Studies on inflammatory bowel disease and functional gastrointestinal disorders in children and adults
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Introduction and outline
Abdominal pain is a common reason to consult a general practitioner or pediatrician. Indeed, approximately 3% of all consultations with a general practitioner or pediatrician are related to abdominal pain. In approximately 10% of cases, it is caused by an acute disease requiring immediate therapy (e.g. appendicitis acuta). In most cases, however, abdominal pain represents a less acute or chronic problem, usually with a functional cause.

This thesis will focus on two different underlying causes of abdominal pain: functional gastrointestinal disorders (FGIDs) and inflammatory bowel diseases (IBDs). The former is by far the most common cause of abdominal pain. The latter is one of the most common organic causes of chronic abdominal pain.

By definition, FGIDs encompass a spectrum of disorders characterized by chronic gastrointestinal symptoms in the absence of an evident organic etiology (i.e. the absence of an inflammatory, anatomic, metabolic, or neoplastic process that explains the subjects symptoms). On the contrary, IBDs are a group of disorders that are by definition characterized by gastrointestinal inflammation. Thus, at first glance, FGIDs and IBDs appear to be very different entities. However, several recent findings indicate that the boundaries between FGIDs and IBDs are becoming blurred with respect to both pathophysiology and symptomatology.

In this introduction, a brief general overview of both FGIDs and IBDs will be given. Furthermore, several topics of FGIDs and IBDs will be highlighted that are related to the remaining chapters of this thesis, such as costs and different treatment strategies. Finally, differences and similarities between FGIDs and IBDs will be discussed.

**Functional gastrointestinal disorders (FGIDs)**

FGIDs are a group of disorders that are characterized by chronic gastrointestinal symptoms, in the absence of evidence for an inflammatory, anatomic, metabolic, or neoplastic process that explains the subjects symptoms. FGIDs are divided into several domains (e.g. esophageal, gastroduodenal or anorectal disorders) and further subdivided using diagnostic criteria into specific syndromes based on the predominant gastrointestinal symptom (e.g. irritable bowel syndrome or functional constipation). The most commonly used diagnostic criteria to identify and classify FGIDs are the Rome III criteria. One of the most prevalent FGIDs in both children and adults is irritable bowel syndrome (IBS). According to the Rome III criteria, IBS is characterized by recurrent or persisting abdominal pain or discomfort associated with changes in bowel habits.

**Abdominal pain-related functional gastrointestinal disorders**

Meta-analyses indicate that 9.8% to 12.8% of adults and 6.2 to 11.9% of children fulfill criteria for IBS, making it one of the most prevalent chronic medical conditions. Adults with IBS utilize more health care resources, are more likely to require time off work and are less productive.
at work, compared to those without IBS. Consequently, the financial burden to society of IBS is enormous; annual costs of care for adults with IBS in the USA alone are estimated to be over $20 billion. To date, data on costs of care of pediatric IBS are not available. Therefore, in chapter 2, we aim to investigate the annual costs of care for children with IBS.

A large proportion of patients with FGIDs respond to placebo in clinical trials. Meta-analyses of randomized controlled trials (RCTs) in adult IBS patients revealed a weighted average placebo response rate of 40.2 to 42.6%. Similarly, high placebo response rates are reported for other FGIDs such as functional dyspepsia (35%) and functional constipation (22%). These high placebo response rates have several implications. Firstly, a high placebo response results in reduced assay sensitivity (i.e. the ability of a trial to distinguish detect true differences between active treatment and placebo or less active treatment) and thus inefficient trials. Therefore, randomized clinical trials should aim to minimize the placebo response to allow for the conduct of more efficient trials. In clinical practice on the other hand, the placebo effect can be considered a valuable and powerful clinical tool. Indeed, it could be argued that clinicians should aim to maximize the placebo response to enhance patient benefit from any treatment strategy, since maximal efficacy is desirable irrespective of whether improvements are based on specific treatment effects, placebo mechanisms or a combination.

Thus, identification of determinants of the placebo response is important for both clinical trial design and clinical practice.

Meta-analyses of studies in adults with FGIDs have identified several variables that may affect the placebo response in clinical trials, including entry criteria, number of office visits, body mass index, a consistent symptom pattern, duration of therapy, country of trial origin and outcome assessor. Data on the magnitude and determinants of the placebo response in pediatric FGIDs are lacking. In chapter 3, we aim to investigate the magnitude and determinants of the placebo response in pediatric FGIDs.

**Functional gastrointestinal disorders: functional constipation**

Treatment of FGIDs depends on the predominant symptoms and thus the specific syndrome. For example, if the FGID is accompanied by symptoms of constipation (as is the case in constipation-predominant IBS and functional constipation), laxatives are usually prescribed. Currently, a number of laxatives are available for treating symptoms of constipation children and adults. In chapter 4, we provide an overview of current and future pharmacological therapies for functional constipation in childhood. Based on the currently available data, there is insufficient evidence to prefer one laxative over the other in treating childhood constipation. In chapter 5, we report findings of a double-blind randomized head-to-head study of two different formulations of polyethylene glycol, the first-line laxative in children with functional constipation.
Inflammatory Bowel Diseases (IBDs)

The IBDs Crohn’s disease (CD) and ulcerative colitis (UC) are chronic disorders characterized by relapsing and remitting inflammation of the gastrointestinal tract, causing symptoms such as abdominal pain or discomfort, weight loss, diarrhea and fatigue. While in UC the inflammation is limited to the colon, inflammation in CD can affect any part of the digestive tract, “from mouth to anus”. In addition to causing symptoms, inflammation in IBD is associated with significant long-term sequelae, such as strictures and malignancies. The vast majority of CD patients will eventually undergo gastrointestinal surgery\(^{22}\), and 20 to 30% of UC patients will eventually require a colectomy\(^{23-25}\). Thus, it is of great importance to control inflammation in patients with IBD, not only to control symptoms, but also to halt disease progression and prevent complications.

Treatment of IBD

Over the last decades, important advances have been made in the treatment of IBD. The introduction of treatment with antibodies to tumor necrosis factor (TNF) has changed the management of IBD drastically, particularly in those who do not respond to conventional therapy. The therapeutic anti-TNF-antibodies infliximab, adalimumab and more recently golimumab are very effective in inducing and maintaining remission in both CD and UC\(^{26-31}\) (although the efficacy of golimumab in CD has not been evaluated in randomized controlled trials). More recently, infliximab and adalimumab have also been shown to be effective in children with CD or UC\(^{32-35}\) (although a clinical trial of the efficacy of adalimumab in pediatric UC is still ongoing [NCT02065557]).

Challenges in treating IBD

Despite their proven efficacy, several challenges exist with anti-TNF-agents. Firstly, a significant proportion of patients do not respond to anti-TNF-treatment (primary non-response)\(^{26-35}\). Furthermore, a substantial proportion of patients gradually lose response over time (secondary non-response)\(^{26,36,37}\). Primary and secondary non-response are related to low serum drug concentrations and the development of anti-drug-antibodies\(^{38-45}\). Consequently, therapeutic drug monitoring (TDM; comprising measurement of levels of drug and anti-drug-antibodies and adjusting treatment [dose and interval] accordingly) strategies have been recommended\(^{46}\). Although the first data from studies on TDM-guided maintenance treatment with infliximab showed no benefit compared to clinically based adjustments with respect to the primary outcome\(^{47,48}\), data from ongoing trials will determine the potential value of TDM strategies in the treatment of IBD.

The phenotype of IBD in children often differs from that in adult patients\(^{49,50}\). For example, childhood-onset IBD is usually characterized by a more extensive phenotype\(^{46}\). Additionally, several studies have reported higher rates of secondary non-response to anti-TNF-treatment
in children than in adults\textsuperscript{51–54}, suggesting that pharmacodynamics and pharmacokinetics of anti-TNF-agents may differ in children compared to adults. Thus, data from adult studies cannot be directly extrapolated to children. Nevertheless, pediatric series investigating the association between IBD activity and levels of drug and anti-drug-antibodies in patients receiving anti-TNF-treatment are scarce. \textbf{In chapter 6, we aim to investigate the relationship between IFX serum levels and anti-infliximab-antibodies in children receiving infliximab as maintenance therapy for IBD.}

Another challenge in the treatment with anti-TNF-agents is the fact that current TDM strategies are based solely on the measurement of levels of drug and anti-drug-antibodies at trough (i.e. immediately prior to administration of the next dose). Since a point-of-care test for levels of drug and anti-drug-antibodies is not readily available, the results of testing are only available after the next dose has been administered. This potentially causes a delay in TDM dose adjustments. It would be of value if a physician can determine whether a patient’s dosage is adequate at other time points than at trough. \textbf{In chapter 7 we aim to investigate the relationship between intermediate serum infliximab concentration and infliximab trough concentration in adult CD patients receiving infliximab maintenance therapy.}

Another challenge in treating IBD is when to start anti-TNF-agents. Most current treatment guidelines recommend the use of a so-called \textit{step-up} approach for mild to moderate IBD, which comprises initial treatment with less potent medication such as steroids, followed by more potent medications or procedures if the initial therapy fails\textsuperscript{55,56}. It is hypothesized that early combined immunosuppressive (i.e. \textit{top-down}) treatment may alter the disease course and slow disease progression. To date, two prospective studies investigated the short-term efficacy of step-up vs. top-down treatment in CD. In the randomized controlled \textit{Step-up/Top-down-trial}, D’Haens et al. compared the efficacy of early combined immunosuppression (consisting of three infliximab infusions combined with maintenance treatment with an immunomodulator) to conventional management (consisting of initial treatment with corticosteroids, followed, in sequence, by an immunomodulator and infliximab when necessary) in patients with newly diagnosed CD. Steroid-free remission rates were significantly higher in patients receiving early combined immunosuppression up to 1 year after randomization. However, this effect did not persist beyond 1 year\textsuperscript{57}. In a follow-up study of the participants in an endoscopic substudy 2 to 4 years after randomization, mucosal healing (defined as the absence of ulcers and strictures in the colon and terminal ileum) 2 years after randomization but not treatment allocation was associated with stable, steroid-free remission\textsuperscript{58}. The long-term outcomes however, of early combined immunosuppression vs. conventional management are currently unknown. \textbf{In chapter 8, we aim to compare the long-term outcome of early combined immunosuppression to that from conventional management in patients with newly diagnosed CD, by analyzing outcomes of patients who participated in the Step-up/Top-down-trial\textsuperscript{57}.}
**Current management and outcomes of IBD in the Netherlands**

Current Dutch guidelines regarding the management of IBD do not give specific guidance regarding the dose, frequency and duration of anti-TNF-treatment. It is unknown how many IBD patients receive anti-TNF-treatment and at what dose and for what duration they receive it. Furthermore, data are scarce on the costs associated with anti-TNF use. Furthermore, there are few real-world data regarding long-term outcome of patients receiving anti-TNF-treatment. In chapter 9, we aimed to describe and analyze the use of anti-TNF agents in IBD patients and the associated costs and health outcomes.

**Discrepancy between symptoms and disease activity**

CD and UC often have a relapsing and remitting clinical course. Patients typically experience episodes of active disease, alternated with periods of remission (i.e. the absence of evidence of inflammation). Also during periods of remission, a significant proportion of patients continues to suffer from gastrointestinal symptoms (discussed below). Furthermore, many asymptomatic IBD patients have ongoing inflammation. Especially in CD, gastrointestinal symptoms seem to be virtually independent of the endoscopic severity of the disease. In UC, symptoms are more closely related to the endoscopic severity of the disease, although still only a small proportion of the variation in clinical activity is explained by variation in endoscopic severity. In children, the relationship between IBD activity and gastrointestinal symptoms is less well documented. In chapter 11, we aimed to evaluate the relationship between biochemical markers of endoscopic disease activity and gastrointestinal symptoms in pediatric IBD. Furthermore, in chapter 12, we aim to evaluate the predictive value of fecal calprotectin for the risk of relapse in pediatric IBD patients in clinical remission.

The strong discrepancy between symptoms and endoscopic inflammation poses important challenges in the management of IBD: how to measure disease activity, and what should be the goal of therapy? Traditionally, treatment of IBD was (mainly) guided by symptoms. However, symptomatic treatment does not improve the long-term outcome or slow disease progression. This is thought to be related to the fact that traditional treatment often does not result in the complete disappearance of gastrointestinal inflammation (“mucosal healing”). Indeed, only a minority of patients on glucocorticoids, azathioprine or methotrexate achieve endoscopic remission. Meanwhile, there is increasing evidence that mucosal healing is associated with a long-term beneficial outcome in both CD and UC, indicating that mucosal healing is an important therapeutic target. Consequently, it has been suggested that mucosal healing should be a primary outcome measure in clinical trials. Nevertheless, symptomatic improvement of course remains an important goal when treating IBD. Until recently, clinical disease activity in CD trials was evaluated using the Crohn’s Disease Activity Index (CDAI) or its simpler counterpart, the Harvey-Bradshaw Index. Both indices however are no longer
considered to be acceptable as endpoints in clinical trials, since the FDA demands patient-reported outcomes, defined as “a measurement of any aspect of a patient’s health status that comes directly from the patient (i.e., without the interpretation of the patient’s responses by a physician or anyone else)”\textsuperscript{78}. In chapter 10, we aim to evaluate the responsiveness to treatment of several patient-reported outcomes in CD patients who required treatment intensification and received treatments of known efficacy for active Crohn’s disease.

**FGIDs and IBDs: differences and similarities**

At first sight, FGIDs and IBDs appear to be very distinct entities: while the former is characterized by the absence of gastrointestinal inflammation, the latter is characterized by the presence of gastrointestinal inflammation. Nonetheless, FGIDs, especially IBS, have several similarities with IBDs, with respect to both pathophysiology and symptoms. Differences and similarities between IBS and IBD will be discussed below.

**Pathophysiology**

Despite a growing body of evidence regarding potential mechanisms, the pathophysiology of both IBS and IBD remains largely unknown. Traditionally, IBS has been considered a purely functional disorder, that arises from brain-gut dysregulation and is driven by psychological factors\textsuperscript{7,79}. In support of this view, several studies have shown higher levels of anxiety and depression in patients with IBS\textsuperscript{80}, and an association between stressful life events and abuse and the onset of IBS\textsuperscript{81}. More recently, evidence has accumulated indicating that IBS is probably not a purely functional disorder, but may also have an organic component\textsuperscript{82}. At the same time, while IBDs have been traditionally viewed as purely organic conditions, evidence is accumulating, indicating that psychological factors also play a role in IBD\textsuperscript{83}. Both IBD and IBS are probably multifactorial, with a potential role in the pathophysiology for genetic factors, environmental factors and the immune system.

**Genetics**

Familial aggregation studies and twin studies suggest a modest contribution of genetics to the pathophysiology of IBS\textsuperscript{84}. Several candidate genes have been identified that may predispose to the development of IBS, although results have not been unequivocal\textsuperscript{85}, potentially since studies to date have been limited in number and sample size\textsuperscript{85}. The contribution of genetics to the risk of developing IBD is likely to be much larger than with IBS, especially for CD. First-degree relatives of IBD patients have a significantly increased risk for developing IBD\textsuperscript{86–91}, and over 160 susceptibility loci have been identified so far\textsuperscript{92}. Nevertheless, only a small proportion of the variance in the risk of developing IBD is explained by these loci, suggesting that other factors play a more important role\textsuperscript{92}. 
**Environmental factors**  
The vast majority of patients with IBS indicate that certain foods can trigger or worsen symptoms\(^93,94\). Furthermore, studies have shown that IBS patients can benefit from dietary interventions, such as a diet low in fermentable oligo-, di-, and monosaccharides and polyols (FODMAP)\(^95\). Similarly, a large proportion of IBD patients report intolerance to certain foods\(^96\), and exclusive enteral nutrition (a dietary intervention) is an effective therapy for CD in children\(^97\).

Why IBD or IBS patients may benefit from dietary interventions is unknown. One hypothesis builds on potential alterations of the intestinal microbiota. Studies have shown that both IBD and IBS are associated with an abnormal intestinal microbiota composition\(^98,99\), and that dietary interventions can induce beneficial effects, potentially through modulation of the microbiota of patients with IBS or IBD\(^97,100\). Recently, fecal microbiota transplantation has gained much attention as a potentially powerful method for altering the intestinal microbiota\(^101\). Indeed, evidence to date suggests that fecal microbiota transplantation may be a promising treatment for IBD and IBS\(^102-107\).

**Immune system**  
Gastrointestinal inflammation is a hallmark of IBD, which is thought to result from dysregulation of the immune system resulting in an inappropriate response against contents of the gastrointestinal lumen\(^108\). In contrast, IBS is characterized by the absence of (evident signs of) inflammation\(^6\). Nevertheless, some evidence suggests that the immune system may also play a role in the pathophysiology of IBS\(^109\). For example, colonic biopsies of IBS patients showed increased numbers of activated immunocompetent cells in the intestinal mucosa\(^110\), and IBS patients have an increased frequency of activated T-cells in colonic biopsies and blood samples\(^111\). Recently, two studies showed no benefit of mesalazine (an anti-inflammatory drug used for the treatment of ulcerative colitis) in patients with IBS with respect to the primary outcome, although there appeared to be some effect in subgroups of patients\(^112,113\). Furthermore, prednisolone was not superior to placebo in improving symptoms in post-infectious IBS\(^114\). On the other hand, the mast cell stabiliser ketotifen was shown to improve IBS symptoms\(^115\). Future studies are required to evaluate the therapeutic potential of anti-inflammatory and immunomodulatory agents in the treatment of IBS.

**Symptoms**  
IBS is characterized by recurrent or persisting abdominal pain or discomfort that is associated with changes in bowel habits\(^6,10\). Furthermore, patients often complain of fatigue\(^116\). Similarly, diarrhea and abdominal pain are the most common clinical manifestations in both CD\(^117\) and UC\(^118,119\), and many patients with IBD suffer from fatigue\(^118,120\). Some signs and symptoms are more specific for CD and/or UC (e.g. lower gastrointestinal bleeding, weight loss, fever, perianal abscesses or fistulas)\(^117-119\), and allow for the differentiation between IBS and IBD.
However, these symptoms are absent in a large proportion of IBD patients, making it difficult to distinguish IBD from IBS on clinical grounds alone\textsuperscript{117–119,121}.

\textbf{IBS-type symptoms in IBD}

\textit{Prevalence}

As mentioned, many patients with quiescent IBD suffer from ongoing gastrointestinal symptoms. These symptoms often mimic IBS symptoms and are therefore referred to as IBS-like or IBS-type symptoms. In a systematic review of 11 studies including 1,197 patients with IBD in remission, the pooled prevalence of IBS-type symptoms was 35\%, with a higher prevalence in patients with CD (41\%) compared to those with UC (31\%)\textsuperscript{62}. These IBS-type symptoms have a negative impact on patients’ quality of life\textsuperscript{122}. The prevalence of IBS-type symptoms in children is unknown. \textbf{In chapter 14, we aim to investigate the prevalence of IBS-type symptoms in children with IBD.}

\textit{Pathophysiology}

The pathophysiology of IBS-type symptoms in IBD remains to be elucidated. A proportion of IBS-type symptoms may be “true IBS”\textsuperscript{123} and can thus be explained by the high prevalence of IBS in the general population in adults (10–13\%)\textsuperscript{8} and children (6–12\%)\textsuperscript{8}. This, however, does not explain the higher prevalence of IBS-type symptoms in quiescent IBD, compared to the general population. It has been proposed that IBS-type symptoms result from ongoing low-grade inflammation\textsuperscript{124}. Indeed, two studies reported higher levels of fecal calprotectin (FC; a surrogate marker for endoscopic lesions in IBD\textsuperscript{125}) in IBD patients in clinical remission with IBS-type symptoms compared to those without IBS-type symptoms\textsuperscript{124,126}. However, other studies have failed to demonstrate this association\textsuperscript{123,127–129}. If IBS-type symptoms are related to low-grade inflammation, a low prevalence of IBS-type symptoms is expected in patients with quiescent IBD as defined by low surrogate markers of inflammation. This has not been investigated. \textbf{In chapter 15, we aim to investigate the prevalence of IBS-type symptoms in adult patients with IBD in biochemical remission (as determined by FC). Furthermore, in chapters 14 and 15, we aim to investigate the relationship of IBS-type symptoms with levels of FC in respectively pediatric and adult IBD patients.}

\textit{Treatment}

Despite the high prevalence of IBS-type symptoms in IBD, little is known about how it should be treated. If IBS-type symptoms reflect underlying inflammation, anti-inflammatory therapy would be a logical strategy. To our knowledge, this has never been thoroughly investigated, although a subgroup analysis of a previously performed trial suggests that potent anti-inflammatory therapy is probably ineffective in symptomatic IBD patients with no objective evidence of inflammation\textsuperscript{71}.

We hypothesize that IBS-type symptoms reflect “true IBS” (and thus do not reflect ongoing
IBD activity). Consequently, we expect that IBD patients with IBS-type symptoms and IBS patients respond similarly to treatment.

Various effective treatment options are available for patients with IBS, such as fibers, probiotics, antidepressants and psychological interventions (such as hypnotherapy). The efficacy of these treatments in IBD patients with IBS-type symptoms has not yet been investigated, with the exception of retrospective and small prospective studies. Therefore, in chapter 16, we aim to compare the efficacy of hypnotherapy with standard IBS treatment (according to Dutch guidelines for the management of IBS) in a randomized, controlled trial.