aggravating gastrointestinal symptoms in patients with IBS. This approach may be worthwhile to modulate gut microbiota of IBS patients toward a healthier profile.

Strömbeck A. et al, BMC Gastroenterol (May 2020);

Fecal microbiota composition is linked to the postoperative disease course in patients with Crohn's disease.

Background:
The role of the fecal microbiota composition for the postoperative disease course of patients with Crohn's disease (CD) who have undergone ileocecal resection remains to be established. In this study, we investigated if the fecal microbiota composition, determined by a high throughput test quantifying a pre-selected set of bacteria, is associated with the postoperative disease course of CD patients.
Methods:
Fecal samples were obtained from healthy subjects as well as from CD patients, 3-10 weeks and 1 year after ileocaecal resection. The fecal microbial composition was analysed by Genetic Analysis GA-map Dysbiosis test, targeting ≥300 bacteria on different taxonomic levels. Postoperative disease status was assessed endoscopically according to Rutgeerts scoring system 1 year after surgery. Differences in fecal microbiota composition between groups were analyzed by multivariate factor analyses and cluster analysis. Microbial stability over time was determined using Bray-Curtis dissimilarity.
Results:
One year after surgery, the fecal microbiota composition differed between CD patients (n = 21) and healthy subjects (n = 7). At this time point, the microbiota composition of CD patients was associated with disease course, clearly separating patients with disease relapse (n = 8) and patients in remission (n = 13). Further, the microbial within-patient stability was high during the first year after surgery, irrespective of disease course.
Conclusion:
The fecal microbiota composition of CD patients, analysed by GA-map Dysbiosis test, is subject to little variation over time, and may potentially be used as a non-invasive diagnostic tool for the postoperative disease course.

Farup PG. et al, Nutrients. (Mar 2020);

Changes in Faecal Short-Chain Fatty Acids after Weight-Loss Interventions in Subjects with Morbid Obesity.

Background:
The gut microbiota and their metabolites, e.g., short-chain fatty acids (SCFA), are associated with obesity. The primary aims were to study faecal SCFA levels and the changes in SCFA levels after weight-loss interventions in subjects with obesity, and secondarily, to study factors associated with the faecal SCFA levels. In total, 90 subjects (men / women: 15/75) with a mean age of 44.4 (SD 8.4) years, BMI 41.7 (SD 3.7) kg/m2 and morbid obesity (BMI > 40 or > 35 kg/m2 with obesity-related complications) were included. Faecal SCFA and other variables

were measured at inclusion and after a six-month conservative weight-loss intervention followed by bariatric surgery (RouxenY gastric bypass or gastric sleeve). Six months after surgery, the total amount of SCFA was reduced, the total and relative amounts of the main straight SCFA (acetic-, propionic-, and butyric- acids) were reduced, and the total and relative amounts of branched SCFA (isobutyric-, isovaleric-, and isocaproic- acids) were increased. The changes indicate a shift toward a proteolytic fermentation pattern with unfavourable health effects. The amount of SCFA was associated with the diet but not with metabolic markers or makers of the faecal microbiota composition. Dietary interventions could counteract the unfavourable effects.

Mazzawi T. et al, Gastroenterol Res Pract. (Feb 2020);

Abnormal Uroguanylin Immunoreactive Cells Density in the Duodenum of Patients with Diarrhea-Predominant Irritable Bowel Syndrome Changes following Fecal Microbiota Transplantation.

Abstract:
Altered densities of enteroendocrine cells play an important role in patients with irritable bowel syndrome (IBS). Uroguanylin activates guanylate cyclase-C to regulate intestinal electrolyte and water transport. Aim. To quantify uroguanylin immunoreactive cells density in the duodenum of diarrhea-predominant IBS (IBS-D) patients compared to controls and to investigate the effect of fecal microbiota transplantation (FMT) on these cell densities. Method. Twelve patients with IBS-D according to Rome III criteria were included. The cause was identified as post infectious (PI, n = 6) or idiopathic (n = 6). They completed the IBS-symptom questionnaire before and 3 weeks after FMT. Thirty grams of fresh feces donated from healthy relatives were diluted with 60 ml normal saline and instilled via endoscope into the duodenum. Biopsies were taken from the patients' duodenum before and 3 weeks after FMT. Duodenal biopsies taken from eight healthy controls were also included. The biopsies were immunostained for uroguanylin and quantified using computerized image analysis. Results. Uroguanylin immunoreactive cells were found both in duodenal villi and crypts in both controls and IBS-D patients. The densities of uroguanylin immunoreactive cells were significantly lower in the villi ($P < 0.0001$) and higher in the crypts ($P < 0.0001$) for the patients than the controls. Following FMT, the densities of uroguanylin immunoreactive cells for the total group and idiopathic subgroup decreased significantly in the duodenal crypts ($P = 0.049$ and 0.04, respectively) but not in the villi. No significant changes were shown in the PI-IBS subgroups. The cells density in only the crypts correlated with diarrhea ($r = 0.97$, $P = 0.001$) and bloating ($r = -0.91$, $P = 0.01$) in the PI-IBS subgroup before FMT and with abdominal pain ($r = 0.63$, $P = 0.03$) in the total group of IBS-D patients after FMT. Conclusion. Altered uroguanylin immunoreactive cells density was found in IBS-D patients compared to controls. Changes in these cells' density following FMT correlated with IBS symptoms (diarrhea, bloating, and abdominal pain).

2019

El-Salhy M. et al, Gut. (Dec 2019);

Efficacy of faecal microbiota transplantation for patients with irritable bowel syndrome in a randomized, double- blind, placebo- controlled study

Objective:
Faecal microbiota transplantation (FMT) from healthy donors to patients with irritable bowel syndrome (IBS) has been attempted in two previous double- blind, placebo- controlled studies. While one of those studies found improvement of the IBS symptoms, the other found no effect. The present study was conducted to clarify these contradictory findings.
Design:
This randomised, double- blind, placebo- controlled study randomised 165 patients with iBs to placebo (own faeces), 30 g FMT or 60 g FMT at a ratio of 1:1:1. The FMT was obtained from one healthy, well- characterised donor, frozen and administered via gastroscope. The primary outcome was a reduction in the IBS symptoms at 3 months after FMT (response). a response was defined as a decrease of 50 or more points in the total iBs symptom score. The secondary outcome was a reduction in the dysbiosis index (DI) and a change in the intestinal bacterial profile, analysed by 16S rRNA gene sequencing, at 1 month following FMT.
Results:
Responses occurred in 23.6%, 76.9% ($p<0.0001$) and 89.1% ($p<00.0001$) of the patients who received placebo, 30 g FMT and 60 g FMT, respectively. These were accompanied by significant improvements in fatigue and the quality of life in patients who received FMT. The intestinal bacterial profiles changed also significantly in the groups received FMT. The FMT adverse events were mild self- limiting gastrointestinal symptoms
Conclusions:
FMT is an effective treatment for patients with IBS. Utilising a well-defined donor with a normal DI and favourable specific microbial signature is essential for successful FMT. The response to FMT increases with the dose.

Klingberg E. et al, Arthritis Res Ther. (Nov 2019);

A distinct gut microbiota composition in patients with ankylosing spondylitis is associated with increased levels of fecal calprotectin.

Background:
Ankylosing spondylitis (AS) shares many characteristics with inflammatory bowel disease (IBD). Intestinal microbiota most likely plays an important role in the development of IBDs and may also be involved in the pathogenesis of AS. We aimed to define and compare the faecal microbiota composition in patients with AS, ulcerative colitis (UC), and healthy controls (HC) and to determine relationships between faecal microbiota, faecal calprotectin, and disease-related variables in AS.
Methods:
Fecal microbiota composition was assessed with GA-map® Dysbiosis Test (Genetic Analysis, Oslo, Norway), which also reports the degree of deviation of the microbiota composition compared with a healthy control population, a Dysbiosis Index (DI) score 1-5. The AS patients were assessed with questionnaires, back mobility tests, fecal calprotectin, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP).

Results:
Totally, 150 patients with AS (55% men, median age 55.5 years, median BASDAI 3.2), 18 patients with UC (56% men, median age 30.5 years), and 17 HC (65% men, median age 22 years) were included. Principal component analysis showed highly separate clustering of faecal microbiota from the patients with AS, UC, and HC. Compared with HC, faecal microbiota in AS was characterized by a higher abundance of Proteobacteria, Enterobacteriaceae, Bacilli, Streptococcus species, and Actinobacteria, but lower abundance of Bacteroides and Lachnospiraceae. Further, faecal microbiota composition differed between patients with normal (≤ 50 mg/kg, n = 57) and increased (≥ 200 mg/kg, n = 36) faecal calprotectin. Patients with increased faecal calprotectin had lower abundance of bacteria with anti-inflammatory properties such as Faecalibacterium prausnitzii and Clostridium and higher abundance of the genus Streptococcus. No association was found between the faecal microbiota composition and HLAB27 status, disease activity, function, or medication. Dysbiosis (defined as DI ≥ 3) was found in 87% of AS patients.
Conclusion:
Patients with AS have a distinct faecal microbiota signature, which is linked to faecal calprotectin levels, a marker of intestinal inflammation, but not to other clinical parameters. These findings suggest a local interplay between intestinal microbiota and gut inflammation in AS.

Farup PG et al, J Obes. (Oct 2019);

Are Nonnutritive Sweeteners Obesogenic? Associations between Diet, Faecal Microbiota, and Short-Chain Fatty Acids in Morbidly Obese Subjects.

Abstract:
Obesity has been associated with changes in the gut microbiota and its metabolites. The study explored changes in the faecal microbiota and short-chain fatty acids (SCFA) associated with the diet (including non-nutritive sweeteners (NNSs)) and evaluated metabolic consequences in subjects with morbid obesity. The diet was assessed with a validated food frequency questionnaire. One unit of NNSs was 100 mL beverage with NNSs or 2 tablets/teaspoons of NNSs. The faecal microbiota was assessed with GA-map® dysbiosis test and SCFA with gas chromatography and flame ionisation detection. Fourteen men and 75 women with a mean age of 44.6 (SD 8.7) years, BMI 41.8 (SD 3.6) kg/m2, and intake of NNSs 7.5 units/day (SD 3.2; range 0-43) were included. Faecal butyric acid was positively and negatively associated with the intake of starch (partial correlation = 0.264; p=0.015) and NNSs (partial correlation = -0.274; p=0.011), respectively. NNSs were associated with changes in four out of 39 bacterial groups. Butyric acid has ant obesogenic effects, reduces insulin resistance, and improves dyslipidaemia. Since the weight-reducing effect of NNSs on obese adults trying to lose weight is dubious, it seems imprudent to use NNSs that might counteract the favourable effects of butyric acid.

El-Salhy M. et al, Nutrients. (Jun 2019);

Increasing the Dose and/or Repeating Faecal Microbiota Transplantation (FMT) Increases the Response in Patients with Irritable Bowel Syndrome (IBS).

Background:
Faecal microbiome transplantation (FMT) appears to be an effective method for treating irritable bowel syndrome (IBS) patients. However, it is not clear if a high transplant dose and/or repeating FMT are/is needed to ensure a response. The present study was undertaken to clarify this matter.
Methods:
Ten IBS patients who did not respond to a 30-g transplant subsequently received a 60-g transplant into the duodenum via a gastroscope. The patients provided faecal samples before and 1 month after FMT. They completed five questionnaires measuring symptoms, fatigue and quality of life at baseline and then at 2 weeks, 1 month and 3 months after FMT. The dysbiosis index (DI) was measured using the GA-map® Dysbiosis Test.
Results:
Seven patients (70%) responded to the 60-g transplant, with significant clinical improvements in the abdominal symptoms, fatigue and quality of life in 57%, 80% and 67% of these patients. The 60-g transplant also reduced the DI.
Conclusion:
FMT is an effective treatment for IBS. A high-dose transplant and/or repeated FMT increase the response rate and the intensity of the effects of FMT.

Olbjørn C. et al, Clin Exp Gastroenterol. (Jan 2019);

Fecal microbiota profiles in treatment-naïve paediatric inflammatory bowel disease - associations with disease phenotype, treatment, and outcome

Purpose:
Imbalance in the microbiota, dysbiosis, has been identified in inflammatory bowel disease (IBD). We explored the faecal microbiota in paediatric patients with treatment naïve IBD, non-IBD patients with gastrointestinal symptoms and healthy children, its relation to IBD subgroups, and treatment outcomes.
Patients and methods:
Faecal samples were collected from 235 children below 18 years of age. Eighty children had Crohn's disease (CD), 27 ulcerative colitis (UC), 3 IBD unclassified, 50 were non-IBD symptomatic patients, and 75 were healthy. The bacterial abundance of 54 predefined DNA markers was measured with a 16S rRNA DNA-based test using GA-Map® technology at diagnosis and after therapy in IBD patients.
Results:
Bacterial abundance was similarly reduced in IBD and non-IBD patients in 51 of 54 markers compared to healthy patients (P<0.001). Only *Prevotella* was more abundant in patients (P<0.01). IBD patients with ileocolitis or total colitis had more *Ruminococcus gnavus* (P=0.02) than patients with colonic CD or left-sided UC. CD patients with upper gastrointestinal manifestations had higher *Veillonella* abundance (P<0.01). IBD patients (58%) who received biologic therapy had lower baseline Firmicutes and *Mycoplasma hominis* abundance

(P<0.01) than conventionally treated. High Proteobacteria abundance was associated with stricturing/penetrating CD, surgery (P<0.01), and nonmucosal healing (P<0.03). Low *Faecalibacterium prausnitzii* abundance was associated with prior antibiotic therapy (P=0.001), surgery (P=0.02), and nonmucosal healing (P<0.03). After therapy, IBD patients had unchanged dysbiosis.

Conclusion:

Fecal microbiota profiles differentiated IBD and non-IBD symptomatic children from healthy children but displayed similar dysbiosis in IBD and non-IBD symptomatic patients. Pre-treatment fecal microbiota profiles may be of prognostic value and aid in treatment individualization in paediatric IBD as severe dysbiosis was associated with an extensive, complicated phenotype, biologic therapy, and non-mucosal healing. The dysbiosis persisted after therapy, regardless of treatments and mucosal healing.

2018

Farup PG. et al, BMC Obes. (Dec 2018);

Separating "good" from "bad" faecal dysbiosis - evidence from two cross-sectional studies

Background:

Faecal dysbiosis associated with the use of metformin has been conceived as a favourable ("good") dysbiosis and that with intake of non-nutritive sweeteners (NNS) as unfavourable ("bad"). The study aimed to construct an alternative dysbiosis index (ADI) for the separation of the dysbiosis into "good" and "bad", and to validate the ADI.

Methods:

Subjects with morbid obesity were included. Use of NNS and drugs were noted, IBS was classified according to the Rome III criteria and the severity measured with the Irritable bowel severity scoring system (IBSSS). Faecal dysbiosis was tested with GA-Map® Dysbiosis test (Genetic Analysis AS, Oslo, Norway). The result was given as Dysbiosis Index (DI) scores 1-5, score > 2 indicates dysbiosis. An ADI was constructed and validated in subjects with IBS at another hospital.

Results:

Seventy-six women and 14 men aged 44.7 years (SD 8.6) with BMI 41.8 kg/m2 (SD 3.6) were included. Dysbiosis was associated with the use of NNS and metformin, but not with IBS or IBSSS. An ADI based on differences in 7 bacteria was positively and negatively associated with the "good" metformin dysbiosis and the "bad" NNS dysbiosis, respectively. The ADI was also negatively associated with IBSSS (a "bad" dysbiosis). The negative associations between ADI and IBS and IBSS were confirmed in the validation group.

Conclusions:

The new ADI, but not the DI, allowed separation of the "good" and "bad" faecal dysbiosis. Rather than merely reporting dysbiosis and degrees of dysbiosis, future diagnostic tests should distinguish between types of dysbiosis.

Mazzawi T. et al, PLoS One. (Nov 2018);

The kinetics of gut microbial community composition in patients with irritable bowel syndrome following fecal microbiota transplantation

Background:

Gut microbiota alterations are important in irritable bowel syndrome (IBS). The aim was to investigate the effect of fecal microbiota transplantation (FMT) on gut microbiota and the symptoms in patients with IBS.

Material and methods:

The study included 13 IBS patients according to Rome III criteria and 13 healthy donors. Freshly donated feces were administered to the descending part of the duodenum via a gastroscope. Feces were collected from donors and patients before FMT, and from the patients at 1, 3 and 12 weeks and donors and patients at 20/28 weeks after FMT. Microbiota analysis was performed using GA-map® Dysbiosis test (Genetic Analysis AS, Oslo, Norway). The patients completed the following questionnaires before and at the aforementioned weeks after FMT: IBS Symptom Questionnaire (IBS-SQ), IBS-Symptom Severity Scoring system (IBS-SSS), Short Form of Nepean Dyspepsia Index (SF-NDI), Bristol stool form scale, the Eysenck Personality Questionnaire-Neuroticism and Hospital Anxiety and Depression.

Results:

Donors and IBS patients had significantly different bacterial strain signals before FMT (Ruminococcus gnavus, Actinobacteria and Bifidobacteria) that became non-significant after 3 weeks following FMT. The changes in gut microbiota were similar between donors and patients at 20/28 weeks after FMT. Thus, patients' microbiota profiles became more-or-less similar to donors. The scores of all the questionnaires were significantly improved at all time points following FMT. No reported adverse effects.

Conclusions:

FMT was associated with a change in gut microbiota and improvement in IBS symptoms and quality of life lasting for up to 28 weeks.

Farup PG. et al., Behav Sci (Basel) (Sept 2018);

Faecal microbial markers and psychobiological disorders in Subjects with Morbid Obesity. A Cross-Sectional Study.

Abstract:

Morbidly obese subjects have a high prevalence of comorbidity and gut microbial dysbiosis and are thus suitable for the study of gut-brain interactions. The aim was to study the associations between the faecal microbiota's composition and function and psychobiological comorbidity in subjects with BMI > 40 kg/m² or >35 kg/m² with obesity-related complications. The faecal microbiota was assessed with GA-Map® dysbiosis test (Genetic Analysis, Oslo Norway) and

reported as dysbiosis (yes/no) and degree of dysbiosis, and the relative abundance of 39 bacteria. The microbiota's function was assessed by measuring the absolute and relative amount of faecal short chain fatty acids. Associations were made with well-being, mental distress, fatigue, food intolerance, musculoskeletal pain, irritable bowel syndrome, and degree of abdominal complaints. One hundred and two subjects were included. The results confirmed the high prevalence of comorbidity and dysbiosis (62/102; 61%) and showed a high prevalence of significant associations (41/427; 10%) between the microbiota's composition and function and the psychobiological disorders. The abundant, but in part divergent, associations supported the close gut-brain interaction but revealed no clear-cut and straightforward communication pathways. On the contrary, the study illustrates the complexity of gut-brain interactions.

Aasbrenn M. et al., Scand J Clin Lab Invest. (Feb 2018);
Evaluation of a faecal dysbiosis test for irritable bowel syndrome in subjects with and without obesity.

Abstract:
Biomarkers for irritable bowel syndrome (IBS) are demanded. An altered faecal microbiome has been reported in subjects with IBS and could be a valuable biomarker. This study evaluated the diagnostic properties of a new test for faecal dysbiosis, designed to distinguish IBS from healthy volunteers and compared the prevalence rates of dysbiosis related to IBS and morbid obesity. Subjects with and without morbid obesity and IBS were included. The faecal microbiota was assessed with GA-map® Dysbiosis Test (Genetic Analysis AS, Oslo, Norway). The test result was given as dysbiosis (yes/no). Comparisons were made between four groups: subjects with IBS and morbid obesity (IBS+/MO+); subjects without IBS and with morbid obesity (IBS-/MO+); subjects with IBS and without morbid obesity (IBS+/MO-); and healthy volunteers (IBS-/MO-).The prevalence rates of dysbiosis in the groups IBS+/MO+, IBS-/MO+, IBS+/MO- and IBS-/MO- were 18/28 (64%), 45/71 (63%), 31/63 (49%) and 38/91 (42%). Dysbiosis was more prevalent in subjects with morbid obesity, both in those with and without IBS, than in healthy volunteers (p values .04 and .006). Used as a diagnostic test for IBS in subjects without morbid obesity, the positive and negative likelihood ratios (LR) were 1.18 (0.83-1.67) and 0.87 (0.65-1.18), respectively, and in subjects with morbid obesity the LR were 1.01 (95% CI: 0.73-1.41) and 0.98 (0.54-1.75) respectively. The dysbiosis test was unsuitable as a diagnostic test for IBS. Dysbiosis was statistically significantly associated with morbid obesity, but not with IBS.

Valeur J. et al. Dig. Diseases and Sciences (Feb 2018);
Exploring Gut Microbiota Composition as an Indicator of Clinical Response to Dietary FODMAP Restriction in Patients with Irritable Bowel Syndrome.

Background:
A diet low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) may relieve symptoms of irritable bowel syndrome (IBS). However, nutritional counseling is resource-demanding and not all patients will benefit.
Aims:
To explore whether gut microbial composition may identify symptom response to a low-FODMAP diet in patients with IBS.
Methods:
Patients were recruited consecutively to participate in a 4-week FODMAP-restricted diet. Response to diet was defined as ≥ 50% decrease in IBS symptom severity scores (IBS-SSS) compared to baseline. Fecal microbiota was analyzed by a commercially available method (the GA-map® Dysbiosis Test), assessing 54 bacterial markers targeting more than 300 bacteria at different taxonomic levels.
Results:
Sixty-one patients (54 F; 7 M) were included: 32 (29 F; 3 M) classified as responders and 29 (25 F; 4 M) as non-responders. Ten of the 54 bacterial markers differed significantly between responders and non-responders. Based on median values (used as cutoff) of responders for these 10 bacterial markers, we constructed a Response Index (RI): Each patient was given a point when the value for each selected bacterial marker differed from the cutoff. These points were summed up, giving an RI from 0 to 10. Patients with RI > 3 were 5 times more likely to respond (OR = 5.05, 95% CI [1.58; 16.10]), and the probability to respond was 83.4%, 95% CI [61.2–94%].
Conclusions:
Gut microbial composition, assessed by using a new RI, may constitute a tool to identify patients that are likely to respond to dietary FODMAP restriction.

2017

Mandl T. et al., Arthritis Res Ther. (Oct 2017);
Severe intestinal dysbiosis is prevalent in primary Sjögren's syndrome and is associated with systemic disease activity.

Background:
Altered microbial composition of the intestine, commonly referred to as dysbiosis, has been associated with several autoimmune diseases including primary Sjögren's syndrome (pSS). The aims of the current study were to study the intestinal microbial balance in pSS and to identify clinical features associated with dysbiosis.
Methods:
Forty-two consecutive pSS patients and 35 age-matched and sex-matched control subjects were included in the study in an open clinic setting. Stool samples were analyzed for intestinal dysbiosis using a validated 16S rRNA-based microbiota test (GA-map® Dysbiosis Test; Genetic Analysis, Oslo, Norway). Dysbiosis and severe dysbiosis were defined in accordance with the manufacturer's instructions. Patients were evaluated

with regard to disease activity (European League Against Rheumatism (EULAR) Sjögren's Syndrome Disease Activity Index (ESSDAI) and Clinical ESSDAI (ClinESSDAI)). In addition, patients were examined for laboratory and serological features of pSS as well as fecal calprotectin levels. Furthermore, patients were investigated regarding patient-reported outcomes for pSS (EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI)) and irritable bowel syndrome (IBS)-like symptoms according to the Rome III criteria.

Results:

Severe dysbiosis was more prevalent in pSS patients in comparison to controls (21 vs 3%; p = 0.018). Subjects with pSS and severe dysbiosis had higher disease activity as evaluated by the ESSDAI total score (13 vs 5; p = 0.049) and the ClinESSDAI total score (12 vs 5; p = 0.049), lower levels of complement component 4 (0.11 vs 0.17 g/L; p = 0.004), as well as higher levels of fecal calprotectin (110 vs 33 µg/g; p = 0.001) compared to the other pSS patients. In contrast, severe dysbiosis among pSS patients was not associated with disease duration, IBS-like symptoms, or the ESSPRI total score.

Conclusions:

Severe intestinal dysbiosis is a prevalent finding in pSS and is associated both with clinical and laboratory markers of systemic disease activity as well as gastrointestinal inflammation. Further studies are warranted to elucidate a potential causative link between dysbiosis and pSS.

Magnusson et al., Inflammatory, Bowel Dis. (Jun 2017);

The Mucosal Antibacterial Response Profile and Fecal Microbiota Composition Are Linked to the Disease Course in Patients with Newly Diagnosed Ulcerative Colitis

Background:

The clinical disease course of ulcerative colitis (UC) varies substantially between individuals and can currently not be reliably predicted. The gut microbiota and the host's immune defense are key players for gut homeostasis and may be linked to disease outcome. The aim of this study was to determine fecal microbiota composition and mucosal antibacterial response profile in untreated patients with newly diagnosed UC and the impact of these factors on disease course.

Methods:

Stool samples and intestinal biopsies were obtained from therapy-naive newly diagnosed patients with UC. Patients were defined to have mild or moderate/severe disease course assessed by disease activity during the 3 years follow-up. Fecal microbiota was analyzed by the GA-map® Dysbiosis test (n = 18), and gene expression in intestinal biopsies was analyzed by RT Profiler polymerase chain reaction array (n = 13) and real-time polymerase chain reaction (n = 44).

Results:

At the time of diagnosis of UC, the fecal microbiota composition discriminated between patients with mild versus moderate/severe disease course. Also, the mucosal antibacterial gene expression response profile differed between patients with mild versus moderate/severe disease course with bactericidal/permeability-increasing protein (BPI) being most important for the discrimination. Mucosal bactericidal/permeability-increasing protein gene expression at diagnosis was higher in patients with mild versus moderate/severe disease course when confirmed in a larger patient cohort (P = 0.0004, n = 44) and was a good predictor for the number of flares during the 3 years follow-up (R = 0.395, P < 0.0001).

Conclusions:

In patients with newly diagnosed UC, fecal microbiota composition and mucosal antibacterial response profile, especially bactericidal/permeability-increasing protein, are linked to disease course.

Hustoft TM et al., Neurogastroenterol Motil. (Apr 2017);

Effects of varying dietary content of fermentable short-chain carbohydrates on symptoms, fecal microenvironment, and cytokine profiles in patients with irritable bowel syndrome.

Background:

A diet low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) is increasingly recommended for patients with irritable bowel syndrome (IBS). We aimed to investigate the effects of a blinded low-FODMAP vs high-fructo-oligosaccharides (FOS) diet on symptoms, immune activation, gut microbiota composition, and short-chain fatty acids (SCFAs).

Methods:

Twenty patients with diarrhea-predominant or mixed IBS were instructed to follow a low-FODMAP diet (LFD) throughout a 9-week study period. After 3 weeks, they were randomized and double-blindly assigned to receive a supplement of either FOS (FODMAP) or maltodextrin (placebo) for the next 10 days, followed by a 3-week washout period before crossover. Irritable bowel syndrome severity scoring system (IBS-SSS) was used to evaluate symptoms. Cytokines (interleukin [IL]-6, IL-8, and tumor necrosis factor alpha) were analyzed in blood samples, and gut microbiota composition (16S rRNA) and SCFAs were analyzed in fecal samples.

Key results:

Irritable bowel syndrome symptoms consistently improved after 3 weeks of LFD, and significantly more participants reported symptom relief in response to placebo (80%) than FOS (30%). Serum levels of proinflammatory IL-6 and IL-8, as well as levels of fecal bacteria (Actinobacteria, Bifidobacterium, and *Faecalibacterium prausnitzii*), total SCFAs, and n-butyric acid, decreased significantly on the LFD as compared to baseline. Ten days of FOS supplementation increased the level of these bacteria, whereas levels of cytokines and SCFAs remained unchanged

Conclusions and inferences:

Our findings support the efficacy of a LFD in alleviating IBS symptoms, and show changes in inflammatory cytokines, microbiota profile, and SCFAs, which may have consequences for gut health.

Bennet, Sean MP, et al., Gut (Apr 2017);

Multivariate modelling of faecal bacterial profiles of patients with IBS predicts responsiveness to a diet low in FODMAPs

Objective:
The effects of dietary interventions on gut bacteria are ambiguous. Following a previous intervention study, we aimed to determine how differing diets impact gut bacteria and if bacterial profiles predict intervention response.
Design:
Sixty-seven patients with IBS were randomized to traditional IBS (n=34) or low fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAPs) (n=33) diets for 4 weeks. Food intake was recorded for 4 days during screening and intervention. Faecal samples and IBS Symptom Severity Score (IBS-SSS) reports were collected before (baseline) and after intervention. A faecal microbiota dysbiosis test (GA-map® Dysbiosis Test) evaluated bacterial composition. Per protocol analysis was performed on 61 patients from whom microbiome data were available.
Results:
Responders (reduced IBS-SSS by ≥50) to low FODMAP, but not traditional, dietary intervention were discriminated from non-responders before and after intervention based on faecal bacterial profiles. Bacterial abundance tended to be higher in non-responders to a low FODMAP diet compared with responders before and after intervention. A low FODMAP intervention was associated with an increase in Dysbiosis Index (DI) scores in 42% of patients; while decreased DI scores were recorded in 33% of patients following a traditional IBS diet. Non-responders to a low FODMAP diet, but not a traditional IBS diet had higher DI scores than responders at baseline. Finally, while a traditional IBS diet was not associated with significant reduction of investigated bacteria, a low FODMAP diet was associated with reduced *Bifidobacterium* and Actinobacteria in patients, correlating with lactose consumption.
Conclusions:
A low FODMAP, but not a traditional IBS diet may have significant impact on faecal bacteria. Responsiveness to a low FODMAP diet intervention may be predicted by faecal bacterial profiles.

2016

Andréasson et al., Arthritis Res & Therapy (Nov 2016);
Intestinal dysbiosis is common in systemic sclerosis and associated with gastrointestinal and extraintestinal features of disease

Background:
Recent evidence suggests a link between autoimmunity and the intestinal microbial composition in several rheumatic diseases including systemic sclerosis (SSc). The objective of this study was to investigate the prevalence of intestinal dysbiosis in SSc and to characterize patients suffering from this potentially immunomodulatory deviation.
Methods:
This study consisted of 98 consecutive patients subject to in-hospital care. Stool samples were analyzed for intestinal microbiota composition using a validated genome-based microbiota test (GA-map® Dysbiosis Test, Genetic Analysis, Oslo, Norway). Gut microbiota dysbiosis was found present as per this standardized test. Patients were examined regarding gastrointestinal and extraintestinal manifestations of SSc by clinical, laboratory, and radiological measures including esophageal cineradiography, the Malnutrition Universal Screening Tool (MUST), levels of plasma transthyretin (a marker of malnutrition) and faecal (F-) calprotectin (a marker of intestinal inflammation).
Results:
A majority (75.5%) of the patients exhibited dysbiosis. Dysbiosis was more severe ($r_s = 0.31$, $p = 0.001$) and more common ($p = 0.013$) in patients with esophageal dysmotility. Dysbiosis was also more pronounced in patients with abnormal plasma levels of transthyretin ($p = 0.045$) or micronutrient deficiency ($p = 0.009$). In 19 patients at risk for malnutrition according to the MUST, 18 exhibited dysbiosis. Conversely, of the 24 patients with a negative dysbiosis test, only one was at risk for malnutrition. The mean ± SEM levels of F-calprotectin were 112 ± 14 and 45 ± 8µg/g in patients with a positive and negative dysbiosis test, respectively. Dysbiosis was more severe in patients with skin telangiectasias ($p = 0.020$), pitting scars ($p = 0.023$), pulmonary fibrosis ($p = 0.009$), and elevated serum markers of inflammation ($p < 0.001$). However, dysbiosis did not correlate with age, disease duration, disease subtype, or extent of skin fibrosis.
Conclusions:
In this cross-sectional study, intestinal dysbiosis was common in patients with SSc and was associated with gastrointestinal dysfunction, malnutrition and with some inflammatory, fibrotic and vascular extraintestinal features of SSc. Further studies are needed to elucidate the potential causal relationship of intestinal microbe-host interaction in this autoimmune disease.

Magnusson et al., J Crohns Colitis. (Aug 2016);
Anti-TNF Therapy Response in Patients with Ulcerative Colitis Is Associated with Colonic Antimicrobial Peptide Expression and Microbiota Composition

Background and Aims:
Anti-tumor necrosis factor [TNF] therapy is used in patients with ulcerative colitis [UC], but not all patients respond to treatment. Antimicrobial peptides [AMPs] and the gut microbiota are essential for gut homeostasis and may be important for treatment outcome. The aim of this study was to determine AMP and microbiota profiles in patients with UC before anti-TNF therapy start and correlate these data to treatment outcome.

Methods:
Serum and biopsies were obtained from UC patients naïve to biological therapy [n = 56] before anti-TNF therapy start [baseline]. Fecal samples were taken at baseline and Weeks 2 and 6. Quantitative proteomic analysis was performed in mucosal biopsies. Expression of AMPs and cytokines was determined in biopsies and serum. Microbiota analysis of fecal samples was performed using GA-map® Dysbiosis Test and real-time quantitative polymerase chain reaction [rtPCR]. Treatment response was evaluated 12–14 weeks after baseline.
Results:
At baseline, proteomic analysis of biopsies showed that treatment responders and non-responders had differential expression of AMPs. Eleven AMP and AMP-related genes were analyzed by rtPCR in mucosal biopsies and could together discriminate responders from non-responders at baseline. The most important nominators for response were increased expression of defensin 5 and eosinophilic cationic protein. Microbiota analysis revealed lower dysbiosis indexes and higher abundance of *Faecalibacterium prausnitzii* in responders compared with non-responders at baseline. Also, abundance of *F. prausnitzii* increased during induction therapy in responders.
Conclusions:
Anti-TNF therapy responders and non-responders display distinctly separate patterns of mucosal AMP expression and gut microbiota before treatment start. This indicates that intestinal antimicrobial/microbial composition can influence treatment outcome.

Vebø et al., J. of Microbiological Methods (Oct 2016);
Bead-beating artefacts in the Bacteroidetes to Firmicutes ratio of the human stool metagenome

Abstract:
We evaluated bead-beating cell-lysis in analyzing the human stool metagenome, since this is a key step. We observed that two different bead-beating instruments from the same producer gave a three-fold difference in the Bacteroidetes to Firmicutes ratio. This illustrates that bead-beating can have a major impact on downstream metagenome analyses.

2015-2011

Casén et al., Aliment Pharmacol Ther (Jul 2015);
Deviations in human gut microbiota: a novel diagnostic test for determining dysbiosis in patients with IBS or IBD

Background:
Dysbiosis is associated with many diseases, including irritable bowel syndrome (IBS), inflammatory bowel diseases (IBD), obesity and diabetes. Potential clinical impact of imbalance in the intestinal microbiota suggests need for new standardized diagnostic methods to facilitate microbiome profiling.
Aim:
To develop and validate a novel diagnostic test using faecal samples to profile the intestinal microbiota and identify and characterize dysbiosis.
Methods:
Fifty-four DNA probes targeting ≥300 bacteria on different taxonomic levels were selected based on ability to distinguish between healthy controls and IBS patients in faecal samples. Overall, 165 healthy controls (normobiotic reference collection) were used to develop a dysbiosis model with a bacterial profile and Dysbiosis Index score output. The model algorithmically assesses faecal bacterial abundance and profile, and potential clinically relevant deviation in the microbiome from normobiosis. This model was tested in different samples from healthy volunteers and IBS and IBD patients (n = 330) to determine the ability to detect dysbiosis.
Results:
Validation confirms dysbiosis was detected in 73% of IBS patients, 70% of treatment-naïve IBD patients and 80% of IBD patients in remission, vs. 16% of healthy individuals. Comparison of deep sequencing and the GA-map® Dysbiosis Test, (Genetic Analysis AS, Oslo, Norway) illustrated good agreement in bacterial capture; the latter showing higher resolution by targeting pre-determined highly relevant bacteria.
Conclusions:
The GA-map® Dysbiosis Test identifies and characterizes dysbiosis in IBS and IBD patients and provides insight into a patient's intestinal microbiota. Evaluating microbiota as a diagnostic strategy may allow monitoring of prescribed treatment regimens and improvement in new therapeutic approaches.

Thorkildsen et al. Gastroenterology Res Pract (Nov 2013)
Dominant Fecal Microbiota in Newly Diagnosed Untreated Inflammatory Bowel Disease Patients

Abstract:
Our knowledge about the microbiota associated with the onset of IBD is limited. The aim of our study was to investigate the correlation between IBD and the fecal microbiota for early diagnosed untreated patients. The fecal samples used were a part of the Inflammatory Bowel South-Eastern Norway II (IBSEN II) study and were collected from CD patients (*n* = 30), UC patients (*n* = 33), unclassified IBD (IBDU) patients (*n* = 3), and from a control group (*n* = 34). The bacteria associated with the fecal samples were analyzed using a direct 16S rRNA gene-sequencing approach combined with a multivariate curve resolution (MCR) analysis. In addition, a 16S rRNA gene clone library was prepared for the construction of bacteria-specific gene-targeted single nucleotide primer extension (SNuPE) probes. The MCR analysis resulted in the recovery of five pure components of the dominant bacteria present: Escherichia/Shigella, *Faecalibacterium*, Bacteroides, and two

components of unclassified Clostridiales. Escherichia / Shigella was found to be significantly increased in CD patients compared to control subjects, and *Faecalibacterium* was found to be significantly reduced in CD patients compared to both UC patients and control subjects. Furthermore, a SNuPE probe specific for Escherichia/Shigella showed a significant over-representation of Escherichia / Shigella in CD patients compared to control subjects. In conclusion, samples from CD patients exhibited an increase in Escherichia / Shigella and a decrease in *Faecalibacterium* indicating that the onset of the disease is associated with an increase in proinflammatory and a decrease in anti-inflammatory bacteria.

Vebø et al., Clinical Vaccine Immunology (Jun 2011);

Temporal Development of the Infant Gut Microbiota in Immunoglobulin E-Sensitized and Non-sensitized Children Determined by the GA-Map Infant Array

Abstract:

At birth, the human infant gut is sterile, but it becomes fully colonized within a few days. This initial colonization process has a major impact on immune development. Our knowledge about the correlations between aberrant colonization patterns and immunological diseases, however, is limited. The aim of the present work was to develop the GA-map (Genetic Analysis microbiota array platform) infant array and to use this array to compare the temporal development of the gut microbiota in IgE-sensitized and nonsensitized children during the first 2 years of life. The GA-map infant array is composed of highly specific 16S rRNA gene-targeted single nucleotide primer extension (SNuPE) probes, which were designed based on extensive infant 16S rRNA gene sequence libraries. For the clinical screening, we analyzed 216 fecal samples collected from a cohort of 47 infants (16 sensitized and 31 non-sensitized) from 1 day to 2 years of age. The results showed that at a high taxonomic level, Actinobacteria was significantly overrepresented at 4 months while Firmicutes was significantly overrepresented at 1 year for the sensitized children. At a lower taxonomic level, for the sensitized group, we found that *Bifidobacterium longum* was significantly overrepresented at the age of 1 year and *Enterococcus* at the age of 4 months. For most phyla, however, there were consistent differences in composition between age groups, irrespective of the sensitization state. The main age patterns were a rapid decrease in staphylococci from 10 days to 4 months and a peak of bifidobacteria and bacteroides at 4 months. In conclusion, our analyses showed consistent microbiota colonization and IgE sensitization patterns that can be important for understanding both normal and diseased immunological development in infants.

Poster presentations and Prizes

2021

UEG Week 2021

GUT BACTERIA FUNCTIONALITY PROFILES AND DIVERSITY INDEX DETECTED BY THE GA-MAP® DYSBIOSIS TEST LX. P0525

Kristin Gravdal[1], Graceline Tina Kirubakaran[1], Anja Bråthen Kristoffersen[1], Christina Casén[1]
[1]Genetic Analysis AS, Oslo, Norway

Introduction:

The diversity and functionality of gut microbiota is increasingly being recognized as important biomarkers for gut health.

To quantitatively estimate the bacteria diversity of a sample, GA has developed the GA-map® diversity index. For easy recognition of the presence or deficiency of bacteria maintaining important gut functions, GA has established functional bacteria profiles, based on the GA-map® Dysbiosis Test1. The functional bacteria profiles and diversity index will enhance the clinical reasoning and interpretation of the microbiota results for the clinicians.

Aims & Methods:

The GA-map® Dysbiosis Test Lx uses molecular techniques for detection of predefined bacteria markers in human stool samples. Based on the resulting signal data from 48 bacteria markers the GA-map® algorithm calculates a dysbiosis index (DI), as well as relative abundance of each bacteria marker. Relative abundance is reported on a scale from -3 (reduced) to +3 (increased), where the score 0 indicates the healthy control (HC) reference level.

GA developed the GA-map® diversity index, which quantitatively measures the bacteria diversity of a sample from the signal strength data generated by 28 non-correlated bacteria markers from the GA-map® Dysbiosis Test Lx. To maximize the variance in diversity between diseased and healthy subjects, the 28 markers were assigned different weights calculated using R's optim function() from a selected subset (healthy (N=17) and C. diff patients (N=15)). The diversity function() from vegan R package was used to calculate the diversity of the samples from the weighted signal strength data. Each sample is assigned a diversity index value ranging from 0 to 5 where the higher the value, the greater the diversity.

Based on literature search for known functionality among the gut bacteria and our own findings, selected bacteria markers were consolidated into five profiles representing different bacteria functions in the gut (Table 1). Utilizing the abundance scores from the GA-map® Dysbiosis Test Lx, criteria were set for each profile and further investigated in different groups (N=1015, healthy controls (HC), IBS and IBD patients - Table 1). The percent distribution per group was calculated with confidence interval (CI) using the binom.test() in R.

Results:

GA-map® diversity index evaluation on various disease cohorts, healthy (N=297), IBS (N=60), systemic sclerosis (N=27) and IBD (N=86), estimated a median diversity of 3.9, 3.7, 3.6 and 3.3, respectively.

For each of the functional bacteria profiles, 3-6% of healthy controls (HC, N=224), 9-22% of IBS patients (N=470) and 36-51% of IBD patients (N=321) fulfilled the set profile criteria (Table 1).

Conclusions:

The GA-map® Dysbiosis Test Lx results provide a comprehensive list of increase or deficiency of several bacteria in the human gut. With the additional new tools - GA-map® diversity index and functional bacteria profiles - clinicians can gain perspective of the magnitude of the imbalance and its potential effects on the gut functions. In line with the ongoing increasing knowledge about gut bacteria functionality, we will see more functional profiles established in the future.

References:

1. Casén C, Vebø HC, Sekelja M, Hegge FT, Karlsson MK, Ciemniejewska E, Dzankovic S, Frøyland C, Nestestog R, Engstrand L, Munkholm P, Nielsen OH, Rogler G, Simrén M, Öhman L, Vatn MH, Rudi K. Deviations in human gut microbiota: a novel diagnostic test for determining dysbiosis in patients with IBS or IBD. Aliment Pharmacol Ther. 2015 Jul;42(1):71-83. doi: 10.1111/apt.13236. Epub 2015 May 14. PMID: 25973666; PMCID: PMC5029765.

UEG Week 2021

EFFICACY OF FAECAL MICROBIOTA TRANSPLANTATION FOR PATIENTS WITH IRRITABLE BOWEL SYNDROME THREE YEARS AFTER TRANSPLANTATION. P0613

M. El-Salhy, C. Casen, J. Valeur, T. Hausken and J. G. Hatlebakk

Introduction:

Faecal microbiota transplantation (FMT) is a promising treatment for patients with irritable bowel syndrome (IBS). However, its long-term efficacy and long-term adverse events are unknown.

Aims & Methods:

The present study is a 3-years follow up of the IBS patients participated in our previous RCT (1) in order to establish the long-term efficacy and possible long-term side-effects of FMT. A total of 127 patients out of the 164 patients in our previous RCT were included in this study. Of these patients 38 were belonging to the placebo group (own faeces), 42 patients belonging to the 30-g (received 30 g donor's faeces) group and 45 patients belonging to 60-g (received 60 g donor's faeces) group. Patients provided a faecal sample and completed five questionnaires to assess their symptoms and quality of life at the baseline, 2 and 3 years after FMT. Abdominal symptoms, fatigue and quality of life were assessed using the IBS Severity Scoring System (IBS-SSS), Birmingham IBS Symptom, Fatigue Assessment Scale (FAS), IBS Quality of Life and the Short-Form Nepean Dyspepsia Index (SF-NDI) questionnaires. The

dysbiosis index (DI) and faecal bacterial profile were analysed using 16S rRNA gene PCR DNA amplification covering the variable genes V3–V9, followed by hybridisation of pre-targeted bacterial markers.

Results:

The response rates to FMT after 2 years were 26.3%, 68.9% and 77.8% in the placebo, 30-g and 60-g groups, respectively. The corresponding values after 3 years were 27.0%, 64.9% and 70.0%. The response rates in 30-g and 60-g groups were significantly higher than placebo after 2 years (p=0.0001 and <0.0001, respectively) and after 3 years (p=0.002 and 0.0003, respectively). The response rates were significantly higher and IBS-SSS total scores were significantly lower in females than males, both after 2 and 3 years following FMT. Total scores of IBS-SSS, Birmingham IBS Symptom, FAS and SF-NDI were significantly reduced and that of IBS-QoL were significantly increased in the 30-g and 60-g groups, but not in the placebo group both 2 and 3 years after FMT. The DI decreased significantly in the 30-g and 60-g groups but not in the placebo group both 2 and 3 years after FMT. A large number of bacteria markers were significantly changed from those at the baseline at 2 and 3 years after FMT in the placebo, 30-g and 60-g groups. Eleven of these bacteria markers that changed in the 30-g and 60-g groups were not changed in the placebo groups. The levels of 9 of these bacteria markers were significantly correlated to the total IBS-SSS scores. These bacteria were Alistipes, Bacteroides spp. & Prevotella spp., Parabacteroides johnsonii, Firmicutes spp, Coprobacillus cateniformis, Eubacterium biforme, Faecalibacterium prausnitzii, Streptococcus salivarius ssp. thermophilus, and Enterobacteriaceae. No adverse events were reported during the observation period.

Conclusions:

The present study showed that a single FMT improves the symptoms and quality of life of IBS patients up to 3 years without any long-term side effects. It identified 9 bacteria markers that seem to play a role in this improvement. The successful outcome of this study could be explained by a careful donor selection, the preparation methods of faecal transplant including direct freezing of the faecal transplant and mixing it manually without any mixing devices and route of transplant administration, namely to the small intestine.

References:

1. El-Salhy M, Hatlebakk JG, Gilja OH, Bråthen Kristoffersen A and Hausken T: Efficacy of faecal microbiota transplantation for patients with irritable bowel syndrome in a randomised, double-blind, placebo-controlled study. Gut 69: 859-867, 2020.

UEG Week 2021

RESPONSES TO FAECAL MICROBIOTA TRANSPLANTATION IN FEMALE AND MALE PATIENTS WITH IRRITABLE BOWEL SYNDROME. P0612

M. El-Salhy, C. Casen, J. Valeur, T. Hausken and J. G. Hatlebakk

Introduction:

The intestinal microbiota plays a pivotal role in the pathophysiology of irritable bowel syndrome (IBS) and faecal microbiota transplantation (FMT) is a promising intervention for IBS patients. There is a sex difference in IBS, with a female: male ratio of 2:1. A sex difference in the response to FMT has been reported recently in IBS patients (1).

Aims & Methods:

The present study aimed at investigating whether there is a sex difference in the response to FMT in terms of symptoms, dysbiosis, bacteria and short chain fatty acids (SCFAs) profiles in the same cohort of patients that we had investigated in our previous randomized double-blind placebo-controlled trial (RCT). The study included 164 IBS patients (132 females and 32 males) who participated in our previous RCT (2). These patients had moderate-to-severe IBS symptoms belonging to the with diarrhoea-predominant (IBS-D), constipation-predominant (IBS-C) and mixed diarrhoea and constipation (IBS-M) subtypes. They belonged in three groups: placebo (own faeces), and active treated group (30-g or 60-g super-donor faeces). The patients completed the IBS Severity Scoring System (IBS-SSS), Fatigue Assessment Scale (FAS) and the IBS Quality of Life Scale (IBS-QoL) questionnaires at the baseline and 2 weeks, 1 month and 3 months after FMT.They also provided faecal samples at the baseline and 1 month after FMT. The faecal bacteria profile and dysbiosis were determined using a 16S rRNA gene PCR DNA amplification covering the variable genes V3–V9; hybridization and probe labelling by single nucleotide extension and fluorescent signal detection. The levels of SCFAs were determined by vaccum distillation followed by gas chromatography.

Results:

There was no sex difference in the response to FMT either in the placebo group or active treated group. There was no difference between females and males in either the placebo group or actively treated groups in the total score of the IBS-SSS, FAS or IBS-QoL, in dysbiosis, or in the faecal bacteria or SCFAs levels. However, the response rates in females with diarrhoea-IBS-D was 90% both 1 month, and 3 months after FMT. The corresponding values in males were 42% both after 1 month and 3 months following FMT. The response rates in females with IBS-D, 1 month and 3 months after FMT were significantly higher than those of males (p=0.0003 in both). There was no significant difference between females and males with IBS-C and IBS-M regarding the response rates at all the observation intervals. Moreover, IBS-SSS total score in female patients with IBS-D was 177.8±94.9 (mean±SD) and 157.8±102.9 1 month and 3 months after FMT, respectively. In male patients with IBS-D the IBS-SSS total scores were 226.9±73.3 and 212.3±96.9 1 month and 3 months after FMT, respectively. The IBS-SSS total scores were significantly lower in female patients with IBS-D than that of male patients both 1 month and 3 months after FMT (p= 0.02 and 0.03, respectively). The IBS-SSS total scores did not differ between females and males with either IBS-C or IBS-M.

Conclusions:

There was no general sex difference in the response to FMT among IBS patients with moderate-to-severe symptoms. However, female patients with IBS-D respond better and have less symptoms than males after FMT. These observations could explain the findings of Holvoet et al where the cohort of patients included in their RCT were IBS-D and IBS-M IBS-subtypes.

References:

1. Holvoet T, Joossens M, Vázquez-Castellanos JF, et al.: Fecal Microbiota Transplantation Reduces Symptoms in Some Patients With Irritable Bowel Syndrome with Predominant Abdominal Bloating: Short- and Long-Term Results from a Placebo-Controlled Randomized Trial. Gastroenterology 160:145-157, 2021. doi: 10.1053/j.gastro.2020.07.013. Online ahead of print.2020.

2. El-Salhy M, Hatlebakk JG, Gilja OH, Bråthen Kristoffersen A and Hausken T: Efficacy of faecal microbiota transplantation for patients with irritable bowel syndrome in a randomised, double-blind, placebo-controlled study. Gut 69: 859-867, 2020.

EHMSG 2021

GUT BACTERIA FUNCTIONALITY PROFILES AND DIVERSITY INDEX DETECTED BY THE GA-MAP® DYSBIOSIS TEST LX.

P13.02

K. Gravdal, G. Kirubakaran, A. Bråthen Kristoffersen, C. Casén
Genetic Analysis AS, Oslo, Norway.

The GA-map® Dysbiosis Test Lx results provide a comprehensive list of increase or deficiency of several bacteria in the human gut based on detection of 48 bacteria markers. To enhance the clinical reasoning and interpretation of the microbiota results, GA has additionally developed the GA-map® diversity index and functional bacteria profiles. GA-map® diversity index quantitatively estimate the bacteria diversity of a sample using signal strength data from 28 non-correlated bacteria markers. Each sample is assigned a diversity index value ranging from 0 to 5 where the higher the value, the greater diversity. Functional bacteria profiles enable easy recognition of the presence or deficiency of bacteria maintaining important gut functions. Based on literature search and our own findings, selected bacteria markers were consolidated into five profiles representing different functions (Table 1). Utilizing the bacteria abundances from the GA-map® Dysbiosis Test Lx, criteria were set for each profile. With the additional new tools – GA-map® diversity index and functional bacteria profiles – clinicians can gain perspective of the magnitude of the gut bacteria imbalance and its potential effects on gut functions. In line with the increasing knowledge about gut bacteria functionality, we will see more functional profiles established in the future.

TABLE 1. GUT BACTERIA FUNCTIONALITY PROFILES AND SET PROFILE CRITERIA.

Functional bacteria profiles	Bacteria marker	Criteria (abundance of one/several bacteria markers)
Butyrate producing bacteria	*Anaerobutyricum hallii* *[Eubacterium] rectale* *Faecalibacterium prausnitzii*	Reduced abundance in at least two markers
Gut mucosa protective bacteria	*Faecalibacterium prausnitzii* *Akkermansia muciniphila*	Reduced abundance in both markers
Gut intestinal health marker	*Faecalibacterium prausnitzii*	Reduced abundance, at least below -1
Gut barrier protective and potentially harmful bacteria	*Faecalibacterium prausnitzii* *Ruminococcus gnavus* *Proteobacteria* *Shigella spp./Escherichia spp.*	Reduced abundance in protective marker (F. prausnitzii) and increased abundance in at least one potentially harmful bacteria marker
Pro-inflammatory bacteria	*Proteobacteria* *Shigella spp./* *Escherichia spp.*	Increased abundance in both markers, and at least one above +1

2020

UEG Week 2020

LONG-TERM EFFECTS OF FAECAL MICROBIOTA TRANSPLANTATION (FMT) IN PATIENTS WITH IRRITABLE BOWEL SYNDROME. OP059

El-Salhy M.[1], Bråthen Kristoffersen A.[2], Valeur J.[3], Casén C.[4], Hatlebakk J.G.[5,6,7], Gilja O.H.[8,9], Hausken T.[10]
[1] Stord Hospital Medical Clinic/University of Bergen, Gastroenterology, Stord, Norway,
[2] Genetic Analysis, Oslo, Norway,
[3] Lovisenberg Diakonale Hospital, Unger-Vetlesens Institute, Oslo, Norway,
[4] Genetic Analysis AS, Clinical Department, Oslo, Norway,
[5] Haukeland University Hospital, Medicine, Bergen, Norway,
[6] Bergen University, Clinical Medicine, Bergen, Norway,
[7] National Centre for Functional Gastrointestinal Disorders, Medicine, Bergen, Norway,
[8] University of Bergen, Clinical Medicine, Bergen, Norway,
[9] Haukeland University Hospital, National Centre for Ultrasound in Gastroenterology, Bergen, Norway,
[10] Haukeland University Hospital, Medical Department, Bergen, Norway

Introduction:

A recently published randomized double-blind placebo-controlled study from our group found faecal microbiota transplantation (FMT) to be an effective and safe treatment for irritable bowel syndrome (IBS) after 3 months (1). The present follow-up study investigated the efficacy and safety of FMT at 1 year after treatment

Aims & Methods:

This study included 77 of the 91 IBS patients who had responded to FMT in our previous study (i.e. 14 patients were either excluded or dropped out). Patients provided a faecal sample and completed five questionnaires to assess their symptoms and quality of life at 1 year after FMT. Abdominal symptoms, fatigue and quality of life were assessed using the IBS Severity Scoring System (IBS-SSS), Birmingham IBS Symptom, Fatigue Assessment Scale (FAS), IBS Quality of Life and the Short-Form Nepean Dyspepsia Index questionnaires. The dysbiosis index (DI) and faecal bacterial profile were analyzed using a CE marked 16S rRNA gene-based DNA probe hybridization method (2). The levels of faecal short-chain fatty acids (SCFAs) were determined by gas chromatography

Results:

The response to FMT was maintained at 1 year after treatment in 32 (86.5%) and 35 (87.5%) patients who received 30-g and

60-g FMT, respectively. In the 30-g FMT group, 12 (32.4%) patients showed complete remission (had an IBS-SSS total score of ≤75) at 1 year, compared with 8 (21.6%) after 3 months. In the 60-g FMT group, 18 (45%) patients were in complete remission at 1 year, compared with 11 (27.5%) after 3 months. Abdominal symptoms, fatigue and the quality of life were improved at 1 year compared with 3 months after FMT. These findings were accompanied by a significant improvement in the DI and comprehensive changes in the faecal bacterial profile. The levels of *Alistipes* spp. — which belong to the phylum Bacteroidetes— were significantly lower in the relapsed patients at baseline than in the responders and patients in remission at 1 year after FMT. Furthermore, *Alistipes* spp. levels increased as early as 1 month after FMT and remained high in responders at 1 year after FMT. Moreover, they were strongly correlated with the total scores on both IBS-SSS and FAS (r=-0.479 and P< 0.001, and r=0.436 and P< 0.001, respectively). Changes in the levels of faecal SCFAs indicated that the microbial metabolism changed from a saccharolytic to a proteolytic fermentation pattern in IBS patients at 1 year after FMT. The level of faecal acetic acid was reduced compared with that at baseline. The clinically relapsed patients had significantly lower fatigue scores and significant changes in the bacterial profile and the levels of SCFAs compared with those at baseline. No adverse events were reported.

Conclusion:

Most of the IBS patients who responded to FMT after 3 months maintained a response at 1 year after FMT. Moreover, the improvements in symptoms and quality of life increased significantly over time. Changes in the faecal bacterial profile and SCFAs also increased over time. The finding that FMT induced remission in about half of the patients with IBS emphasizes the importance of the intestinal microbiota as an aetiological factor of IBS. Alistipes spp. seem to play a central role in the improvements seen after FMT and levels of Alistipes spp. could probably be used to predict the outcome of FMT. The reduction of acetic acid levels could be relevant since acetic acid has been found to induce visceral hypersensitivity in rodents (3).

References:

1. El-Salhy M, Hatlebakk JG, Gilja OH, Brathen Kristoffersen A and Hausken T: Efficacy of faecal microbiota transplantation for patients with irritable bowel syndrome in a randomized, double-blind, placebo-controlled study. Gut2019.

2. Casen C, Vebo HC, Sekelja M, et al.: Deviations in human gut microbiota: a novel diagnostic test for determining dysbiosis in patients with IBS or IBD. Alimentary pharmacology & therapeutics 42: 71-83, 2015.

3. Winston J, Shenoy M, Medley D, Naniwadekar A and Pasricha PJ: The vanilloid receptor initiates and maintains colonic hypersensitivity induced by neonatal colon irritation in rats. Gastroenterology 132: 615-627, 2007.

PREDICTORS OF TREATMENT RESPONSE TO THE LOW FODMAP AND THE TRADITIONAL DIET IN PATIENTS WITH IRRITABLE BOWEL SYNDROME. P0786

Colomier E.[1,2], van Oudenhove L.[3,4], Tack J.[1], Böhn L.[2], Bennet S.[2,5], Störsrud S.[2], Öhman L.[2], Törnblom H.[2], Simrén M.[2]

[1] KU Leuven, Translational Research Center for GI Disorders (TARGID), Leuven, Belgium,

[2] University of Gothenburg, Sahlgrenska Academy, Clinical Nutrition and Internal Medicine, Göteborg, Sweden,

[3] KU Leuven, Laboratory for Brain-Gut Axis Studies, Translational Research Center for GI Disorders, Leuven, Belgium,

[4] Dartmouth College, Cognitive & Affective Neuroscience Lab, Department of Psychological and Brain Sciences, Hanover, United States,

[5] Queen's University, Gastrointestinal Disease Research Unit, Kingston, Canada

Introduction:

The NICE traditional diet for irritable bowel syndrome (IBS) patients and the low fermentable oligo-, di-, monosaccharides, and polyols (FODMAP) diet have shown efficacy in IBS. Predictors of dietary treatment response remain to be identified

Aims & Methods:

Therefore, we aimed to investigate psychological, nutritional, and microbial factors as diet response predictors for 4 IBS symptoms. Seventy-five IBS patients were randomized to the low FODMAP (n=38) or NICE diet (n=37) for 4 weeks. Baseline measures included stool samples evaluated by the GA-map™ Dysbiosis Test, generating a Dysbiosis Index, 4-day food diaries for the calculation of the average daily energy and FODMAP intake (DIETIST XP V.3.1, Kostdata.se, Sweden), Patient Health Questionnaire and Hospital Anxiety & Depression Scale to measure somatic symptoms and psychological distress, respectively. Outcome measures were 4 subscales (bloating, constipation, diarrhea, and pain) of the Gastrointestinal Symptom Rating Scale treated as continuous variables in linear mixed models. Models included the main effect of baseline predictors on subscale scores, the main effect of time as a linear slope, and the interaction effect testing if baseline variables predict the response slope. Lastly, a diet variable (including its main effect and all interactions) was added to test if baseline variables deferentially predict response to the low FODMAP and NICE diet

Results:

We included 65 patients; 32 on low FODMAP and 33 on NICE diet. In models without covariates, both diets were shown to be effective and reduced the severity of bloating, diarrhea, pain (all p<0.0001), and constipation (p<0.05). Adding the diet variable to the model without covariates indicated absence of differences in response between the diets for any of the symptoms, thereby confirming an earlier analysis of Böhn et al. For pain, a lower dysbiosis index (p=0.02) and higher energy intake (p=0.003) predicted better response to both diets. For constipation, lower dysbiosis index predicted better response to both diets (p=0.009). For diarrhea, FODMAP intake tended to be associated with response to both diets (p=0.057), driven by a significant association between higher baseline FODMAP

intake and better response to the NICE diet. For bloating, higher levels of psychological distress predicted worse response to both diets (p=0.03). FODMAP intake emerged as a differential predictor for treatment response (interaction effect: p=0.04), with higher baseline intake associated with worse response to the low FODMAP diet, and better response to the NICE diet.

Conclusion:

Patterns of psychological, nutritional, and microbial factors predict treatment response to the low FODMAP and NICE diet for specific symptoms. These findings may inform individual tailoring of dietary treatment advice in IBS patients.

References:

Böhn L, Störsrud S, Liljebo T, Collin L, Lindfors P, Törnblom H, Simrén M. Diet low in FODMAPs reduces symptoms of irritable bowel syndrome as well as traditional dietary advice: a randomized controlled trial. Gastroenterology 2015, 149(6):1399-1407.e2

UEG Week 2020

A DISTINCT INTESTINAL MICROENVIRONMENTAL PROFILE IS LINKED TO BOWEL HABITS IN PATIENTS WITH IRRITABLE BOWEL SYNDROME. P0651

Iribarren C.[1], Ahluwalia B.[1,2], Magnusson M.K.[1], Sundin J.[3], Savolainen O.[4], Ross A.[4,5], Törnblom H.[3], Simrén M.[3,6], Öhman L.[1]

[1] Institute of Biomedicine, University of Gothenburg, Microbiology and Immunology, Gothenburg, Sweden,
[2] Calmino group AB, Gothenburg, Sweden,
[3] Institute of Medicine, University of Gothenburg, Internal Medicine and Clinical Nutrition, Gothenburg, Sweden,
[4] Chalmers Mass Spectrometry infrastructure, Chalmers University of Technology, Biology and Biological Engineering, Gothenburg, Sweden,
[5] AgResearch Lincoln Research Centre, Lincoln, New Zealand,
[6] Center for Functional Gastrointestinal and Motility Disorders, University of North Carolina at Chapel Hill, Chapel Hill, United States

Introduction:

Patients with irritable bowel syndrome (IBS) are suggested to have an altered intestinal microenvironment compared to healthy subjects. Previous studies have explored either microbiota composition or metabolic parameters, but none has yet studied these variables in combination, in IBS patients of all subtypes. We therefore aimed to determine the overall intestinal microenvironment profile, including fecal microbiota and metabolites, in IBS patients (all subtypes) and healthy subjects, and the potential link to symptoms related to IBS.

Aims & Methods:

Fecal samples were collected from IBS patients fulfilling the ROME III criteria (all subtypes) and healthy subjects. Fecal microbiota was evaluated by GA-map™ Dysbiosis Test, while tandem mass spectrometer (GC-MS/MS) was used for metabolomic profiling. Symptom severity as well as anxiety and depression in IBS patients was assessed by IBS Severity Scoring System (IBS-SSS) and Hospital Anxiety and Depression Scale (HADS), respectively. Patients were characterized according to Rome III IBS subtypes based on predominant bowel habits using the Bristol Stool Form (BSF) scale (IBS with constipation (IBS-C) or diarrhea (IBS-D), Mixed IBS (IBS-M) or Unsubtyped IBS (IBS-U). Multivariate analyses were applied to the data set comprising fecal microbiota and metabolites to identify patterns and relationships between the variables. Ingenuity Pathway Analysis Core Analysis (IPA, version 2.3) (Qiagen) was carried out to identify biological functions associated to metabolomic differences between IBS patients and healthy subjects.

Results:

A principal component analysis of the intestinal microenvironmental profile, comprising fecal microbiota (n = 54) and metabolites (n = 155), showed that IBS patients (n=40) and healthy subjects (n=18) tended to cluster separately. As shown in table 1, a large number of metabolites along with a few bacterial taxa were found in higher levels in IBS patients, whereas only a few variables were lower in IBS patients as compared to healthy subjects. Thus, the distinct intestinal microenvironmental profile of IBS patients was mostly driven by metabolites. Additionally, the intestinal microenvironmental profile differed between IBS-C (n=15) and IBS-D (n=11), where IBS-D patients were mainly defined by higher levels of several metabolites and few bacterial taxa as compared to IBS-C patients (Table 1). However, no clustering based on fecal bacteria and metabolites was seen when patients were subgrouped according to symptom severity or anxiety and depression. Further, IPA Core Analysis predicted amino acid metabolism and several cellular and molecular functions to be altered in IBS patients based on differences in the metabolite profile between patients with IBS and healthy subjects.

Intestinal microenvironmental profile	↑IBS*	↓IBS*	↑IBS-D⁰	↓IBS-D⁰
Bacterial taxa (no.)	3	5	2	4
Metabolites (no.)	67	2	27	5

The number (no.) of bacterial taxa (n=54) and metabolites (n=155) being different in IBS patients (n=40) as compared to healthy subjects (n=18)*, as well as variables being different in IBS patients with diarrhea (IBS-D, n=11) compared to IBS patients with constipation (IBS-C, n=15)⁰. Upward pointing arrow represents upregulation and downwards arrow represents downregulation.

[The intestinal microenvironmental profile is distinct in patients with irritable bowel syndrome and is linked to bowel habits]

Conclusion:

The intestinal microenvironment, including microbiota and metabolites, differentiates IBS patients from healthy subjects, as well as discriminates IBS subgroups based on the predominant bowel habit. Moreover, IPA Core Analysis predicted amino acid metabolism and certain cellular and molecular functions to be of importance in the pathophysiology of IBS.

2019

UEG Week 2019

Presentation from Opening Session: Part II at UEG Week 2019 – **Top Abstract Prize 2019**

EFFECTS OF FAECAL MICROBIOTA TRANSPLANTATION IN PATIENTS WITH IRRITABLE BOWEL SYNDROME (IBS): A RANDOMISED, DOUBLE-BLIND PLACEBO-CONTROLLED STUDY.

Magdy El-Salhy (1), Jan Gunnar Hatlebakk (2), Odd Helge Gilja (3), Anja Kristoffersen (4), Trygve Hausken (5)
(1) Stord Hospital Medical Clinic, University of Bergen, Stord, Norway
(2) Haukeland University Hospital Dept. of Medicine, Bergen, Norway
(3) University of Bergen, Bergen, Norway
(4) Genetic Analysis AS, Oslo, Norway
(5) Institute of Clinical Medicine, University of Bergen, Bergen, Norway

Introduction:

The intestinal bacterial profile in IBS patients differs from that of the healthy subjects with a low diversity (dysbiosis) (1,2,3). Microbiota dysbiosis in IBS patients is believed to play an important role in the pathophysiology of this disorder (3). Faecal microbiota transplantation (FMT) has been tried in two double-blind placebo-controlled studies (4,5). While the first study showed improvement of the IBS symptoms, the other study did not show any effect at all. The present study was conducted to study the effect of FMT using a single donor with a favourable microbiota profile.

Aims & Methods:

A randomised, double-blind placebo-controlled study was conducted, where 164 IBS patients were randomised to either placebo, 30 g transplant or 60 g transplant in ratio 1:1:1. The primary outcome was a reduction in the IBS-symptoms defined as a decrease in the IBS-SSS total score with ≥50 points 3 months after FMT. The secondary outcome was a reduction in the Dysbiosis index (DI) and a change in the intestinal bacterial profile 3 months following FMT. Abdominal symptoms, fatigue and quality of life were assessed by the IBS-SSS and Birmingham IBS symptom, fatigue Assessment Scale, IBS-Quality of Life and the Short-Form Dyspepsia index Questionnaires. Gut bacterial analysis was done using a commercially available test, GA-map Dysbiosis Test® (Genetic Analysis AS, Oslo, Norway).

Results:

The response to FMT occurred in 23.6, 75.9 and 87.3% of patients received placebo, 30 g and 60 g transplant, respectively. This was accompanied by a significant improvement in fatigue and quality of life in these patients. Symptom remission (SSS≥175 points) occurred in 5.5, 35.2 and 47.3% in placebo, FMT 30 g and FMT 60 g groups, respectively. Similarly, a significant clinical improvement in fatigue (FAS≥4 points) was found in 21.8, 53.7 and 52.7% of patients received placebo, FMT30 g and FMT 60 g, respectively. The corresponding figures for the quality of life (IBS-QoL≥14 points) were 7.3, 61.1 and 58.2%. DI did not decrease significantly in patients received FMT or placebo. The intestinal bacterial profiles changed in both groups received 30 and 60 g transplant, but not in the placebo group.

Conclusion:

FMT is an effective treatment for patients with IBS. A well-defined donor with normal DI and favourable specific microbial signature is essential for the success of FMT. Response to FMT increases with increased dose. There was a significant difference in the intestinal bacterial profile between responders and non-responders, which might be used to identify candidates for FMT.

UEG Week 2019

THE EFFECTS OF HUMAN MILK OLIGOSACCHARIDES ON BIFIDOBACTERIA AND GASTROINTESTINAL SYMPTOMS IN IRRITABLE BOWEL SYNDROME PATIENTS: A PARALLEL, DOUBLE BLIND, RANDOMIZED, PLACEBO-CONTROLLED TRIAL

Cristina Iribarren (1), Hans Törnblom (2), Imran Aziz (2), Maria K. Magnusson (1), Johanna Sundin (2), Louise Vigsnaes (3), Ingvild Amundsen (4), Bruce McConnell (5), Dorthe Seitzberg (6), Lena Öhman (1), Magnus Simrén (2)
(1) University of Gothenburg. Institute of Biomedicine, Göteborg, Sweden
(2) University of Gothenburg. Institute of Medicine, Göteborg, Sweden
(3) Glycom A/S, Hoersholm, Denmark
(4) GlycomA/S, Hørsholm, Denmark
(5) Glycom A/S, Horsholm, Denmark
(6) Glycom, Hørsholm, Denmark

Introduction:

Gut microbiota alterations seem to be a relevant factor in the pathophysiology of irritable bowel syndrome (IBS). Therefore, modulating the gut microbiota by using prebiotics, such as human milk oligosaccharides (HMO), might influence gastrointestinal (GI) symptoms through their effect on specific gut bacteria. However, the safety and tolerance of HMO have not been assessed in IBS patients. Thus, we aimed to determine the dose of a HMO mix of 2'-O-Fucosyllactose (2'FL) and Lacto-N-neotetraose (LNnT) that increased fecal bifidobacteria abundance in IBS patients without aggravating overall GI symptoms.

Aims & Methods

We performed a parallel, double-blind, randomized, placebo-controlled trial in an IBS patient cohort diagnosed according to the Rome IV criteria. We studied the effects of 5g and 10g doses of 4:1 mix of 2'FL and LNnT (2'FL/LNnT) compared to placebo (powdered glucose) after 4 weeks of oral intake, followed by a 4 weeks wash-out period. Gastrointestinal Symptom Rating Scale-IBS (GSRS-IBS) and fecal samples were collected at baseline, at the end of intervention and the washout period. Fecal bifidobacteria abundance was analyzed by the GA-map™ platform technology. Non-parametric analysis was performed between and within intervention groups.

Results:

We included 61 IBS patients, (41 women; median age 45 (19 - 73) years); 27 IBS with diarrhea, 14 IBS with constipation and 20 mixed IBS. During the intervention phase, two patients, one from the placebo group and one from the 10g group,

discontinued prematurely (after 2 weeks of intervention) due to worsening symptoms.

As can be seen in table 1, the bifidobacteria abundance differed between the groups after the intervention period, with higher abundance in the 10g group compared with the other intervention groups ($p< 0.05$). Within-group comparisons demonstrated a significant increase in bifidobacteria abundance in the 10g group at the end of the intervention period compared to baseline ($p=0.018$). However, after the 4 weeks washout period no difference between the groups was detected. Overall GI symptom severity (GSRS-IBS total score) or individual GI symptoms did not differ between the groups after the treatment (ns, non-significant). However, tendencies towards improvements of GI symptom severity within the groups were observed at the end of the intervention (week 4). The 10g group showed a trend towards reduction in overall GI symptom severity (GSRS-IBS total score) compared to baseline ($p=0.076$), whereas the placebo group showed reduction of overall GI symptom severity, bloating and diarrhea at the end of the intervention ($p< 0.05$ for these comparisons). No symptom deterioration was seen in any of the groups.

Conclusion:

In conclusion, 10g HMO dose of 2'FL/LNnT mix is able to induce the growth of the beneficial bacteria Bifidobacterium in patients with IBS without aggravating gastrointestinal symptoms. This approach may be worthwhile to restore IBS gut microbiota towards a healthy profile.

ESNM 2019

FÆCAL MICROBIOTA TRANSPLANTATION (FMT) IN IBS USING A SUPER-DONOR: A RANDOMISED, DOUBLE -BLIND PLACEBO-CONTROLLED STUDY

M. El-Salhy1, T. Hausken2, O. H. Gilja3, A. Kristoffersen4, J. G. Hatlebakk3

1 Stord Hospital, Stord, Norway; 2 Department of Clinical Medicine, Bergen, Norway; 3 University of Bergen, Bergen, Norway; 4 Department of Clinical Medicine, Oslo, Norway

Objective:

FMT has been tried in IBS patients in two double-blind placebo-controlled studies with contradictory results. The present study was conducted to study the effect of FMT using a single donor with a favorable microbiota profile.

Methods:

A randomized, double-blind placebo-controlled study was conducted, in which 164 IBS patients were randomized to a either placebo, 30 g or 60 g transplant in ratio 1:1:1. A single well-defined donor was used, which was normobiotic and with a favorable specific microbial signature as recently defined. Abdominal symptoms, fatigue and quality of life were assessed by the IBS-SSS, Birmingham IBS symptom Fatigue Assessment Scale, IBS-QoL and the Short-Form Dyspepsia index Questionnaires. Gut bacterial analysis was done using a commercially available test, GA-map Dysbiosis Test ®. The primary outcome was a reduction in IBS-SSS score ≥ 50 points 3 months after FMT. The secondary outcome was a change in the intestinal bacterial.

Results:

The responses to FMT were 23.6, 75.9 and 87.3% of patients received placebo, 30 g and 60 g transplant, respectively. Symptom remission (SSS ≥ 175 points) occurred in 5.5, 35.2 and 47.3% in placebo, FMT 30 g and FMT 60 g groups, respectively. Similarly, a significant clinical improvement in fatigue (FAS ≥ 4 points) was found in 21.8, 53.7 and 52.7% of patients received placebo, FMT30 g and FMT 60 g, respectively. The corresponding figures for the quality of life (IBS-QoL ≥ 14 points) were 7.3, 61.1 and 58.2%. DI did not decrease in patients received FMT or placebo. However, the intestinal bacterial profiles changed in patients received 30 and 60 g transplant, but not in the placebo group.

Conclusions:

FMT is a highly effective treatment for patients with IBS when using well-defined donor with normal DI and a favourable microbial signature and is essential for the clinical success of FMT. Response to FMT increases with increased dose of transplant.

2018

UEG Week 2018

EFFECTS OF ALOE BARBADENSIS MILL. EXTRACT ON SYMPTOMS AND FAECAL MICROBIOTA PROFILE IN PATIENTS WITH IRRITABLE BOWEL SYNDROME; P1076

Bani Ahluwalia (1), Lena Böhn (2), Stine Störsrud (2), Fredrik Larsson (3), Maria K. Magnusson (1), Magnus Simrén (2), Lena Öhman (1)

(1) University of Gothenburg, Institute of Biomedicine, Gothenburg, Sweden

(2) University of Gothenburg, Institute of Medicine, Gothenburg, Sweden

(3) Calmino Group AB, Gothenburg, Sweden

Introduction:

Aloe barbadensis Mill. has been suggested to reduce symptoms in patients with irritable bowel syndrome (IBS).

Aims & Methods:

We aimed to determine the effects of a commercially available Aloe barbadensis Mill. (Aloe) extract AVH200®, on symptoms and fecal microbiota in patients with IBS, in a randomized, double-blind, placebo-controlled study. After a 2 week screening period, 173 patients with IBS according to the ROME III criteria, were randomized to active treatment (n = 91) (250 mg aloe extract, 60 mg ascorbic acid and inulin) or placebo (n = 82) (60 mg ascorbic acid and inulin), for 4 weeks. Patients completed IBS Symptom Severity Scoring (IBS-SSS) questionnaires on a weekly basis. Response was defined as a reduction of IBS-SSS ≥50, compared with baseline. Faecal samples were collected before and after the intervention from 52 patients and microbiota composition was evaluated by GA-map Dysbiosis Test of 54 DNA probes targeting ≥300 bacteria which were analyzed with Orthogonal Projections to Latent Structures Discriminatory Analysis (OPLS-DA) implementing a VIP cut-off of 0.7. Statistical analysis was carried out using non-parametric tests.

Results:

In total, 160 IBS patients completed the study. The overall severity of IBS symptoms was reduced in patients receiving active treatment (n=84; 242 (199-291) vs. 218 (138-281), P< 0.001) and placebo (n=76; 236 (171-289) vs. 197 (126-258), P< 0.001) comparing baseline vs. end of intervention, without difference between the groups (P = 0.61). However, a reduction in overall symptom severity was recorded in diarrhea predominant patients (IBS-D) receiving active treatment (n= 21; 273 (196-330) vs. 226 (101-308), P = 0.003) but not placebo (n= 22; 229 (138-259) vs. 196 (118-238), P=0.07), without difference between the groups (P = 0.21). Further, pain severity, pain frequency, bloating and daily life were similarly reduced in both groups (data not shown). However, bowel habit was improved by active treatment (70 (52-88) vs. 60 (41-81), P=0.001), but not placebo (70 (46-85) vs. 66(46-80), P=0.17), although without difference between the two groups (P=0.43). The frequency of responders did not differ between active treatment (n=27, 32%) and placebo (n=31, 41%) (P= 0.26).

In the active treatment group, faecal microbiota profiles differed between responders (n=10) and non-responders (n=14) both before (R2 = 0.96, Q2 = 0.55) and after intervention (R2=0.94, Q2=0.73). The abundance of Akkermansia muciniphila was higher in responders than non-responders before (65.5 (35.8-187.3) vs. 3.5 (1-44), P =0.03) but not after the intervention (54 (14.5-226.8) vs. 23 (1-106.78), P=0.32). In the placebo group, the fecal microbiota profiles of responders (n=12) and non-responders (n=16) did not differ before or after the intervention.

Conclusion:

Aloe extract and placebo were similarly effective in reducing overall symptoms of IBS patients, but a tendency towards better effect of aloe extract were seen in IBS-D patients. Further, faecal microbiota profiles may help predict IBS patients' responsiveness to aloe extract.

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LOWER FECAL BACTERIAL ABUNDANCE IS ASSOCIATED WITH DISEASE RECURRENCE ONE YEAR AFTER ILEOCAECAL RESECTION IN PATIENTS WITH CROHN'S DISEASE; P0270

Anna Strömbeck (1), Hans Strid (2), Maria K. Magnusson (3), Stefan Isaksson (4), Per-Ove Stotzer (5), Anders Lasson (2), Lena Öhman (6)

(1) University of Gothenburg, Inst of Biomedicine, Göteborg, Sweden

(2) Södra Älvsborg Hospital, Borås, Sweden

(3) University of Gothenburg, Göteborg, Sweden

(4) University of Gothenburg, Institute of Biomedicine, Göteborg, Sweden

(5) Sahlgrenska University Hospital Dept. of Medicine, Göteborg, Sweden

(6) University of Gothenburg Sahlgrenska Academy Dept. of Microbiology and Immunology, Gothenburg, Sweden

Introduction:

Dysbiosis has been proposed to be a key antigenic driver for the inflammation in Crohn's disease (CD). However, the role of the fecal microbial composition for the post-operative disease course in CD patients remains to be established.

Aims & Methods:

Our aim was to determine if the fecal microbial composition at the time of ileocaecal resection or one year after surgery was associated with endoscopic disease recurrence in CD patients one year after surgery.

Patients with CD who had undergone ileocaecal resection were included in the study. Approximately one year after surgery, clinical evaluation by ileocolonoscopy was performed. The mucosa in the neoterminal ileum and ileocolonic anastomosis was assessed according to Rutgeerts' scoring system. Five or less aphtoid lesions were considered as remission (i,0-i,1), and >5 aphtoid lesions, lesions or ulcers confined to the anastomosis or diffuse inflammation were considered as endoscopic disease recurrence (i,2-i,4).

Fecal microbial composition was analyzed using the Genetic Analysis GA-map Dysbiosis test, which consists of 54 DNA probes targeting ≥300 bacteria on different taxonomic levels. Logarithmic data were analyzed in SIMCA using orthogonal partial least squares discriminate analysis (OPLS-DA) to identify discrimination between groups. Bacteria with the strongest discriminatory power were further analyzed by univariate analysis (Mann-Whitney U-test).

Results:

In total, 22 CD patients from Southwestern Sweden (8 women) with median age 30 (17-63) years and median disease duration of 3 (0-11) years at the time of resection was included. At inclusion, 8 patients were treated with 5-aminosalicylic acid (5-ASA), 14 with corticosteroids, 11 with thiopurines, 1 with anti-tumor necrosis factor, and 4 patients had none of the treatments above. At the one year follow up, 9 patients were treated with 5-ASA, 2 with corticosteroids, 6 with thiopurines, and 8 patients had no treatment.

Stool samples were collected by 9 patients at the time of resection and by 21 patients at the one-year post surgery follow up. At the one year follow up, 13 patients were in endoscopic remission (i,0-i,1) and 9 patients had endoscopic recurrence (i,2-i,3).

At the time of resection, fecal microbial composition discriminated patients whom at the one year post surgery follow up were in endoscopic remission or with recurrence, respectively, although the predictive ability was low (R2=0.94, Q2= -0.1; i,0-i,1: n=5; i,2-i,3: n=4). Similarly, fecal microbiota at the one year post surgery follow up discriminated patients in endoscopic remission from those in recurrence, yet with low predictability (R2=0.71, Q2= -0.47; i,0-i,1: n=13; i,2-i,3: n=8).

The OPLS-DA models at the time of resection and at one-year post surgery follow up demonstrated that endoscopic remission was associated with a higher bacterial abundance, both among the Firmicutes and Bacteroidetes, as compared to patients with recurrence. In addition, univariate analysis showed that patients in remission one year after surgery tended to have higher abundance of Pseudomonas spp at the time of surgery (p=0.06) and Parabacteroides spp at the one

year post surgery follow up (p=0.08), as compared to patients with recurrence.

Conclusion:

Our results suggest that CD patients with endoscopic disease recurrence one year after ileocaecal resection have lower fecal bacterial abundance, both at the time of resection and one year after surgery, as compared to patients in remission. Thus, a lower intestinal bacterial abundance may be a contributing factor to disease relapse in these patients.

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DOES FAECAL MICROBIAL DYSBIOSIS CORRELATES WITH DISEASE ACTIVITY MEASURES, FAECAL CALPROTECTIN AND SYMPTOM SCORES IN ADULT PATIENTS WITH INFLAMMATORY BOWEL DISEASE; P0942

Dorit Ankersen (1), Dorte Marker (1), Thor Bech Johannesen (2), Søren Iversen (2), Malin Petra Ulfsdotter Weimers (1), Johan Burisch (1), Paal Skytt Andersen (2), Kristine Paridaens (3), Christina Casén (4), Pia Munkholm (1)

(1) North Zealand University Hospital, Frederikssund, Denmark

(2) Statens Serum Institute, Copenhagen, Denmark

(3) Ferring International, Saint-Prex, Switzerland

(4) Genetic Analysis AS, Oslo, Norway

Introduction:

Inflammatory bowel disease (IBD) which primarily consists of Crohn's disease (CD) and Ulcerative Colitis (UC) has a chronic relapsing nature. Therefore, it is of importance to detect, predict and treat a relapse as soon as possible in order to decrease the inflammation and avoid further intestinal damage. There is increasing evidence substantiating that intestinal microbial dysbiosis in IBD plays a role in the pathogenesis and progression hereof. Dysbiosis is poorly understood and therefore not yet considered in clinical use for optimizing treatment of IBD.

Aims & Methods:

The aim was to characterize the microbiome in IBD in a consecutive cohort, and correlate dysbiosis index and other findings to conventional disease activity measures in understanding and interpreting the microbiome in IBD.

For 1 year, 120 consecutive IBD patients in any IBD therapy were enrolled in the web-outpatient clinic at North Zealand University Hospital, Capital Region of Denmark to monitor on Constant.care.dk. Patients were randomized to home-monitoring every 3rd month or on demand (monitoring after patients' choice) on Constant care © and CalproSmart™ app. All home-monitoring data were visualized to the patients in a traffic light manner: Harvey-Bradshaw Index (HBI) for CD or Simple Clinical Colitis Activity Index (SCCAI) for UC and faecal calprotectin (FC) using CalproSmart™ Self-Test Kit (Calpro AS, Norway).

The microbial dysbiosis index (DI); 1-5 normo-dysbiosis, GA-map™ (Genetic Analysis AS, Norway)1 was correlated to disease activity indices and FC. Polymerase chain reaction (PCR) of faecal bacteria's 16S rRNA, Illumina was additionally analyzed and subsequent bioinformatic analyses were performed.

Patients were asked to send faecal samples for both microbiome analyses longitudinally every time they were scoring themselves on the apps.

Results:

Eighty-four IBD patients consented to send faecal samples for microbiome analysis. 64 (76%) send longitudinal samples, 14 (17%) handed in only one sample each and 6 (7%) did not send any samples at all. Out of the 78 patients that sent faecal samples - 11 (14%) were diagnosed with CD (n=36 samples), 63 (81%) with UC (n=230) and 4 (5%) with IBDU (n=22). Median (IQR) for the following variables FC, SCCAI, HBI and DI were respectively: 82 (28-455), 1 (0-2), 3 (1-9), 3 (2-4). Spearman correlations between FC and DI: 0.24 (p< 0.01), DI and SCCAI: 0.17 (p=0.01), DI and HBI: 0.25 (p=0.17). Based on Illumina microbial data 3 clusters (PCoA) according to FC values categorized as; remission (0-200 mg/kg), moderate activity (200-600 mg/kg) and severe activity (>600mg/kg) showed a trend towards separation in these 3 groups, ANOSIM R=0.15, P=0.001. No clear clusters were observed in regard to HBI and SCCAI.

Conclusion:

Disease activity measures FC and SCCAI showed relatively small but significant correlations with DI-Dysbiosis Index. Illumina microbial data showed a trend in separating FC in mild, moderate and severe inflammation. Further bioinformatic analyses are awaiting on the individual longitudinal data in relation to disease course and changes in disease activity.

References:

1. Casén C et al. Deviations in human gut microbiota: a novel diagnostic test for determining dysbiosis in patients with IBS or IBD. ATP 2015.

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MICROBIOTA PROFILE AND DYSBIOSIS ASSESSMENT IN CLINICAL PRACTICE: A PILOT STUDY ON IBD PATIENTS; P0332

Sonia Facchin (1), Andrea Buda (2), Barbara Perini (1), Renata D'Incà (1), Edoardo Vincenzo Savarino (1)

(1) University of Padua,Padova,Italy

(2) UOC Gastroenterology,Feltre,Italy

Introduction:

A growing body of evidence suggests that dysbiosis plays a key role in the pathogenesis of inflammatory bowel disease (IBD). However, due to intrinsic limitations in current diagnostic methods and lack of agreement on the appropriate test to use, in clinical practice the characterization of dysbiosis in IBD patients remains challenging.

Aims & Methods:

We compared a commercially available dysbiosis test and a stool standard analysis test to profile the microbiota at phylum level in IBD patients and healthy control subjects.

Human fecal samples from 13 IBD patients and 4 healthy control subjects were examined by the GA-map™ Dysbiosis Test (Oslo, Norway) and Illumina Mi-Seq test by BMR-genomics (Padova, Italy). GA-Map is a 16S rRNA test that utilize 54 DNA probes based on seven variable regions (V3-V9) and

recognizing gut bacteria profiles for identification and characterization of dysbiosis. The BMR-genomic test applies the universal primer based on the V3-V4 hypervariable region of 16S rRNA using an Illumina Mi-Seq next-generation sequencer. The correlation between variation of microbiota expressed as the Dysbiosis Index (DI) and fecal calprotectin (FC) levels in IBD patients was also investigated.

Results:

BMR-genomics reports on the relative abundance (ra) of the major phyla on IBDs microbiota. So far, we compared the trend of ra with normalized signal for fluorescent probes of DI between the two techniques. From descriptive analysis, the two methods show a similar trend for Actinobacteria, Bacteroidetes and Proteobacteria, especially on CD disease. However, there was a substantial difference in the trend on Firmicutes. FC levels were correlated with the DI in CD but not in UC patients ($r = 0.74$ vs $r = 0.2$, respectively). Indeed, 100% of CD patients and 75% of UC patients with dysbiosis (DI 3-5) showed an increased FC (>50µg/g). Finally, only by BMR-genomics analysis we found a significant variation on Faecalbacterium prausnitzii between IBD and controls ($p< 0.05$).

Conclusion:

We observed that GA-Map™ Dysbiosis Test and the BMR-genomic test produce comparable results in terms of degree of variation of microbiota in IBD patients and thus both can be used to identify and characterize dysbiosis in IBD patients. Furthermore, dysbiosis as assessed by these methods seems to well correlate with biochemical activity in CD patients and thus could be considered a potential target for treatment.

References:

[1] Casen C. et al. Aliment Pharmacol Ther 2015; 42: 71-83 [2] Takahashi S. et al. Plos one2014; 9, 8:1-9

UEG Week 2018

CHARACTERIZATION OF GUT MICROBIOTA IN A COHORT OF NORMAL ITALIAN SUBJECTS; RESULTS FROM A CROSS-COUNTRY POPULATION STUDY; P1637

Magdalena Kauczynska Karlsson (1), Angelo Zullo (2), Sergio Peralta (3), Fabio Pace (4), Christina Casén (1)
(1) Genetic Analysis AS,Oslo,Norway
(2) Ospedale Nuovo Regina Margherita,Roma,Italy
(3) Azienda Ospedaliera Universitaria,Palermo,Italy
(4) Bolognini Hospital,Seriate (BG),Italy

Introduction:

The composition of intestinal microbiota is gaining importance in human health studies since there is increasing evidence that bacteria play a role in disease etiology. The composition of the gut microbiota is relatively stable throughout adult life but can be transiently or permanently altered as a result of bacterial infections, antibiotic treatment, lifestyle, surgical, and a long-term change in diet.

Aims & Methods:

To characterize normal Italian gut microbiota and identify factors shaping its composition, we conducted 16S rRNA analysis using GA-map™ Dysbiosis Test1 of fecal samples collected from normal Italian adults residing in 3 regions of Italy (Milan, Rome, Palermo). Participants were recruited from subjects coming to the clinic for colonoscopy in connection to the national screening program, with no abnormal findings. Each participant also completed a 16-question questionnaire.

The GA-map™ Dysbiosis Test1 is composed of 54 pre-selected highly specific 16S rRNA gene-targeted single nucleotide primer extension (SNuPE) probes, detecting at least 300 bacteria on different taxonomic levels, for detection and characterization of dysbiosis. The test reports a Dysbiosis Index (DI), where DI = 1-2 is considered normobiosis, and DI = 3-5 is dysbiosis. Fecal-Calprotectin (FCal) analysis was performed using BÜHLMANN fCAL® ELISA with a cut-off of ≤200mg/kg. Chi-square test was used to determine differences in proportions, with $p < 0.05$ for significance.

Results:

We collected fecal samples from 78 normal Italian adults (39 females, 39 males; median age, 55; range age, 24-73; median FCal, 37; range FCal 6-190; median BMI, 23.4; range BMI, 18.4-28.4). 27 (35%) of study participants were smokers.

In total 60% (47/78) of normal Italian adults were determined to be normobiotic, 36% (28/78) were determined to have mild dysbiosis, and 4% (3/78) were determined to have severe dysbiosis. However, no subjects were found to have the highest degree of dysbiosis with DI = 5. Site-wise, the results show 58% normobiosis in Milan, 68% in Rome, and 38% in Palermo.

Of note, 15 (56%) of 27 smoking subjects versus 16 (31%) of 51 non-smoking subjects were determined to be dysbiotic ($p = 0.04$). No significant difference in proportion of dysbiosis between sites ($p > 0.01$) or gender ($p = 0.8$).

We observed high variability in the profiles of fecal microbiota among the Italian adults. The profiles were generally dominated by Actinobacteria (mainly the genus Bifidobacterium), Firmicutes (with diverse representation from numerous genera), Verrucomicrobia (Akkermansia muciniphila), and Bacteroidetes (mainly Bacteroides and Prevotella).

Conclusion:

We used GA-map™ technology to characterize the gut microbiota in normal Italian adults. The present study showed that the composition of the fecal microbiota of normal Italian adults at the national level, while highly variable, was not strongly associated with subjects´ area of residence or gender. However, smoking was found to be associated with dysbiosis. Altogether, our results indicate a 40% proportion of dysbiosis in normal Italian adults, which may possibly be caused by environmental factors such as dietary or smoking habits, as we observe a 25% higher proportion of dysbiosis among smokers as compared to non-smokers.

References:

1 Casén C, et al. (2015) Deviations in human gut microbiota: a novel diagnostic test for determining dysbiosis in patients with IBS or IBD. Aliment Pharmacol Ther.; 42(1):71-83

UEG Week 2017

FÆCAL MICROBIOTA IN PÆDIATRIC INFLAMMATORY BOWEL DISEASE BEFORE AND AFTER THERAPY

Christine Olbjørn (1), Milada Cvancarova Småstuen (2), Espen Thiis-Evensen (3), Britt Nakstad (4), Christina Casén (5), Morten Harald Vatn (6), Gori Perminow (7)

(1) University of Oslo, Campus Ahus, Institute of Clinical Medicine,Oslo,Norway

(2) Oslo and Akershus University College of Applied Sciences, Faculty of Health Sciences, Oslo, Norway

(3) Oslo University Hospital, Department of Gastroenterology, Rikshospitalet, Oslo, Norway

(4) Akershus University Hospital,Pediatric and Adolescent Medicine,Lørenskog,Norway

(5) Genetic Analysis AS,Dept. of Genetics,Oslo,Norway

(6) University of Oslo,Epigen, Faculty Divison Ahus, Institute of Clinical Medicine,Oslo,Norway

(7) Oslo University Hospital,Department of Pediatrics, Ullevål,Oslo,Norway

Introduction:

Imbalances in the faecal microbiota with a reduction in biodiversity; dysbiosis, have been reported in inflammatory bowel disease (IBD).

Aims & Methods:

Our aim was to study and compare the faecal microbiota in paediatric patients with newly diagnosed untreated IBD with the microbiota of healthy children and paediatric patients with gastrointestinal symptoms but no IBD. We also wanted to study microbiota changes in IBD patients one year after initiation of treatment. Faecal samples were collected from 235 children below 18 years of age. IBD was diagnosed in 110 patients, 80 had Crohn's disease (CD), 27 had ulcerative colitis (UC) and 3 had IBD unclassified. Fifty patients had gastrointestinal symptoms but no IBD; non-IBD symptomatic patients, and 75 were healthy children. Of the IBD patients, 31 (9 with UC and 22 with CD) had repeated faecal analysis one year after therapy, 16 (52%) had been treated with infliximab. The microbiota was analysed at baseline and follow-up using a 16s rRNA DNA based test with the GA-map® technology, measuring probe signal intensity (PSI) of 54 DNA probes targeting 300 bacteria on different taxonomic levels.

Results:

At baseline the majority of bacterial PSIs were reduced in IBD and non-IBD patients (both p< 0.001) compared to healthy controls. IBD patients had significantly reduced abundance of various Firmicutes p<0.01 (Eubacterium rectale, Eubacterium biforme), Bacteroidetes p=0.02 (Parabacteroidetes), and of Bifidobacterium p=0.02, compared to non-IBD patients. In the 31 IBD patients with repeated faecal samples the microbiota was more dysbiotic after therapy, regardless of IBD type and whether the IBD patient had received infliximab or not, with less abundance of the Clostridia species Dorea spp., Lachnospiraceae and Eubacterium hallii (p<0.001). Compared to healthy and non-IBD patients the microbiota composition after treatment had significantly (p<0.001) less abundance of Akkermansia muciniphila, Bacteroides spp., Prevotella spp. And Veillonella spp. besides higher abundance of Streptococcus sanguinis, Atopobium rimae and pro-inflammatory Proteobacteria (Shigella spp., Escherichia spp.)

Conclusion:

The faecal microbiota composition is significantly different in paediatric IBD and non-IBD symptomatic patients compared to healthy children and may be of value in diagnosing IBD. A severe dysbiotic microbiota profile seem to persist and even worsen after treatment in pediatric IBD patients regardless of treatment with infliximab or not.

References:

1. Casén C et al. Deviations in human gut microbiota: a novel diagnostic test for determining dysbiosis in patients with IBS or IBD. Aliment Pharmacol Ther. 2015 Jul;42(1):71-83.

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DYSBIOSIS OF THE GUT MICROBIOTA IN RELATION TO DISEASE ACTIVITY IN INFLAMMATORY BOWEL DISEASE

P. Ricanek, R. Kalla, Y. Ber, S. Vatn, M.K Karlsson, L. Finnby, D. Bergemalm, A. Carstens, J.D. Söderholm, J. Jahnsen, F. Gomollon, J. Halfvarson, J. Satsangi, C. Casén, M.H. Vatn, and the IBD-Character consortium.

Background:

The gut microbiome is thought to be relevant to the pathogenesis of inflammatory bowel disease (IBD). We aimed to explore associations between measures of gut microbiota and clinical as well as inflammatory disease activity in an inception cohort of treatment-naïve IBD patients as well as with inflammatory activity in symptomatic non-IBD patients and healthy controls. The term 'dysbiosis' expresses alterations in the gut microbial community.

Methods:

Patients were diagnosed according to international criteria, including endoscopic and histopathologic assessment. Clinical disease activity in Crohn's Disease (CD) patients was measured by the Harvey-Bradshaw index (HBI), and in ulcerative colitis (UC) patients by the Simple Clinical Colitis Activity Index (SCCAI). Inflammatory activity was assessed by CRP and faecal calprotectin (FCal), (fCAL® ELISA, Bühlmann laboratories AG). Stool samples were collected within 60 days prior to and 14 days after the diagnosis and stored at –80°C. Antibiotic treatment within the last two months was an exclusion criterion. Faecal microbiota profiles were generated by 16S rRNA analyses, using the GA-map® Dysbiosis Test. Dysbiosis was defined as non, mild or severe (1). Differences in disease activity between levels of dysbiosis severity were analysed using ANOVA at a significance level of $p < 0.05$, and univariate associations between inflammatory activity and log-transformed microbiota profiles were analysed using ANCOVA. P-values corrected for multiple testing, using Benjamini-Hochberg correction, are presented.

Results:

Data on dysbiosis, bacteria profiles, and FCal were available in 57 CD, 80 UC, 12 IBD-U patients and 100 symptomatic non-IBD patients, and 45 healthy controls. CRP was available for 52 CD, 74 UC, 10 IBD-U patients, and 88 symptomatic non-IBD

patients. HBI was available for 50 CD patients, while SCCAI was available for 77 UC patients.

Disease activity: No association was found between FCal and dysbiosis in UC patients (P=0.08), CD patients (P=0.22), and healthy controls (P=0.57). However, an association was found between FCal and dysbiosis in symptomatic non-IBD patients (P=0.04) and in IBD-U (P=0.005). An association was found between CRP and dysbiosis in CD patients (P=0.02), while not for UC and symptomatic non-IBD patients. No association was found between HBI and dysbiosis in CD patients (P=0.23), and between SCCAI and dysbiosis in UC patients (P=0.32).

Microbiota: Increasing dysbiosis severity in UC, CD and non-IBD patients yielded lower abundance of Faecalibacterium prausnitzii, and higher abundance of Proteobacteria, a profile typically observed in gut inflammatory conditions. In addition, the commensal bacteria Bifidobacterium yielded lower abundance with increased dysbiosis severity in UC and non-IBD patients, and in combination with elevated levels of FCal and/or CRP in UC patients. In the healthy controls, increasing dysbiosis severity yielded higher abundance of Proteobacteria.

Conclusion:

In conclusion, a relationship between faecal dysbiosis in sub-groups of IBD and non-IBD was found, in CD patients also with CRP. Accordingly, gut bacteria profiles and abundance may potentially be used to differentiate between severity in UC and CD patients, as a non-invasive tool to monitor disease activity in IBD.

Reference:

(1) Casén et al. Aliment Pharmacol Ther 2015; 42: 71–83

2016

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MULTIVARIATE MODELLING OF GUT MICROBIAL PROFILES PREDICTS RESPONSIVENESS TO A DIET LOW IN FODMAPS

S. Bennet, L. Böhn, S. Störsrud, T. Liljebo, L. Collin, P. Lindfors, H. Törnblom, L. Öhman & M. Simrén

Published in GUT, see above.

UEG Week 2016

PERFORMANCE EVALUATION OF DYSBIOSIS STATUS AS A TOOL FOR CLINICAL INVESTIGATION IN PATIENTS WITH FUNCTIONAL GASTROINTESTINAL DISORDERS

Wolfgang Kruis, Torbjørn Lindahl, Elke Christiane Bästlein, Thomas Fiedler, Sven Georgi, Jörg Ringel, Lars Konopka, Michael Mross, Ulf Helwig, Grischa Terheggen, Ewa Ciemniejewska & Christina Casén

Introduction:

Probiotic treatments in patients with functional gastrointestinal disorders (FGID) show promising effects. Because of a lack of tests for routine diagnosis of dysbiosis as yet bacteriotherapy cannot be targeted.

Aims & Methods

A commercially available stool dysbiosis test (GA-map® Dysbiosis Test) was performed in patients with FGID to analyze individual microbiota and to define goups of patients according to their symptoms and microbiota profiles. The dysbiosis test is a 16S rRNA DNA test that utilizes DNA probes in recognizing gut bacteria profiles for identification and characterization of dysbiosis. The study took place in 7 private gastroenterology praxes all over Germany and included 99 eligible outpatients. Age of the patients ranged from 16 to 84 years (median age 44) and sex ratio was 70% females. Informed, written consent was given by each patient.

Results:

Stool testing was feasible and complete in all included patients. A dysbiosis index score (DI) consisting of 5 levels (1-2: non dysbiotic, 3-5 dysbiotic) was defined in 99 patients. According to the cut off of the dysbiosis test, 31 patients (31%) had no dysbiosis while the majority of patients (69%) were dysbiotic. Dysbiosis was mainly associated with augmented Ruminococcus gnavus, and Proteobacteria and diminished Faecalibacterium prausnitzii. Subgroups with elevated levels of dysbiosis could be identified such as FGID after travelers-diarrhea (82 % dysbiosis, 9/11 patients), as compared to diarrhea predominant FGID (69 %, 42/61 patients) with dysbiosis not different from the majority of patients, and a group of 13 low-grade inflammatory patients harboring severe dysbiosis. All subgroups showed different bacterial profiles.

Conclusion

The dysbiosis test available for clinical routine testing is able to identify dysbiosis in symptomatic patients with FGID in a daily routine setting. Accurate diagnosis of the microbiota offers the possibility of targeted acteriotherapy.

References

1 Casén C et al Aliment Pharmacol Ther 2015;42:71-83

UEG Week 2016

KINETICS OF MICROBIAL COMMUNITY COMPOSITION IN PATIENTS WITH DIARRHEA-PREDOMINANT IRRITABLE BOWEL SYNDROME FOLLOWING FAECAL MICROBIOTA TRANSPLANTATION

Tarek Mazzawi (1), Gülen Arslan Lied (2), Magdy El-Salhy (3), Odd Helge Gilja (2), Jan Gunnar Hatlebakk (2), Trygve Hausken (2)

(1) Haukeland University Hospital, Gastroenterology-Medicine, Bergen, Norway

(2) Haukeland University Hospital, Gastroenterology-Medicine, Bergen, Norway

(3) Stord Helse-Fonna Hospital, Gastroenterology- Medicine, Stord, Norway

Introduction:

Alterations in gut microbiota are suggested to play an important role in the development of irritable bowel syndrome (IBS). Through manipulating the gut microbiome of the new host, faecal microbiota transplantation (FMT) has

been used to treat patients with treatment-resistant, antibiotic-associated Clostridium difficile colitis.

Aims & Methods:

The aim was to investigate the effect of FMT on the symptoms and on modifying the gut microbiota in patients with IBS. The study included 13 patients (4 females and 9 males, age range 20-44 years) with diarrhea-predominant IBS (IBS-D) according to Rome III criteria and 13 healthy asymptomatic donors. The patients received freshly donated faeces from a relative and was administered in to the descending part of the duodenum via a gastroscope. Faeces were collected from the donors and the patients before FMT and again from the patients after 1 week and 3 weeks. The samples were stored in freezers (-80°C) until analysis. Microbiota analysis was performed using the GA-map® Dysbiosis test (Genetic Analysis AS, Oslo, Norway) by algorithmically assessing faecal bacterial abundance and profile (dysbiosis index, DI), and potential deviation in the microbiome from normobiosis [1]. DI is based on 54 DNA probes targeting more than 300 bacterial strains based on their 16S rRNA sequence in seven variable regions (V3-V9). A DI above 2 shows a microbiota profile that differs from that of the normobiotic reference collection [1]. In addition, the donors and patients completed the following questionnaires before FMT and again for the patients at 3 weeks after FMT: IBS symptom questionnaire (IBS-SQ), IBS-symptom severity scoring system (IBS-SSS), short form of Nepean Dyspepsia Index (SF-NDI) and Bristol stool scale form.

Results:

The DI (mean±SEM) of the donors (1.8±0.23) differed significantly from the patients before FMT (2.7±0.37, P=0.009) and at 1 week after FMT (2.7±0.38, P=0.039) but not at 3 weeks after FMT (2.3±0.29, P=0.1). The profile of a selection of the most important bacteria (Table 1) showed significant differences in several strains of the gut microbiota between the donors and IBS patients before receiving FMT, which became non-significant after 3 weeks from receiving FMT. The scores of IBS-SQ were significantly reduced during the 3 weeks after receiving FMT; total (P<0.0001), nausea (P=0.001), bloating (P<0.0001), abdominal pain (P=0.0005), constipation (P=0.01), diarrhea (P<0.0001), but not for anorexia (P=0.09). The total scores of IBS-SSS, SF-NDI and Bristol stool scale were significantly reduced after receiving FMT (P=0.0004, 0.004 and 0.008, respectively). No adverse effects were reported after FMT.

Bacteria strain	Donors	Patients			P* Before FMT	P** After 1 week	P*** After 3 weeks
		Before FMT	After 1 week	After 3 weeks			
Firmicutes, Tenericutes,	244±29	128±29	143±32	179±50	0.014	0.052	0.31
Ruminococcus gnavus	4.6±1.1	116±68	29±16	26±18	0.003	0.097	0.32
Dialister invisus	193±46.3	37±19.3	114±38.1	130±60.9	0.014	0.2	0.35
Clostridia, Veillonella,	328±34	227±31	272±36	289±38	0.025	0.32	0.5
Lactobacillus, Pediococcus	13±10	3.5±0.2	7.2±3	2.7±0.06	0.02	0.07	0.35
Streptococcus	49.3±9.7	79±15.4	48.8±9.6	52±11.3	0.036	0.72	0.36
Streptococcus sanguinis and	12.2±4.7	67±30.7	26.2±17	29.9±18	0.007	0.53	0.43
Anaerotruncus	61.5±0.5	63.2±0.5	62.7±0.3	61.5±0.5	0.043	0.045	0.98
Bacteroides	144±4.5	169±8.2	149±7.3	143±6	0.003	0.79	0.82
Bacteroides, Prevotella	483±51.4	634±28.5	599±25.8	551±63.9	0.04	0.24	0.59
Proteobacteria	12.4±1.6	26±6	221±91	16.5±3	0.04	0.004	0.43
Pseudomonas	6.98±0.3	7.99±0.3	7.6±0.2	7.3±0.2	0.017	0.03	0.14
Shigella, Escherichia	22±6.8	46±16	240±63	40±13	0.095	0.0003	0.1
Actinobacteria	159±36	25±4.8	47±10	111±33	0.0006	0.0095	0.35
Atopobium	4.8±0.1	4.49±0.1	4.47±0.1	4.59±0.1	0.12	0.02	0.08
Bifidobacterium	189±43	25±5.3	49±11	123±38	0.0004	0.008	0.28
Actinomycetales	11.4±1.0	8.7±0.9	11.2±1.9	11.1±2.1	0.03	0.32	0.42

Data are presented as the mean±SEM. Comparison: Mann-Whitney U test. *Donors vs. patients before FMT, **Donors vs. patients 1 week after FMT, *** Donors vs. patients 3 weeks after FMT.

Comparison: Mann-Whitney U test. *Donors vs. patients before FMT, **Donors vs. patients 1 week after FMT, *** Donors vs. patients 3 weeks after FMT.

Conclusion:

This is the first study to show the kinetics of microbial community composition in IBS patients following FMT. The results show that FMT helps in restoring alterations in the signals of several strains of the gut microbiota in IBS patients. This suggests that the microbiota profile between donors and patients following FMT has become similar and may have contributed in improving the symptoms and quality of life for these patients. FMT may be used as a treatment for IBS.

References:

1. Casen C, Vebo HC, Sekelja M, Hegge FT, Karlsson MK, Ciemniejewska E, Dzankovic S, Froyland C, Nestestog R, Engstrand L, et al: Deviations in human gut microbiota: a novel diagnostic test for determining dysbiosis in patients with IBS or IBD. Aliment Pharmacol Ther 2015, 42:71-83.

UEG Week 2016

CONSISTENT AND REPRODUCIBLE PRODUCTION OF A MICROBIOTA-BASED DRUG FOR RECURRENT C. DIFFICILE INFECTION: APPLICATION OF A NOVEL DIAGNOSTIC FOR DYSBIOSIS

Courtney Jones (1)

(1) Rebiotic Inc., Roseville, United States of America

Introduction:

Antibiotics are the first-line treatment for C. difficile infection (CDI). However, the most commonly prescribed antibiotics for CDI are associated with high recurrence rates. Antibiotics have been shown to disrupt the intestinal microbiota. Restoration of the intestinal microbiota to its pre-disease state protects against recurrence. There is an unmet need for a standardized, reproducible microbiota-based therapy for recurrent CDI. RBX2600, a microbiota-based drug candidate targeted at recurrent CDI, is sourced from human-derived microbes from extensively screened donors and manufactured using standardized, quality-controlled processes.

Aims & Methods:

To compare the bacterial abundance in the source material for RBX2660 (DS) with the bacterial abundance in the finished

drug product (DP) used in the Phase 2B PUNCH CD 2 study. A total of 70 DS samples sourced from 17 unrelated donors (mean age 27; range 18 to 57 years; 94% male) from August 2014 to February 2016 were compared with 70 matched DP samples using the GA-map® Dysbiosis Test (GA-test), Genetic Analysis AS, Oslo, Norway. The GA-test uses 54 probes targeting V3 to V7 of the bacterial 16s rRNA gene to characterize and identify bacteria present. Approximately 300-400 bacteria at different taxonomic levels are covered, providing for an assessment of the microbial community using multiple variable regions. The GA- test enables serial assessment of the faecal bacterial abundance profile as well as potentially clinically relevant alterations in the microbiome over time. These capabilities of the GA-test were used to assess the production processes for RBX2660. The differences in bacterial abundance between the DP and DS were calculated from log10 of the probe values (DP-DS); averaging the differences.

Results:

The GA-test found that the bacterial abundance in the RBX2660 DP was lower than in the DS in 38 of the 54 probes; equal in number in 6 of the probes; and higher in 10. More specifically, Firmicutes and Actinobacterium showed reduced signal strength in the DP compared with the DS. Bacteroidetes showed increased signal strength in the DP compared with the DS, while Proteobacteria demonstrated equal signal strength in both samples. The comparative abundance in the DP vs. the DS is shown in Table 1. Accuracy was as high as 83.4% at cross-validation. Principal component analysis found that the bacterial profiles in the RBX2660 DP, though lower than in the donor source material, were largely kept intact during the production process for all 17 donors.

Table 1. Comparative Signal Strength of Bacteria

Bacteria	Signal Strength in DP vs. DS	Mean Difference (95% CIM)
Bacteroidetes		
Bacteroides fragilis	Increased	0.07 (0.03, 0.11)
Parabacteroides	Increased	0.12 (0.07, 0.17)
Alistipes	Increased	0.17 (0.11, 0.23)
Firmicutes		
Lachnospirae	Decreased	-0.13 (-0.15, -0.11)
Streptococcus	Decreased	-0.16 (-0.20, -0.13
Negativicutes	Increased	0.03 (0.01, 0.06)
Clostridia	Decreased	-0.18 (-0.20, -0.16)
Actinobacteria		
Bifidobacterium	Decreased	-0.33 (-0.38, -0.28)
DP=drug product	DS = drug source	CIM=confidence interval of mean

Conclusion:

GA-test analysis confirmed that RBX2660 can be manufactured in a consistent and reliable manner with the preservation of key bacterial diversity believed critical for protection from recurrent CDI.

References:

1. Kelly CP, Lamont JT. Clostridium difficile- More difficult than ever. N Engl J.Med. 2008;359:1932–40.
2. Casén C, Vebø HC, Sekelja M, et al. Deviations human gut microbiota: A novel diagnostic test for determining dysbiosis in patients with IBS or IBD. Aliment Pharmacol Ther. 2015;42:71-83.

UEG Week 2016

OP239 - MICROBIOTA ALTERATIONS IN TREATMENT NAÏVE IBD AND NON-IBD PATIENTS - THE EU IBD-CHARACTER PROJECT

P. Ricanek, S. Vatn, R. Kalla, Y. Ber, E. Ciemniejewska, M. Pierik, J. Halfvarson, J. Söderholm, J. Jahnsen, F. Gomollon, J. Satsangi, M. Vatn, M. Sekelja, C. Casén &. The IBD-Character consortium

Introduction:

The microbiota is considered important for development of intestinal diseases. In order to create a molecular snapshot of IBD in its early manifestation, one part of the IBD-Character project identified faecal microbiota profiles among the strictly treatment naïve IBD and symptomatic non-IBD patients, and a healthy control group.

Aims & Methods:

Patients where characterized by international criteria including endoscopy and biopsies. Faecal samples collected during five days prior to diagnosis where stored at – 80°C before examination on GA-map® Dysbiosis Test (1), a 16S rRNA DNA test utilizing DNA probes to recognize gut bacteria profiles. In total 54 probes have been selected (1) for recognition of dysbiosis.

Results:

Table 1. Dysbiosis status

Dysbiosis	Patients	Age [med.]	Female	IBD	CD	UC	IBDU	Non-IBD	Healthy control	Unknown
No	72	28 (19-68)	43	22 [18%]	7 [16%]	11 [18%]	4 [31%]	21 [17%]	27 [56%]	2 [100%]
Low	96	33 (19-66)	49	33 [28%]	14 [31%]	15 [24%]	4 [31%]	50 [40%]	13 [27%]	0
High	126	32 (18-69)	80	65 [54%]	24 [53%]	36 [58%]	5 [38%]	53 [43%]	8 [17%]	0
Total	294	NA	172	120	45	62	13	124	48	2

In total 294 adult patients and healthy individuals were investigated for microbiota profiling. Table 1 shows the distribution and frequency of dysbiosis in the diagnose groups, subgroups and healthy controls.

Comparing the bacteria profiles of IBD, non-IBD and control groups, the abundance of Proteobacteria was increased in IBD and non-IBD as compared to the controls ($p<0.02$), while the abundance of Bifidobacterium and Faecalibacterium prausnitzii was decreased ($p<0.02$ and <0.07, respectively). Concerning the CD and UC subgroups, a significantly reduced abundance of Firmicutes, Streptococcus and Clostridia was found in UC patients ($p<0.05$ for all) as compared to CD. Looking at the microbiota profiles of the Montreal classified subgroups of the UC patients, as compared to the healthy controls in a PLS analysis, the healthy controls (n=48) and E1 (n=22) patients clustered together, while the combined group of E2 (n=17) and E3 (n=23) patients made a separate cluster.

Among 10 bacteria groups contributing to the clustering we looked into three of the groups in details; Bifidobacterium and Eubacterium were significantly reduced ($p<0.01$), and Escherichia/Proteobacteria were significantly increased ($p<0.01$) in the E2/E3 group as compared to E1/ healthy controls group. Frequency of high dysbiosis among the healthy individuals was higher than observed in other studies (1).

Conclusion:

The present results support that alterations in microbial composition is important in both IBD and symptomatic non-IBD patients. The result demonstrated:

1) Differences in microbiota profiles between IBD and symptomatic non-IBD patients and healthy individuals

2) Equal levels of dysbiosis frequency in CD and UC, however the bacteria profiles differed

3) In subgroups of UC, microbiota profiles were dependent upon the localization of the inflammation

References:

1 Casén et al. Aliment Pharmacol Ther 2015; 42: 71–83

UEG Week 2016

OP254 - LOW FODMAP DIET ALTERS SYMPTOMS, MICROBIOTA, SHORT-CHAIN FATTY ACIDS AND CYTOKINE PROFILES IN PATIENTS WITH IBS: A RANDOMIZED CONTROLLED TRIAL

T. Hustoft, T. Hausken, S. Ystad, J. Valeur, K. Brokstad, J. Hatlebakk & G. Lied

Introduction:

Irritable bowel syndrome (IBS) is the most common gastrointestinal (GI) disorder worldwide. In the lack of cures, different management strategies have been purposed, including a diet low in FODMAPs (fermentable oligosaccharides, disaccharides, monosaccharides and polyols). Although being increasingly accepted and recommended as one of the most effective therapies, there is insufficient high-quality evidence of its efficacy as well as uncertainties regarding long-term consequences on gut microbiota composition and function.

Aims & Methods:

In the present study we aimed to investigate the effect of a low versus high FODMAP diet on symptoms, gut microbiota, short-chain fatty acids (SCFAs) and pro-inflammatory cytokine profiles in a randomized, double-blinded, crossover trial of Norwegian patients with IBS.

Twenty patients with IBS (15 female/5 male, mean age 34.6 y) were instructed to follow a low FODMAP diet (LFD) throughout a study period of 9 weeks. After 3 weeks they were randomized and double-blindly assigned to receive a daily supplement of either high (16 g fructo-oligosaccharides (FOS)) or low (16 g maltodextrin (= placebo)) FODMAP for the next 10 days, followed by a 3-week washout before crossing-over to the alternative supplementation for 10 new days. IBS Severity Scoring System (IBS-SSS) was used to evaluate symptoms. Blood samples were collected to analyze serum cytokines (IL-6, IL-8, TNF-α), and faeces samples for gut microbiota (s16r RNA) and SCFAs.

Results:

IBS symptoms consistently and significantly improved after 3 weeks of LFD, with a mean overall reduction of 163.8 points ($p < 0.0001$). On average, 4 of 5 symptoms were significantly worsened in response to FOS compared with placebo, with an overall difference of 65.1 points ($p = 0.014$). Serum levels of IL-6 and IL-8, but not TNF-α, significantly decreased on the LFD ($p = 0.001$ and $p < 0.0001$, respectively). The same did apply to luminal Faecalibacterium prausnitzii and Bifidobacterium ($p = 0.0084$ and $p = 0.0094$, respectively). Levels of total SCFAs and butyric acid were also significantly decreased on the LFD ($p = 0.04$ and $p = 0.01$, respectively). Ten days of FOS supplementation normalized the level of bacteria but did not change the levels of cytokines nor SCFAs.

Conclusion:

FODMAP content was related to IBS symptoms, cytokine levels and microbiota composition and function. Our results provide evidence to support the efficacy of a LFD in reducing functional GI symptoms. Further studies are warranted to explore the link between FODMAPs, gut microbiota and immune activation.

UEG Week 2016

THE GUT MICROBIOTA PROFILE AND HOST ANTI-MICROBIAL RESPONSE AT ONSET OF ULCERATIVE COLITIS IS ASSOCIATED WITH DISEASE COURSE

Maria K. Magnusson (1), Hans Strid (2), Magnus Simrén (3), Lena Öhman (4)

(1) University of Gothenburg, Dept. of Microbiology Immunology, Göteborg, Sweden

(2) Södra Älvsborg Hospital, Dept of Internal Medicine, Borås, Sweden

(3) University of Gothenburg, Dept. of Internal Medicine and Clinical Nutrition, Gothenburg, Sweden

(4) University of Skövde, School of Health and Education, Skövde, Sweden

Introduction:

The clinical disease course of ulcerative colitis (UC) is unpredictable; some patients have mild symptoms whereas others suffer from frequent and severe flares and the reason for this is unknown. The gut microbiota and the host immune defense are key players for gut homeostasis and may be linked to disease severity.

Aims & Methods:

Our aim was to determine the gut microbiota profile and mucosal anti-bacterial response in newly diagnosed patients with UC and correlate these data to disease course during the first three years. To do this we obtained rectal biopsies and fecal samples at onset of the disease from 44 therapy-naïve patients with UC. Patients were followed for 3 consecutive years and disease severity was assessed annually. Patients defined as having a mild disease course had -1 flares per year, whereas patients with a relapsing disease course had >1 flare per year at least one of the three years during follow-up.

Microbiota analysis of fecal samples was performed for patients where fecal samples were present using the GA-map® Dysbiosis Test (Genetic Analysis AS, Oslo, Norway). Gene expression in biopsies was analyzed by RT2 Profiler PCR array for 84 genes involved in -Anti-bacterial response- (Qiagen) and confirmed by regular quantitative rtPCR. Multivariate factor analysis using orthogonal partial least squares discriminant analyses (OPLS-DA) (SIMCA-P+ software; Umetrics, Umeå, Sweden) was used to examine the relationship between bacterial content and mRNA expression to disease severity. The quality of the OPLS-DA was based on the parameter R2, defining the goodness of the fit of the model (good fit R2>0.5, best possible fit, R2=1).

Results:

No demographic or disease specific parameters at disease onset discriminated between patients having mild (n=23) or relapsing (n=21) disease. Microbiota analysis of fecal samples (relapsing n=11, mild n=7) revealed differential clustering between the groups for the total set of bacteria (R2=0.55). However, no significant differences for bacterial species of phyla were found. Exploratory mRNA array analysis performed for a subset of patients (mild n=5, relapsing n=8) to get an insight into the mucosal anti-bacterial response showed distinct discrimination between the groups (R2=0.87). Bactericidal/permeability-increasing protein (BPI) and chemokine (C-X-C motif) ligand 2 (CXCL2) were the most important nominators for the discrimination. These data were confirmed in a larger cohort of patients and showed that BPI was increased (0.0002 (0.0001-0.0004) vs. 0.00009 (0.00005-0.0002), (median (IQR), p<0.0001) and CXCL2 decreased (0.091 (0.048-0.154) vs. 0.119 (0.102-0.217), p=0.02) in patients with mild disease vs. patients with a relapsing disease course (mild n=23, relapsing n=21). BPI levels correlated negatively to the total numbers of flares during the three years (r= -0.52, p=0.0003).

Conclusion:

The mucosal anti-bacterial response in patients with newly diagnosed UC is associated to the disease course during follow-up. This indicates that patients with a non-favorable anti-microbial expression pattern could benefit from an intensified treatment regime.

Table 1

Probe name	Responders (median signal)	Non-responders (median signal)	P-value
Bacteroides fragilis [s]	24.8	8.1	0.04
Acinetobacter [g]	187.3	177.2	0.02
Ruminiclostridium [g]	50.9	45.2	0.01
Clostridia [cl], Negativicutes [cl], Bacilli [cl]	497.4	617.1	0.02
Streptococcus III [g]	11.1	8.4	0.03
Actinomycetales [o]	5.8	8.8	0.02
Anaerotruncus [g]	76.8	86.6	0.004
Clostridiales [o]	274.3	288.6	0.004
Eubacterium II [g]	31.3	14.5	0.03
Shigella [g], Escherichia [g]	12.2	15.2	0.04

Abbreviations: s - species; g - genus; o - order; cl - class

UEG Week 2016

DYSBIOSIS AND STABILITY OVER TWO YEARS IN PATIENTS WITH IRRITABLE BOWEL SYNDROME; P1073

Jostein Sauar (1), Fred-Arne Halvorsen (2), Christian Corwin (3), Snorri Olafsson (4)

(1) Telemark Hospital, Gastroenterology, Skien, Norway

(2) Drammen Hospital Vestre Viken HF, Medical, Drammen, Norway

(3) Vestre Viken Hospital, Gastroenterology, Drammen, Norway

(4) Telemark Hosptital, Gastroenterology, Skien, Norway

Introduction:

There is increasing knowledge of a possible role for gut microbiota in the pathophysiology of at least subgroups of irritable bowel syndrome (IBS) patients. Fluctuations in IBS activity should be reflected by changes in gut microbiota and categorization into a status of dysbiosis or no dysbiosis if there is a causal relationship. In the present study, on defined IBS patients, dysbiosis status was studied at baseline and after two years.

Aims & Methods:

Sixty-three patients with IBS according to Rome III criteria were recruited to receive education about treatment options for IBS by a gastroenterologist and to be tested for dysbiosis using the GA-map® Dysbiosis Test. This is a semi-quantitative 16SrRNA-based analysis of fecal bacteriae (Genetic Analysis, Oslo, Norway). The dysbiosis test was repeated two years later. Dysbiosis is defined by a dysbiosis index, DI (1-5), which is calculated by an algorithm based on the abundance and profile of bacteria. DI 3 or higher is defined as dysbiosis. The abundance of bacteria was measured as low, normal or high. All patients were seen by a gastroenterologist at the 2-year follow-up. The present abstract compares the bacterial profile in patients with dysbiosis, those without dysbiosis and any

changes in dysbiosis status after two years according to the present definition of dysbiosis.

Results:

Out of 63 IBS patients at baseline, 60 also provided stool samples after two years. Ten (17%) tested negative for dysbiosis at both rounds (never had dysbiosis=NHD), 33 (55%) had dysbiosis both times (DBT), 8 (13%) went from no dysbiosis to having it, and 9 (15%) went from dysbiosis to losing it. With focus on the first two groups: abundance of Faecalibacterium prausnitzii, Shigella/Escherichia and Bifidobacterium was significantly lower (Fisher-s exact test 0.07, 0.02, 0.04) in the DBT group than the NHD group at baseline, while abundance of Dialister and Bacteroides was significantly higher in the DBT group (0.04, 0.009) after two years (Table 1). In the DBT group, the abundance of Ruminococcus gnavus, Lactobacillus, Strectococcus sanguinis and Alistipes species showed high agreement between visits 1 and 2 (82-85%), but low agreement (52-57%) for Faecalibacterium prausnitzi, Shigellea/Escherichia and Bifidobacterium species (Table 1).

Conclusion:

Fifty-five percent of the patients had dysbiosis at baseline and after two years while 17% tested negative both times. Fifteen percent got dysbiosis and 13% lost it. Some bacteria were very stable, while others were more unstable. To test the stability may be of interest in possible future studies to treat specific disturbances in the gut microbiota.

Table 1. DBT=dysbiosis both times (2013 and 2015). NHD=never had dysbiosis. *Fisher's exact test. **Abundance was measured semi-quantitatively as low, normal or high.

	Comparison of DBT (n=33) vsNHD (n=10)		Comment	Agreement in abundance between test 1 and 2 (%) for DBT**
	Test 1	Test 2		
	p-value			
Bacteria				
Ruminococcus albus/bromii	0.66	0.66		76
Ruminococcus gnavus	1.00	1.00		85
Faecalibacterium prausnitzii	0.07	0.24	DBT lower at test 1	57
Lactobacillus	0.17	1.00		85
Streptococcus sanguinis and S.	1.00	0.61		85
Dialister invisus	0.73	0.04	DBT higher at test 2	67
Akkermansia muciniphilia	0.21	0.66		76
Bacteroides fragilis	0.45	0.28		67
Alistipes	1.00	1.00		82
Shigella/Escherichia	0.02	0.24	DBT lower at test 1	52
Bifidobacterium	0.04	1.00	DBT lower at test 1	52
Bacteroides/Prevotella	0.60	0.01	DBT higher at test 2	61
Firmicutes (Bacillli)	0.85	0.86		63
Firmicutes (Clostridia)	1.00	0.59		58
Proteobacteria	0.29	1.00		70

UEG Week 2016

PREVALENCE OF DYSBIOSIS AND EFFECT OF LOW FODMAP DIET IN CELIAC DISEASE PATIENTS WITH IBS-LIKE SYMPTOMS

Ida Strindmo (1), Kamilla Nuland (1), Gudrun Kahrs (2), Jan Gunnar Hatlebakk (1)

(1) University of Bergen, Department of Clinical Medicine, Bergen, Norway

(2) Haukeland University Hospital, Department of Medicine, Bergen, Norway

Introduction:

A subgroup of celiac disease patients has IBS (irritable bowel syndrome)-like symptoms despite following a gluten free diet (GFD). It is unknown whether the microbiota in these patients differs from an IBS- and a healthy population, and whether it changes during diet interventions.

Aims & Methods:

To study the microbiota profile in patients with celiac disease patients and any change with diet intervention to improve symptoms. 40 celiac disease patients with IBS-like symptoms confirmed by the Rome III-criteria and IBS-SSS (symptom severity scale) were compared to Norwegian IBS and healthy cohorts, and randomized as follows: Group A had a more strict GFD for 6 weeks, whilst patients in group B reduced FODMAPs in their GFD. Faecal samples at baseline and 6 weeks. IBS-SSS at BL, 3 and 6 weeks. The faecal samples were analysed by the GA-Map Method (Genetic Analysis AS) for bacteria and Dysbiosis Index (DI) 1-5, where DI>2 is clinically relevant. Statistics: T-test, Mann-Whitney U, Fisher-s linear discriminant analysis.

Results:

FODMAP intake was reduced from 12g to 2g/day (p=0.0001) in group B only and IBS-SSS improved in both groups. 45% of the patients had dysbiosis at baseline, compared to 73% in an IBS cohort (p<0.0091) and 16% in healthy controls (p<0.0007), with a mean score of 2.5±1.1 vs. 3.0±1.0 and 1.7±0.7, respectively. The patients had significantly more Bacilli and Prevotella than healthy controls. In group A (18F/2M, age 39±15), dysbiosis stayed constant on diet, but more patients had severe dysbiosis (DI>3), 15% vs. 25% (p=0.85). In group B (15F/5M, age 44±12), fewer patients had dysbiosis after diet, 60% vs. 50% (p=0.79). Responders to low FODMAP diet had less Lactobacilli and Firmicutes (Clostridia), and more Atopobium at baseline.

Conclusion:

Celiac disease patients with IBS-like symptoms had less severe dysbiosis than an IBS-population, but more than healthy controls. We found that the level of Lactobacilli, Firmicutes (Clostridia) and Atopobium predicted response to the lowFODMAP diet.

DD Week 2016

MICROBIAL DNA MARKERS ASSOCIATED WITH RESPONSE TO A LOW FODMAP DIET IN PATIENTS WITH IRRITABLE BOWEL SYNDROME

Valeur, Jørgen; Smastuen, Milada C; Knudsen, Torunn; Lied, Gülen A.; Røseth, Arne G.

Background:

Dietary restriction of fermentable oligosaccharides, disaccharides, monosaccharides and

polyols (FODMAP) may relieve symptoms of irritable bowel syndrome (IBS). However, nutritional counselling is cumbersome, costly and time-consuming, and not all patients will benefit. In the present study, we aimed to explore whether microbial DNA markers may be used to identify a positive response to a low FODMAP diet in patients with IBS.

Materials and methods:

Patients with IBS were recruited consecutively from our outpatient clinic to participate in a 4-week FODMAP restricted diet. Symptoms were evaluated by using the IBS severity scoring system (IBS-SSS), and response to diet was defined as > 50% decrease in IBS-SSS compared to baseline. Fecal samples were collected at baseline and analysed for microbial DNA by using the GA-map® Dysbiosis Test (Genetic Analysis AS, Oslo, Norway).

Results:

Sixty-one patients (54 F, 7 M) were included, of whom 32 (29 F; 3 M) were classified as responders and 29 (25 F; 4 M) were classified as non-responders. We assessed microbial DNA using 54 probes. Of those, 10 were significantly different between responders and non-responders (Table 1). Based on median values of responders for these markers, we constructed an index: Each participant was given a point when his/her value for each selected marker differed from the median cut-off value. These points were then summed up, giving a number from 0 to 10. The risk of being a non-responder was calculated using logistic regression. Those who scored 3 or more points using our index were 1.78 times more likely to be non-responders compared to those who scored lower (p = 0.002)

Conclusion:

Our data suggest that microbial DNA markers may be a useful tool to select patients who are more likely to respond to a low FODMAP diet. Further studies are needed to validate these findings.

2015

UEG Week 2015

THE IMPORTANCE OF THE MUCOSAL ANTIMICROBIAL PEPTIDE EXPRESSION AND GUT MICROBIOTA IN ANTI-TNF THERAPY RESPONSE IN PATIENTS WITH ULCERATIVE COLITIS

Stefan Isaksson (1), Anders Lasson (3), Antal Bajor (2), Hans Strid (2), Kjell Arne Ung (4), Lena Öhman (1), Maria K. Magnusson (1)

(1) Dept of Microbiology and Immunology, Inst for Biomedicine, Göteborg, Sweden; Dept of Internal Medicine and Clinical Nutrition, Inst for Medicine, Göteborg, Sweden

(2) Dept of Internal Medicine and Clinical Nutrition, Inst for Medicine, Göteborg, Sweden

(3) Dept of Internal Medicine, Södra Älvsborg Hospital, Borås, Sweden

(4) Dept of Internal Medicine, Kärnsjukhuset, Skövde, Sweden

Introduction:

Anti-TNF therapy is a common treatment for patients with ulcerative colitis (UC). However, about 30-50% of the patients do not respond to the treatment and it is not understood why some patients respond while others do not. Antimicrobial peptides (AMPs), a part of the innate defense against intestinal microorganisms, and the gut microbiota are essential for gut homeostasis and may be of importance for treatment effects of anti TNF therapy.

Aims & Methods:

The aim of this study was to determine AMP and microbiota profiles in patients with UC before start of anti-TNF therapy and correlate these data to therapy outcome. Blood, biopsy and fecal samples were obtained before anti-TNF treatment from anti-TNF therapy-naïve UC patients. Therapy response was assessed by Mayo score 12-14 weeks after treatment initiation, and response was defined as a decrease in Mayo score of ≥3 points. Biopsies were cultured for 24h and used for quantitative proteomic analysis by mass spectrometry or directly frozen for rtPCR analysis. AMP levels in serum were measured by ELISA. Microbiota analysis of fecal samples was performed using the GA-map™ Dysbiosis Test (Genetic Analysis AS, Oslo, Norway) where dysbiosis indexes of 1-2 are considered normal while 3-5 denotes increasing dysbiosis. Multivariate factor analysis (SIMCA-P+ software; Umetrics, Umeå, Sweden) was used to examine relationship between AMP levels and bacterial content to therapy outcome.

Results:

Among the 31 included patients, 17 patients responded to the therapy. According to the proteomic analysis of cultured biopsies (from 3 responders and 3 non-responders) Defensin 5 (Def5), eosinophil cationic protein (ECP) and bactericidal/permeability-increasing protein (BPI) were recorded in responders but not in non-responders. Gene expression of 11 AMPs or genes associated with AMP expression were analyzed in biopsies: Def5, ECP, BPI, Cathelicidin (CAT), Lysozyme, hβ-defensin 2, HMGB1, HMGN2, HistoneH1.5, 40S ribosomal protein S19 and HDAC1. Multivariate data analysis showed that responders and non-responders clustered differently when studying mRNA levels of the 11 genes. The most important nominators for therapy response were increased expression of Def5 (median (IQR), resp vs. non-resp; 0.598 (0.079-2.694) vs. 0.034 (0.005-0.211), p=0.006) and ECP (0.00025 (0.00013-0.00053) vs. 0.00012 (0.00009-0.00014), p=0.03) and decreased expression of CAT (0.0040 (0.0016-0.0133) vs. 0.0133 (0.0057-0.0498), p<0.05). Responders also had higher serum levels of ECP compared with non-responders (33.7 ng/ml (18.7-98.9) vs. 7.5ng/ml (3.4-41.3) p=0.03). Microbiota analysis of fecal samples (4 responders and 3 non-responders) revealed that non-responders tended to have higher dysbiosis indexes compared to responders (4.7 (4-5) vs. 3.3 (2-5), p=0.097). Also, non-responders had low levels of Faecalibacterium prausnitzii while responders showed normal levels.

Conclusion:

Anti-TNF therapy responders and non-responders display different patterns of mucosal AMP expression and gut microbiota before start of therapy. This indicates that infliximab therapy benefits from a defined anti-microbial defense pattern and that the intestinal microbial composition may be different in the two patient cohorts.

GMFH 2015

GUT MICROBIOTA IN IBS PATIENTS BEFORE AND AFTER LOW FODMAP DIET VERSUS LACTOBACILLUS RHAMNOSUS GG INTERVENTION

Kristoffer Kofod Vinding, Natalia Pedersen, Zsuzsanna Vegh1, Christina Casén, Selma Dzankovic, Magdalena Kauczynska Karlsson, Nynne Andersen, Dorit Ankersen, Lisbeth Jensen, Katrine Carlsen, Andreas Munk Petersen, Johan Burisch, Pia Munkholm.

Objectives:
A low FODMAP diet may be effective in patients with irritable bowel syndrome (IBS), and these patients may have altered microbiota (MB). The aim of the study was to investigate the impact of LFD and Lactobacillus rhamnosus GG (LGG) on fecal MB.
Methods:
Fecal samples were collected from IBS patients (ROME III criteria) and randomized to LFD, LGG or normal Western/Danish diet (ND). IBS severity score (IBS-SSS) was registered by patients at week 0 and 6 on an e-health application, www.ibs.constant-care.dk. Bacteria in fecal samples were analysed by Genetic Analysis AS's GA-map® Dysbiosis Test, a test utilizing 16SrRNA DNA to recognize the gut bacteria found to best correlate with dysbiosis in IBD/IBS patients. The degree of dysbiosis is measured on a scale from 1-10 (Dysbiosis Index (DI)), where values above 2 is considered dysbiotic. Change in DI and dysbiosis class between week 0 and 6 were investigated.
Results:
In total 58 patients (median age 39, range 20-74 years, 81% females) were included in the study: 17 LFD, 20 LGG and 21 ND. A substantial part of the patients (35-43%) changed dysbiosis class (dysbiotic, non-dysbiotic) following the 6 week intervention, and alterations in DI were observed in all three groups, both as decreased and increased DI. At week 0, 88% LFD, 65% LGG and 76% ND patients were dysbiotic (DI>2), while 76% LFD, 75% LGG and 81% ND patients were dysbiotic at week 6. There was no correlation between change in IBS-SSS and DI in either LFD or LGG group.
Conclusions:
Both LFD and LGG groups reported significant reduction in IBS-SSS from week 0 to 6. High proportions (65-88%) were dysbiotic at week 0, and alteration in MB was observed in 35-43% of the patients who changed dysbiosis class following dietary intervention. LFD did not significantly alter the gut MB in this study population; however, the test provides information on alterations in bacterial abundance and profiles that may prove valuable for individual patients.

3rd World Congress on Targeting Microbiota

STABILITY OF REPEATED FECAL DNA PREPARATION USING THE GA-MAP® DYSBIOSIS TEST

Caroline Jevanord Frøyland[1], Annette Mahler[2], Christina Casén[1], Kari Stenersen[1], Magdalena Kauczynska Karlsson[1]

1 Genetic Analysis AS, Oslo, Norway, 2 Labor Dr. Bayer, synlab MVZ Stuttgart GmbH, Stuttgart, Germany
ks@genetic-analysis.com

In recent years, repeated reports elevate the importance of standardized sample preparation when working with fecal samples. DNA extraction is one of the main causes for low reproducibility of microbiota results between laboratories and/or methods. A standardized method for extracting fecal DNA has been developed for the GA-map™ Dysbiosis Test[1], which comprises 16S rRNA amplification and a set of 54 selected probes targeting gut bacteria and bacteria groups important in human health. First, fecal DNA was extracted 10 times from three donors and processed according to GA-map™ Dysbiosis Test protocol. All 10 fecal aliquots per donor showed identical Dysbiosis Indices (DI) with standard deviation (SD) ≤0.15. Next, fecal samples from eight donors were analysed at two laboratories (Norway and Germany). DNA was extracted in duplicate and analysed in triplicate (n=48). DI values and bacteria profiles were compared between laboratories, and of 42 overlapping QC approved samples, 35 DI values fall within a 2SD limit with a pass rate of 83%. Likewise, 35/42 microbiota profiles (83%) were equivalent between laboratories. The results show good reproducibility, repeatability and precision, both within run and between sites, for the fecal sample DNA preparation method used for the GA-map™ Dysbiosis Test.

1. Casén, C. et al. Deviations in human gut microbiota: a novel diagnostic test for determining dysbiosis in patients with IBS or IBD. Aliment. Pharmacol. Ther. 1–13 (2015). doi:10.1111/apt.13236

2014

UEG Week 2014

GUT MICROBIOTA ALTERATIONS IN IBS PATIENTS BEFORE AND AFTER 6 WEEKS OF LOW FODMAP DIET VERSUS LACTOBACILLUS RHAMNOSUS GG; P1000

Natalia Pedersen (1), Kristoffer Kofod Vinding (1), Zsuzsanna Vegh (1), Christina Casén (2), Selma Dzankovic (2), Magdalena Karlsson (2), Dorit Ankersen (1), Lisbeth Jensen (1), Katrine Carlsen (1), Andreas Petersen (3), Johan Burisch (1), Pia Munkholm (1)
(1) Gastroenterology, Herlev University Hospital, Herlev, Denmark
(2) Genetics, Genetic Analysis As, Oslo, Norway
(3) Gastroenterology, Hvidovre University Hospital, Hvidovre, Denmark

Introduction:
Low fermentable Oligo-Di- and Mono- saccharides and Polyols (FODMAP) diet (LFD) may be effective in patients with irritable bowel syndrome (IBS), and these patients may have altered microbiota (MB). The aim of the study was to investigate the impact of LFD and lactobacillus rhamnosus GG (LGG) on fecal MB.
Aims & Methods:

Fecal samples were collected from IBS patients (Rome III criteria) and randomized to LFD, LGG or normal Western/Danish diet (ND). IBS severity score (IBS-SSS) was registered by patients at week 0 and 6 on an e-health application, www.ibs.constant-care.dk. Bacteria in fecal samples were analyzed by Genetic Analysis AS's GA-map™ Dysbiosis Test, a test utilizing 16SrRNA DNA to recognize the gut bacteria found to best correlate with dysbiosis in IBD/IBS patients. Dysbiosis Index (DI) is calculated by an algorithm based on bacterial abundance and profile in a fecal sample. DI is measured on a scale from 1-10, where values above 2 is considered dysbiotic. Dysbiosis class is defined as either non-dysbiotic or dysbiotic. Change in DI and dysbiosis class between week 0 and 6 were investigated.

Results:

In total 58 patients (median age 39, range 20-74 years, 81% females) were included in the study: 17 LFD, 20 LGG and 21 ND. A significant improvement in IBS-SSS total score in LFD and LGG patients was observed at week 6 compared to week 0, 308 [150-460] vs. 189 [25-478], p<0.001 and 296 [157-431] vs. 212 [11-471], p<0.01. No significant improvement was observed in ND patients, 303 [82-450] vs. 289 [62-428], p=0.28. There was no significant improvement in DI at week 6 compared to week 0 in LFD (6 vs 6, p= 0.53), LGG (5 vs 8, p=0.88) or ND (7 vs 6, p=0.4). However, a substantial part of the patients (35-43%) changed dysbiosis class (dysbiotic, non-dysbiotic) following the 6-week intervention and alterations in DI were observed in all three groups, both as decreased and increased DI. At week 0, 88% LFD, 65% LGG and 76% ND patients were dysbiotic (DI>2), while 76% LFD, 75% LGG and 81% ND patients were dysbiotic at week 6.There was no correlation between change in IBS-SSS and DI in either LFD or LGG group.

Conclusion:

Both LFD and LGG groups reported significant reduction in IBS-SSS from week 0 to 6. High proportions (65-88%) were dysbiotic at week 0, and alteration in MB was observed in 35-43% of the patients who changed dysbiosis class following dietary intervention. LFD did not significantly alter the gut MB in this study population; however, the test provides information on alterations in bacterial abundance and profiles that may prove valuable for individual patients.

UEG Week 2014

INFLUENCE OF A LOW-FODMAP DIET ON SYMPTOMS AND GUT MICROBIOTA IN PATIENTS WITH IRRITABLE BOWEL SYNDROME; P1549

Jørgen Valeur (1), Torunn Knudsen (2), Tonje Mellin-Olsen (2), Arne Røseth (1)

(1) Unger-Vetlesen Institute, Lovisenberg Diakonale Hospital, Oslo, Norway

(2) Department Of Clinical Nutrition, Lovisenberg Diakonale Hospital, Oslo, Norway

Introduction:

Reducing intake of fermentable oligo-, di- and monosaccharides and polyols (FODMAP) may improve functional bowel symptoms. We aimed to investigate the effect of such a dietary change on intestinal and extra-intestinal symptoms and gut microbiota in patients with irritable bowel syndrome (IBS).

Aims & Methods:

IBS patients admitted to Lovisenberg Diakonale Hospital were investigated consecutively from April 2013 to January 2014. Symptoms were assessed by using validated questionnaires to measure both intestinal (IBS-SSS) and extra-intestinal symptoms (HADS, FIS) before and after 4 weeks on a low-FODMAP diet. Fecal gut bacteria DNA analysis was performed by using the GA-map™ Dysbiosis Test (Genetic Analysis AS, Oslo, Norway). This 16S rRNA DNA test utilizes DNA probes to recognize gut bacteria (1) found to best correlate with dysbiosis in patients with IBD and IBS. Dysbiosis index is an index calculated by an algorithm based on bacterial abundance and profile in a fecal sample, measured on a scale from 1 to 10, where values above 2 are considered abnormal. Change in dysbiosis index between week 0 and 4 were investigated.

Results:

Forty-eight patients (4 M, 44 F) completed the study. At baseline, 23 and 25 patients had a dysbiosis index classified as "normal" and "abnormal", respectively. These two groups were significantly different regarding intestinal symptom severity (mean IBS-SSS scores 263 versus 304, respectively; P = 0.04), but similar regarding extra-intestinal symptom severity. A correlation between dysbiosis index and IBS-SSS was demonstrated (r = 0.29, P = 0.04), including the subscale measuring pain (r = 0.30; P = 0.04). Following dietary intervention, symptomatic improvement was demonstrated as a reduction in IBS-SSS (from 285 to 157; P < 0.0001), HADS (from 14 to 9; P < 0.0001) and FIS (from 72 to 38; P < 0.0001). The dysbiosis index changed in 31 (65%) patients while it remained unchanged in 17 (35%) patients. There was no correlation between change in dysbiosis index and change in symptoms following diet.

Conclusion:

A low-FODMAP diet seems to improve not only intestinal, but also extra-intestinal symptoms in patients with IBS. The GA-map™ Dysbiosis Test showed that patients with higher dysbiosis indices had more severe intestinal symptoms at baseline. The test thus provides information on alterations in bacterial abundance and profiles that may prove valuable for individual patients. However, we did not demonstrate any associations between change in dysbiosis indices and symptoms following dietary intervention.

References:

1. Vebø HC et al. Temporal development of the infant gut microbiota in immunoglobulin E-sensitized and non-sensitized children determined by the GA-map infant array. Clin Vaccine Immunol 2011; 18: 1326-35.

2013

UEG Week 2013

MICROBIOTA ANALYSIS IN IBS AND IBD/NON-IBD PATIENTS AND NORMAL SUBJECTS; P592

Heidi Vebø (1), Christina Casén (1), Monika Sekelja (1), Ragnhild Nestestog (1), Ewa Ciemniejewska (1), Gøri Perminov (2), Petr Ricanec (2), Morten Harald Vatn (2)
(1) Genetic Analysis AS
(2) Oslo University Hospital

Introduction:

The increasing awareness of the gut microbiota's effect on our health has triggered the need for tools to monitor these microbes. The GA-map™ technology platform has been developed to demonstrate profiles of the composition of gut microbiota. The platform provides analysis of a large number of fecal samples in a rapid and cost-effective way. In a multi-center trial among patients diagnosed for IBS in Norwegian hospitals, fecal samples have been collected and compared to a population of normal subjects using GA microbiota test. In addition, a sub-cohort of IBD and non-IBD patients has been analyzed.

Aims & Methods:

Based on peer-reviewed literature and our own research, special sets of DNA probes were designed to facilitate separation between patient groups and normal subjects based on their bacterial profile. The assay was tested in a population of 31 fecal samples from diagnosed IBS patients (confirmed by Rome III criteria and exclusion of inflammation by colonoscopy and/or calprotectin analysis) and a population of 78 normal subjects with no clinical signs of gut disorder (not confirmed by colonoscopy), in addition to 187 samples from the IBSEN II cohort, comprising treatment naïve IBD patients and symptomatic non-IBD patients, confirmed by colonoscopy (1, 2). The GA microbiota test was performed essentially as described in (3), using the BioCode-1000A system for detection and quantification of labeled DNA probes (indicative of presence of different bacteria). Classification was performed using Partial Least Squares Discriminant Analysis (PLS-DA) and the model was validated using leave-one-out validation. Further studies will be performed including independent patient populations.

Conclusion:

The GA microbiota test gives a unique opportunity to study specific profiles of the gut microbiota that may be associated with GI related disorders. The results suggest that the GA test may be a useful tool in differentiating between IBS and normal subjects, and IBD/non-IBD patients, and thus an aid in the diagnosis and follow up of patients with inflammatory and functional GI disorders.

DEVELOPMENT OF A NEW, RAPID GUT MICROBIOTA TEST FOR IBD DIAGNOSTICS

Caroline Frøyland (1), Dina Lilleseth Vangen (1), Heidi Vebø (1), Monika Sekelja (1), Christina Casén (1), Knut Rudi (2), Petr Ricanek (3), Gøri Perminov (3), Morten Harald Vatn (3)
(1) Genetic Analysis AS
(2) University of Life Sciences
(3) Oslo University Hospital

Introduction:

As the awareness of the effect of the gut microbiota on health is increasing, so is the need to find tools to study changes in the gut microbiota in a rapid, cost-effective and high throughput format.

Aims & Methods:

GA-map™ was developed to provide a rapid analysis of many fecal samples in a cost-effective way. Based on the GA-map™ platform, specially designed sets of DNA probes were designed that holds promise to be used as an effective tool for early prediction for Inflammatory Bowel Disease (IBD). Version 1.0 of the assay was tested against samples from 270 patients from the IBSEN II study, where the samples were collected before colonoscopy and before treatment was commenced. Using the GA-map™ IBD test on these treatment naïve patient samples gives a unique opportunity to study any specific profiles of the gut microbiota that may be associated with IBD related diseases.

Results:

Preliminary results of the adolescent portion of the IBSEN II study, shows that the GA-map™ IBD test gives a 86% sensitivity and 82% specificity, after cross-validation with leave-one-out. The overall cross-validated accuracy is 84%.

Conclusion:

These results show promise that the GA-map™ test can be optimized for use in early prediction of patients suspected of developing IBD.

2012

UEG Week 2012

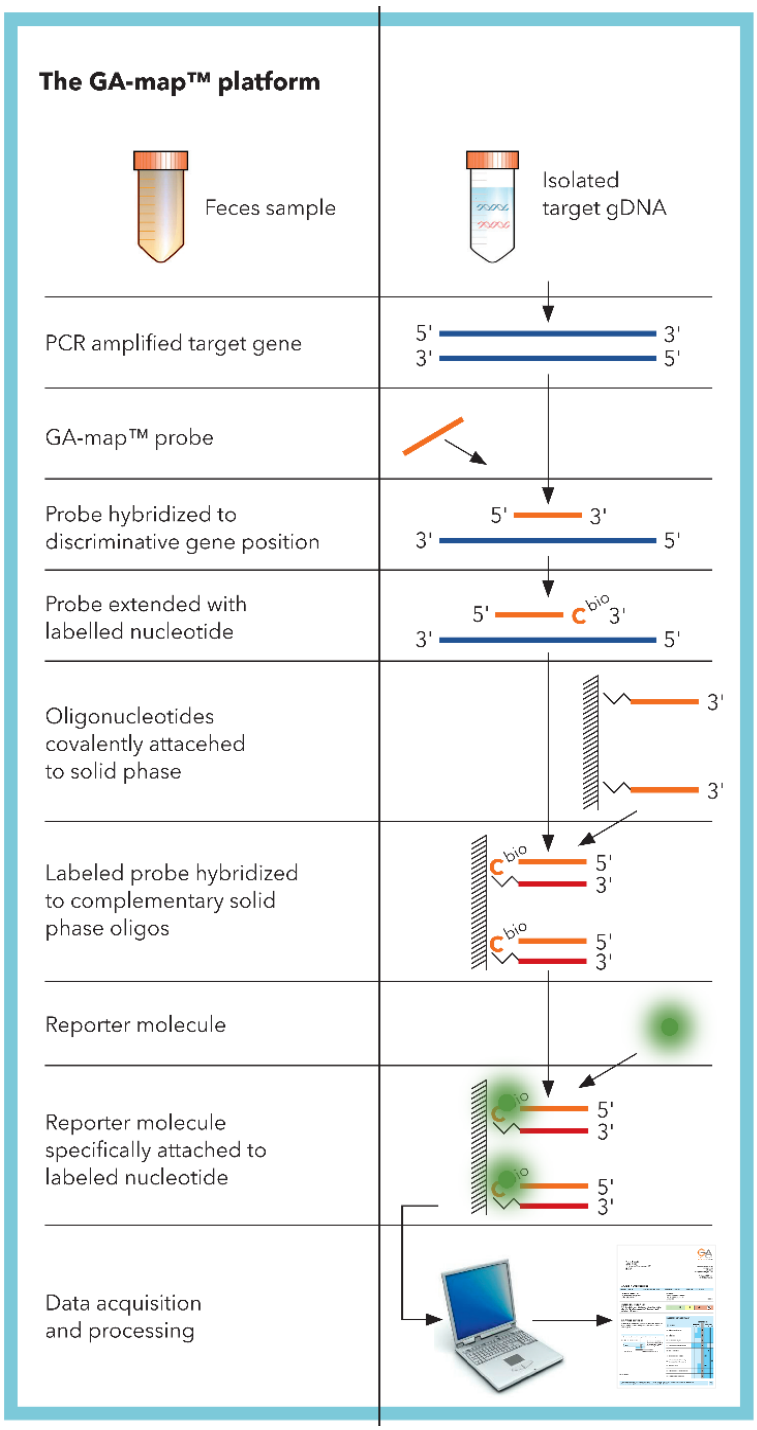

Figure 1: Single NUcleotide Primer Extention (SNuPE) allows the GA-map® platform to identify bacteria and characterize bacteria compositions in the gut.

Genetic Analysis AS
www.genetic-analysis.com

Address: Kabelgaten 8 | 0580 OSLO | Norway
Phone: +47 48 32 16 10
E-mail: info@genetic-analysis.com