General introduction

GENERAL INTRODUCTION

Inflammatory bowel disease

Inflammatory bowel disease (IBD) is a chronic debilitating disease, with inflammation of the gastrointestinal tract as main characteristic. IBD has two main types; Crohn's disease (CD) and ulcerative colitis (UC). In patients who have IBD colitis that cannot (yet) be classified into CD or UC, the term IBD-unclassified (IBD-U) is used. IBD is characterized by periods of active disease (relapses, with increased symptoms) and periods of clinical remission (no symptoms present). Both CD and UC share common symptoms such as abdominal pain, bloody diarrhea, anemia, and systemic symptoms such as fatigue, lack of appetite and weight loss [1, 2]. CD usually has an insidious onset and can affect any part of the gastrointestinal tract from mouth to anus. In CD, inflammation presents itself often in 'skip lesions', in which some parts of the intestines are affected whereas other parts may be not. CD can be complicated by strictures and/or fistulas between parts of the intestinal tract or from intestine to the (perianal) skin. UC often has a more explicit onset, with frequent bloody diarrhea accompanied by abdominal cramping [3, 4]. Suspicion of IBD is present in case of typical symptoms and laboratory abnormalities in blood and stool. A confirmed diagnosis of IBD can only be made after extensive endoscopy of both upper and lower part of the intestinal tract with multiple mucosal biopsies. With respect to the complex etiology, several factors have been implicated. It has been shown that a genetic susceptibility in combination with a dysregulated immunological response to the bacterial gut flora is present. Environmental factors such as infection, certain foods, smoking and psychological stress can further trigger this dysregulation [1, 3].

IBD in children and adolescents

Approximately 10-25% of all patients receives the diagnosis of IBD before they are 18 years of age, and for patients up to 25 years of age this is approximately 35% [2, 5, 6]. Children and adolescents (hereafter referred to as youth) with IBD often present with malnutrition, growth failure, or delayed puberty [4]. In Europe, the incidence rate for pediatric IBD ranges from 3.11 – 12.00 per 100.000 persons, with somewhat higher incidence rates for CD (2.71 – 13.90 per 100.000 cases) than for UC (1.61 – 5.70 per 100.000 persons). These incidence rates are rising, which can be attributed to the rising incidence rates of CD [5]. In the Netherlands over 80.000 patients suffer from IBD, of whom 2500 to 3000 are younger than 18 years.

Medical treatment

Since IBD cannot be cured, its medical treatment is focused on the suppression of the inflammation, aimed at the induction and maintenance of clinical remission

and preferably also healing of the inflamed mucosa [7]. For children with active CD, the first-line treatment is exclusive enteral nutrition. This is less invasive than pharmacological therapy but requires adherence to a liquid formula diet for 8 weeks. Corticosteroids are often used for induction of remission in moderate to severe UC and CD (if enteral nutrition fails). After remission is induced, immunomodulators are used to maintain remission [8, 9]. In case of refractory disease, biologicals such as infliximab or adalimumab (anti-TNF treatments) of vedolizumab (anti-integrin) can be used. Surgery is indicated when non-inflammatory strictures are present in CD, or in UC when all treatments fail.

Psychological aspects of IBD

Psychological problems

The biopsychosocial model implies that psychological and social factors are likely to influence disease symptoms and functional outcomes, in addition to disease mechanisms such as inflammation in IBD [10]. Due to the unpredictable course of the disease and the chronic nature of IBD adolescents frequently experience psychological and social problems [11]. Several studies have shown that youth with IBD have a lower health-related quality of life (HRQOL) compared to healthy youth [12]. Youth with IBD also can experience problems with their self-esteem or social functioning [13, 14].

The psychological problems most studied in IBD patients are anxiety and depression. In adults, a meta-analysis of Neuendorf et al. [15] showed that patients with IBD have a high risk for having anxiety and/or depression, consisting of either subclinical anxiety/depression or clinical anxiety or depressive disorders. In youth, no meta-analysis is performed yet. However, original and review studies showed that youth with IBD also have a high risk for anxiety and/or depression [11, 16-18].

Bidirectional relationship inflammation and anxiety/depression in IBD

In IBD, the relationship between inflammation and anxiety/depression seems bidirectional. Evidence for this bidirectionality mainly comes from studies in adults. On one hand, anxiety and depression are associated with clinical relapse during follow-up [19-21]. More specifically, depression has a negative impact on the disease course [22] and is related to a shorter time to relapse when compared to anxiety [23]. In youth with IBD, Van Tilburg et al. [24] showed that psychological factors (anxiety, depression, coping and pain beliefs) impacted self-reported somatic symptoms and disability. On the other hand, evidence was found for the impact of clinical disease activity on anxiety and depression [25, 26]. In youth, clinical disease activity was associated with more symptoms of anxiety [27] and depression [28], and was a risk factor for having anxiety and depressive disorders [29]. Recently, two studies in adults with IBD provided even more evidence for the bidirectionality of the relationship between inflammation and

anxiety/depression. Sexton et al. [30] reported that clinical disease activity predicted change in perceived stress, where perceived stress predicted change in clinical disease activity. Furthermore, Gracie et al. [31] reported that clinical disease activity gave a 6-fold risk on anxiety 2 years later, and that baseline anxiety and depression were associated with several indicators of increased clinical disease activity.

Brain-gut axis

The brain-gut axis provides an hypothesized explanation for the common combination of IBD inflammation and psychological problems, such as anxiety, depression and stress. This axis involves interactions between the autonomic nervous system, the central nervous system, the stress system (hypothalamic-pituitary-adrenal [HPA] axis), the corticotropin-releasing factor system, and the intestinal response, that make the brain and the gut communicate. This communication seems bidirectional [32]. Increased production of pro-inflammatory cytokines (e.g. tumor necrosis factor α; TNF-α) is known to directly and indirectly affect the brain, with increased symptoms of anxiety and depression as result [33, 34]. On the other hand increased anxiety and/or depression can increase inflammation. In this way a vicious circle arises in which inflammation and anxiety/depression negatively influence each other, to an increasing extent. More inflammation can lead to more anxiety/depression, and vice versa more anxiety/depression can lead to more inflammation [32]. Evidence for the brain-gut hypothesis comes from animal studies showing that stress induces reactive inflammation in colitis models [35]. In addition, studies in humans showed elevated levels of inflammatory markers in otherwise healthy patients with depression [36-39] and anxiety [40-42]. The last decades more evidence has become available for this psychoneuroimmunological approach to mental health problems, such as anxiety and depression [43, 44].

Other psychological factors

Apart from the above described psychological problems, other psychological aspects of IBD also need to be considered. Earlier studies have shown that several psychological factors – often tested separately – were related to negative outcomes in IBD, e.g. functional disability or anxiety and depression. Coping and illness perceptions are two factors that are important in youth with IBD.

Coping. Coping refers to the cognitive and behavioral strategies one uses to deal with negative experiences, such as having a chronic illness [45]. Often a distinction is made between coping styles that are associated with favorable psychological outcomes (adaptive coping), or those associated with unfavorable psychological outcomes (maladaptive coping). Although it is still unclear whether youth with IBD cope differently than healthy controls, it appears that coping impacts psychological outcomes in these

patients [46, 47]. For example, maladaptive or passive coping was associated with more anxiety and depression [48], and adaptive coping (i.e. positive strategies) was associated with better HRQOL [49].

Illness perceptions. Illness perceptions are representations someone has about the illness, its treatment, and consequences of the illness [50]. There are several dimensions of representations: identity (the label that the persons uses to describe the illness), consequences (expected effects of the illness), cause (personal ideas about the cause of the illness), timeline (how long the patient believes the illness will last), and cure (the extent to which the patient believes treatment cures or controls the illness). In patients with IBD, illness perceptions have been shown to affect outcomes and adjustment [47, 51-53], with unfavorable perceptions being related to unfavorable adjustment. Illness perceptions have been less studied in children and adolescents than in adults. However, the few studies conducted suggest that also in youth with IBD, illness perceptions are associated with psychological problems [29].

To describe the potential relationships between illness, illness perceptions, coping, and illness outcomes, Diefenbach & Leventhal developed the Common Sense Model (CSM) [54]. In this model, illness characteristics (such as clinical disease activity) lead to certain thoughts about the illness, the so-called illness perceptions of a patient. These illness perceptions influence the type of coping the patient uses to deal with his/her symptoms. These factors lead to positive or negative illness outcomes, for example anxiety, depression, HRQOL, or adjustment. In turn, via a feedback loop illness outcomes can influence disease factors, coping, and illness perceptions [54, 55]. In adults with IBD, evidence was found for the CSM. That is, illness perceptions and coping were important mediators between clinical disease activity and anxiety and depression [56]. In youth with IBD these interrelationships have not been tested directly. Some evidence exists for separate pathways for different factors. For example, independent from the impact of disease factors on HRQOL, anxiety and depression (separately tested) have a negative impact on HRQOL as well [57-59]. However, the precise pathways between the factors included in the CSM are still unknown.

Cognitive behavioral therapy for youth with IBD

Considering the possible negative impact of anxiety and depression on the mental and somatic health status of children and adolescents with IBD, from a health care perspective it is important to treat not only the somatic symptoms, but also the psychological problems. The bidirectionality of the relationship between inflammation, and anxiety/depression implies that treating the psychological problems may also improve disease course. The most evidence based psychological treatment for anxiety and depression in children and adolescents is cognitive behavioral therapy (CBT) [60,

61]. In children with other chronic illnesses, such as diabetes and asthma, CBT has been shown effective in improving psychological problems [62, 63].

Only a few, and mostly small, studies have been conducted in youth with IBD. In 2007, Szigethy et al. performed a randomized controlled trial (RCT; n=41) and published preliminary, but promising results of cognitive behavioral therapy (CBT) in IBD patients aged 11-17 years with *subclinical depression* [64]. The CBT protocol used was the Primary and Secondary Control Enhancement Training – Physical Illness (PASCET-PI), a disease-specific CBT protocol. The authors found that 3 months of CBT was more effective in improving subclinical depressive symptoms than care-as-usual (CAU), which consisted of standard medical care plus a written information sheet about depression. In a later and larger RCT (n= 217), Szigethy et al. [65] confirmed the effectiveness of the PASCET-PI in improving clinical depressive symptoms in IBD youth aged 9-17 years, although a control group receiving supportive non-directive therapy showed similar results.

Very few studies focused on treating *anxiety* in youth with IBD. Reigada et al. [66] conducted a pilot non-randomized trial (n=22) using CBT in youth (mean age 13.2 years) with IBD, and found promising results in reducing clinical anxiety. More recently, a large RCT (n=185, aged 8-17 years) was conducted in pediatric IBD patients to test the effectiveness of a 3-session social learning CBT (SLCBT) versus educational support, although not focusing specifically on anxiety and/or depression. SLCBT led to a significant better improvement in IBD-related QOL and school attendance than educational support, but no differences were observed in improving subclinical anxiety and depression symptoms [67].

HAPPY-IBD: a study into anxiety and depression in youth with IBD

Until now, studies in youth with IBD mostly focused on either anxiety or depression. Hence, they did not take into account that anxiety and depression are highly comorbid, and that anxiety can precede depression [68, 69]. In addition, some studies included all youth with IBD, i.e. did not select youth on the presence of any psychological problems, such as anxiety and/or depression [67].

Therefore, the current study (HAPPY-IBD) was designed to 1) investigate both anxiety and depression in youth with IBD and 2) test both the short-and long-term effects of a disease-specific CBT protocol on both anxiety and depressive symptoms. HAPPY-IBD included a multi-center RCT, comparing the effects of the CBT protocol to CAU, consisting of standard medical care. The CBT protocol used was the disease-specific PASCET-PI, which also was used in previous studies.

Until now, no disease-specific CBT protocol was available for youth with IBD and their families in the Netherlands. It is innovative that we studied the effects of the PASCET-PI on both anxiety and depression, as well as on other psychological and medi-

cal outcomes, both at short-term (3 months, directly after the CBT) and longer-term (after 6 and 12 months of follow-up), using internationally validated questionnaires and a psychiatric interview.

We included patients with both subclinical anxiety and/or depression, since we were interested in the possible effect of a disease-specific CBT a) to prevent that subclinical anxiety/depression would develop into clinical psychiatric disorders, and b) to have a positive effect on the disease course (e.g. to prevent clinical relapse or worsening of disease severity). Furthermore, we wanted our study to resemble daily clinical practice as much as possible. Therefore, we chose to use a care-as-usual group. Children with clinical anxiety or depressive disorders were excluded from the RCT, since it would be unethical to randomize children with a clinical psychiatric disorder to a control group.

In this PhD thesis, we aim to answer the following research questions:

1. What is the prevalence of anxiety and depressive symptoms and disorders in children and adolescents with IBD (aged 6-18 years)?
2. Which medical variables are associated with the presence of elevated anxiety and/or depression in youth with IBD (aged 10-25 years)?
3. Which psychological variables are associated with HRQOL in youth with IBD (aged 10-20 years)?
4. What is the short-term and long-term effectiveness of a disease-specific CBT in improving symptoms of anxiety and depression (primary outcomes), HRQOL, negative illness perceptions, coping, social functioning, and sleep problems (secondary outcomes)?

Firstly, we hypothesized that anxiety and depressive symptoms are highly prevalent in youth with IBD. Secondly, clinical disease activity and disease duration were hypothesized to be medical factors associated with the presence of anxiety and/or depression. Thirdly, we expected that illness perceptions, coping, anxiety, and depression were psychological factors that are associated with HRQOL. Fourthly and lastly, we hypothesized that patients in the disease-specific CBT group would improve more compared to the CAU group on their symptoms of anxiety and depression, as well as on their HRQOL, negative illness perceptions, coping, social functioning, and sleep problems. The results of the disease-specific CBT on the medical outcomes will be described in a separate PhD thesis, by Gertrude van den Brink, MD.

METHODS

Full details of the study design, inclusion, exclusion criteria, the procedure, the intervention, and the used instruments, are described in Chapter 3 (the description of the study protocol) and can be found in the Methods section of Chapter 5, 6, and 7 as well. In short, the study is a RCT with a baseline screening and three follow-up assessments; at 3 months after the baseline screening (i.e. after the disease-specific CBT for those in the CBT group), at 6 months, and at 12 months after the baseline screening, see Figure 1. The follow-up assessments consisted of the same instruments as the baseline screening. The timing and method was similar for both groups.

Inclusion: adolescents and young adults (10-25 years) with a confirmed diagnosis of IBD (CD, UC, or IBD-U) were eligible. They were recruited between October 2014 and October 2016 from the pediatric or (pediatric) gastroenterology departments of two academic and four community hospitals. The study consisted of two parts: 1) a baseline screening on symptoms of anxiety and depression and 2) for patients with subclinical anxiety and/or depressive symptoms, a RCT with two conditions (CAU + CBT versus CAU only).

Part 1, baseline screening: after providing informed consent, patients, and if applicable parents, filled out online questionnaires for the baseline screening (see below for the included variables). Using age-appropriate questionnaires, patients were screened for anxiety and depression. Patients had elevated symptoms if they scored equal to or higher than the validated cutoffs for elevated anxiety or depression. Those who showed elevated symptoms were invited for a psychiatric interview to determine whether they had clinical anxiety and/or depression. For this study, patients were considered to have clinical anxiety or depression if they met DSM-5 criteria for an anxiety or depressive disorder on the psychiatric interview, and scored equal or above the clinical cutoff on an age-appropriate severity rating scale for anxiety or depression. Scores on these instruments were rated by two independent raters.

Part 2, RCT: patients that showed subclinical anxiety and/or depression (i.e. who had elevated scores on the questionnaires, but did not show clinical anxiety or depression according to the psychiatric interview and rating scales) were included in the RCT. This was a multi-center, parallel group RCT, designed according to the guideline for trials in non-pharmacologic treatments [70]. Patients were randomized at a ratio 1:1 to receive either CAU + CBT versus CAU only. Patients in the control group (CAU only) received standard medical care, since this resembles the current care for these patients best. Patients in the CBT group (CAU + CBT) received a disease-specific CBT protocol (Primary and Secondary Control Enhancement Training for Physical Illness; PASCET-PI) [64] added to standard medical care. See Chapter 3, 5 and 6 for more details of the PASCET-PI.

Psychological and medical variables

In this thesis, the focus will be on the psychological aspects of IBD in youth. The following psychological variables were included in the online questionnaires:

- *Primary psychological outcomes*: anxiety symptoms, depressive symptoms
- *Secondary psychological outcomes*: HRQOL, social functioning
- *Other psychological variables*: illness perceptions, coping styles, quality of sleep, parental anxiety and depression, life events, and family functioning

Simultaneously, information on the following medical variables were collected:

- *Primary medical outcome*: clinical relapse/remission
- *Secondary medical outcomes*: clinical disease activity, inflammatory markers (C-reactive Protein [CRP], Erythrocyte Sedimentation Rate [ESR], and fecal calprotectin), use of IBD medications, necessity of surgical intervention
- *Other medical variables*: disease phenotypes, treatment strategy, Irritable Bowel Syndrome (IBD)-like symptoms, RNA expression profiles and cytokine levels in the plasma and peripheral blood mononuclear cells (PMBC's).

For an extensive description of the assessments instruments, see the Methods sections of Chapter 3-7.

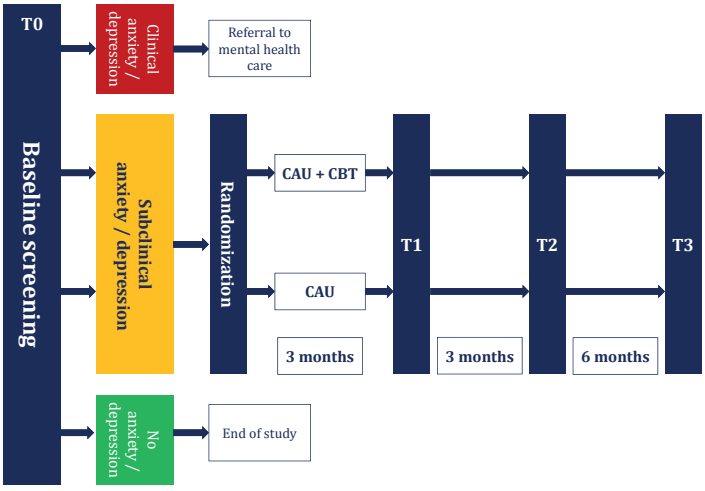

Figure 1 | Study design of HAPPY-IBD
Abbreviations: CAU= care-as-usual; CBT= cognitive behavioral therapy

Aims and outline of this thesis

The focus of the present PhD thesis is twofold: 1) investigating anxiety and depression in youth with IBD and 2) evaluating the effectiveness of a disease-specific CBT

compared to care-as-usual in improving anxiety and/or depressive symptoms, HRQOL and other psychological outcomes in these patients. This study is the first RCT studying the effectiveness of a disease-specific CBT protocol (PASCET-PI) on both anxiety and depression. Moreover, we will also examine other psychological and medical outcomes, using internationally validated questionnaires and a psychiatric interview.

Chapter 2 contains a systematic review and meta-analysis on the prevalence of anxiety and depression in children and adolescents with IBD. Multiple studies have examined psychological problems in pediatric IBD. However, it is still not clear to what extent children and adolescents with IBD experience subclinical anxiety and/or depressive symptoms and clinical anxiety and/or depressive disorders. We summarized all available data to provide insight into prevalence rates of anxiety and depressive symptoms and disorders in children and adolescents with IBD. Mikocka-Walus et al. [71] wrote an editorial to this chapter. The editorial and our response [72] can be found in Appendix A.

Chapter 3 is the description of the study protocol of the RCT, testing the effectiveness of the disease-specific CBT, including information on this intervention, the control condition, the assessment instruments and timing.

Chapter 4 and 5 describe the baseline data of our RCT, derived from the screening phase of the study (part 1). The total group of patients consisted of all patients included in the baseline screening preceding the RCT: 1) those without any anxiety and/or depression, 2) those with subclinical anxiety and/or depression, and 3) those with clinical anxiety and/or depression.

In Chapter 4, we examined which medical variables were associated with the presence of anxiety and/or depressive symptoms, and whether these associations were different for different levels of anxiety/depression (none, subclinical, clinical) or were different for patients aged 10-17 years versus patients aged 18-25 years.

In Chapter 5, the results are presented of a study that investigated whether several psychological variables (illness perceptions, coping, anxiety, and depression) were associated to HRQOL after controlling for several demographic and medical variables.

Chapter 6 presents the short-term results of the RCT, the pre-post treatment effects of the disease-specific CBT (i.e. directly after the treatment or 3 months after the baseline screening) on anxiety and depressive symptoms, as well as on HRQOL, compared to CAU.

In Chapter 7 we describe the longer-term effects of the disease-specific CBT on several psychological outcomes at the long-term follow-up, at 6 and 12 months after then baseline screening.

Finally, Chapter 8 provides an overview of all the previous chapters, an overall discussion of the findings, as well as directions for future research and clinical implications.

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