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**Quality of Life in Inflammatory Bowel Diseases
- aspects on interventions and unconventional treatments**

**by
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*O grant me a house by the beach of a bay,
Where the waves can be surly in winter, and play
With the sea-weed in summer, ye bountiful powers!
And I'd leave all the hurry, the noise, and the fray,
For a house full of books, and a garden of flowers*

*Gods, grant or withhold it; your "yea" and your "nay"
Are immutable, heedless of outcry of ours:
But life IS worth living, and here we would stay
For a house full of books, and a garden of flowers*

Andrew Lang 1844-1912

ABSTRACT

Crohn's disease (CD) and ulcerative colitis (UC) are chronic inflammatory bowel diseases (IBD) of unknown aetiology and characterized by periods of remission and exacerbation. Disabling bowel symptoms, untoward effects of treatments and interventions, the risk of developing colorectal cancer in longstanding UC, ignorance of the disease, disappointment in conventional medicine, all these features may influence the patient's health related quality of life (HRQOL) in various ways.

The aims of this study were to assess the attitudes to and the use of complementary and alternative medicine (CAM) among patients with IBD, and to evaluate interventions such as a group based educational programme, colonoscopic surveillance, treatment with leukocyte apheresis and its effect on HRQOL, functional health status, general state of health as well as anxiety and coping ability in patients with IBD.

Two hundred and eighty-nine IBD patients in four different countries answered a self-administered questionnaire concerning the use of and attitudes to CAM. Fifty-one percent used some form of alternative therapy. The usage was higher in North America than in Europe. The six most commonly used therapies were: exercise (28%), prayer (18%), counselling (13%), massage (11%), chiropractic (11%) and relaxation (10%). Only 7% used acupuncture or homeopathy and 5% used herbal medicine.

Forty-one patients with longstanding, extensive/total UC in remission undergoing colonoscopic colorectal cancer (CRC) surveillance were compared with two groups of UC patients not undergoing surveillance. Four self-administered questionnaires were used: Sickness Impact Profile (SIP), Health Index (HI), State Trait Anxiety Inventory (STAI) and Sense of Coherence (SOC). No significant differences between the groups studied were found using any of the questionnaires nor before or after the colonoscopy.

Thirty-four UC patients underwent weekly one hour apheresis sessions with a selective leukocyte adsorptive device for five consecutive weeks. HRQOL was measured by the Inflammatory Bowel Disease Questionnaire (IBDQ) before, at week 3, and after treatment. The mean IBDQ increased from 138 (range 97-208) at start to 154 (95-214) at week 3 ($p=0.001$) and 163 (117-216) after treatment ($p=0.0006$). When analysed separately, the IBDQ bowel, systemic and emotional dimensions improved significantly during the study.

Forty-four IBD patients in remission or with low disease activity were randomized to a group-based medical and psychological/psychosocial intervention or to a control group. The intervention comprised nine weekly sessions with lectures and psychological/psychosocial group treatment. HRQOL was measured by the IBDQ and coping by the SOC before, at 6 and 12 months. The control patients received conventional medical and psychosocial treatment. No significant change was observed for IBDQ before (173.9) and after the intervention at month 6 (175.7), or at month 12 (171.8) or when comparing intervention (171.8) and controls (173.7) at month 12. Similarly, no significant differences in SOC scores were observed. However, the mean values from a visual analogue scale (VAS) and the results from a content analysis showed a positive trend.

There is an increased interest in CAM among IBD patients, and this may reflect the patients' disappointment of conventional medicine. Complicated and invasive interventions such as colonoscopic surveillance (for detecting CRC), and selective leukocyte apheresis do not seem to impair HRQOL in UC patients. A group based medical and psychological/psychosocial intervention was highly appreciated in IBD patients, but no effect on HRQOL could be demonstrated by using standard HRQOL or coping measurements.

LIST OF PAPERS

This thesis is based on the following papers which are referred to in the following by their Roman numerals (I-IV)

- I. Rawsthorne P, Shanahan F, Cronin N, Anton A, Löfberg R, Bohman L, Bernstein C. An International Survey of the Use and Attitudes Regarding Alternative Medicine by Patients With Inflammatory Bowel Disease. American Journal of Gastroenterology 1999; 94; 1298-1303.
- II. Oxelmark L, Nordström G, Löfberg R. Anxiety and Coping Ability in Patients with Ulcerative Colitis Undergoing Colonoscopic Surveillance. Inflammatory Bowel Diseases 2004; 10; 612-617.
- III. Oxelmark L, Hillerås P, Dignass A, Mössner J, Schreiber S, Kruis W, Löfberg R. Quality of Life in Patients with Active Ulcerative Colitis Treated by Selective Leukocyte Apheresis. Scandinavian Journal of Gastroenterology, accepted for publication
- IV. Oxelmark L, Magnusson A, Löfberg R, Hillerås P. Group-based Intervention in IBD-patients – Effects on Quality of Life Inflammatory Bowel Diseases, submitted for publication

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LIST OF ABBREVIATIONS

CAI	Clinical Activity Index
CAM	Complementary and Alternative Medicine
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
CRC	Colorectal cancer
EWB	Emotional Well Being
GCS	Glucocorticosteroids
HI	Health Index
HRQOL	Health Related Quality of Life
IBD	Inflammatory Bowel Disease
IBDQ	Inflammatory Bowel Disease Questionnaire
SIP	Sickness Impact Profile
SOC	Sense of Coherence
STAI	State Trait Anxiety Inventory
UC	Ulcerative colitis
VAS	Visual Analogue Scale
QoL	Quality of Life

INTRODUCTION

The inflammatory bowel diseases (IBD) studied in this thesis refers to Crohn's disease (CD) and ulcerative colitis (UC). Crohn's disease may affect any part of the gastrointestinal tract from the mouth to the rectum whilst UC only involves the large bowel and/or rectum.

The diseases are characterised by periods of remission and exacerbation. During active disease the patients often have debilitating symptoms including diarrhoea, tenesmi and abdominal pain and impaired control of bowel function despite treatment with oral and rectal remedies, often taken several times per day. Only 70-80 % of IBD-patients respond to standard medication and 20-30 % are more or less refractory to medical treatment and suffer from chronic continuous inflammation [1]. In the most severely affected cases, intensive medical treatment and surgical resection of the affected bowel may become necessary. IBD predominantly affects young individuals, with the highest incidence between the ages of 20-40 years, where UC is slightly more common in men, while CD tends to be marginally more common in women [2].

Troublesome side effects due to medical therapy and extraintestinal manifestations associated with the disease are often bothersome for the patients. Additionally, patients with longstanding extensive UC have an increased risk of developing colorectal cancer [3]. If the disease deteriorates and treatment fails or if the patient does not have confidence in the physician or the treatment methods the patient might turn to other alternative therapies.

The aetiology of IBD is still unknown, but environmental factors and immunological disturbances are currently attracting a lot of researchers. The effects of cigarette smoking, appendectomy, various diets, oral contraceptives, perinatal/childhood infections (mycobacterium, measles infection) have been discussed in combination with a dysregulation of the immune system in genetically predisposed individuals [2, 4, 5].

Living with a chronic disease such as Crohn's disease and ulcerative colitis has an important impact on patients' personal lives – both private, at work and in social life. The disease is always present although it is sometimes quiescent. To deal with his/her professional life and the family network it is important for the patient to learn to cope with the disease and treatment [6]. Altogether, the substantial symptom load profoundly influences the IBD patients' quality of life (QoL).

The meetings with all the IBD patients during the years of my work as a specialist nurse in a gastroenterology clinic have made me curious and deepened my interest for these patients. Therefore, I wanted to study this patient group more closely and examine the impact the chronic diseases had on their life and health related quality of life (HRQOL). The main purposes of this thesis were to study aspects of different interventions and unconventional treatments and the impact on QoL and HRQOL in various situations as measured by self administered questionnaires.

In particular we studied the use and attitudes regarding complementary and alternative therapy (CAM) among IBD patients in an international survey. Moreover, the anxiety levels, functional health status, general state of health and coping ability were studied in patients with longstanding UC undergoing colonoscopic, colorectal cancer (CRC) surveillance. Further, HRQOL was investigated in UC patients treated by a new non-pharmacologic treatment, a selective leukocyte apheresis, and finally, a group-based medical and psychological/psychosocial intervention for IBD patients was developed and evaluated.

BACKGROUND

INFLAMMATORY BOWEL DISEASE

History

Ulcerative colitis

In 1859 Sir Samuel Wilks used the term “ulcerative colitis” in describing the post mortem findings in a young woman with inflamed intestines, however the description seems to be more typical of Crohn's disease [7]. In 1905 the first (electric) sigmoidoscope was invented and the diagnosis of true colitis was established with visible structural lesions [8]. In 1909 a series of more than 300 cases of ulcerative colitis was presented at the Royal Society of Medicine in London. Most of the patients had died due to colonic perforation, peritonitis, haemorrhage or sepsis [9]. In the early twentieth century ‘colitis’ was a fashionable diagnosis in high society as described by Axel Munthe who in his book stated that many sins had been committed in the name of colitis [10].

Crohn's disease

The first description of a condition similar to Crohn's disease was made in 1913 by Dalziel who emphasized the resemblance with Johne's disease in cattle caused by *Mycobacterium paratuberculosis*, [11]. Records from the renaissance and up to the 20th century reveal cases which appear to be a variety of Crohn's disease. Burrill B Crohn (1884-1983) presented “a new intestinal disease, which we have named Terminal Ileitis” at the American Gastroenterological Association, (AGA) meeting in 1932, and a paper was published the year after. The name was later changed to Regional ileitis, and later on the surgeon and friend of Burrill Crohn, Brian Brooke in London, began to refer to the disease as “Crohn's Disease” repeatedly in his editorials in the Lancet [12].

Incidence and prevalence

Chronic Inflammatory Bowel Diseases are more common in the industrial world than in undeveloped countries. Northern Europe and North America are high incidence areas, compared to Asia and Africa. Historically, the incidence has been low in other continents, with the exceptions of Israel, Australia and South Africa. The incidence of UC is rising in Asia, northern India and Latin America. As many as 3.6 million persons in Europe and in

the United States, suffer from IBD [4]. In Europe the incidence rate ranges from 1.5 to 20.3 per 100 000 inhabitants for UC and from 0.7-9.8 per 100 000 inhabitants for CD. The incidence rate in North America ranges from 2.2 to 14.3 per 100.000 inhabitants for UC and from 3.1 to 14.6 per 100.000 inhabitants for CD [4]. The prevalence is approximately 235 per 100 000 inhabitants for UC and the prevalence for CD is approximately 213 per 100 000 inhabitants in Sweden [4, 13, 14]. The most recent epidemiological studies on incidence and prevalence in CD indicates that there is a continuous rise in incidence (8.3 per 100 000 for the time period 1990-2001) in Stockholm County [14, 15].

Aetiology

Psychological and social factors were believed to be the origin of IBD between the years 1940-1960. UC was for many years considered as a typical psychosomatic disorder [16] and it was believed that IBD patients had a special kind of personality. Personality and emotional states are no longer seen as primary cause of the diseases. It is clear that personality and emotions both influence and are influenced by the course of the disease, as is common in most chronic diseases [17]. In the late 1970s there was a paradigm shift from traditional biomedical reductionism (where a medical condition is reduced to a single aetiology) and dualism (where a condition was of either medical or psychiatric cause) to a more holistic theory. In the “biopsychosocial model” proposed by Engel it is the *interaction* between biological, psychological and social subsystems that determines the illness and this may well apply to IBD [18, 19].

Still, the aetiology and pathogenesis of the diseases remain unknown today, but seems to be multifactorial. A hallmark is that some kind of unknown stimuli, or possibly several contributing factors, triggers an abnormal immune response which results in an uncontrolled inflammation and tissue damage of the bowel mucosa in genetically susceptible patients [2]. Five to ten per cent of patients have first-degree relatives with IBD [20].

Several environmental factors have been discussed to be of importance:

There is an inverse association between cigarette smoking and UC and current smokers seem to have a decreased risk of developing UC. Ex-smokers were more likely to have an increased risk compared to those who never smoked [21]. In contrast to UC smoking is a risk factor for CD (smokers have a relative risk of two to five times to develop CD) and smoking can influence the clinical course of CD. Current smokers are more likely to have ileal than colonic or ileocolonic involvement. Women with CD who smoke have

been shown to have poor HRQOL [22]. Appendectomy appears to be protective for UC but increases the risk of CD [23]. Dietary factors have been discussed and differences in diet may explain the significant differences across geographic regions albeit numerous studies no consensus has emerged. A high intake of refined sugar as a risk factor in CD was defined already in 1976, and cola drink and chocolate have also been suggested as possible risk factors. High intake of dietary fibre and fruit or vegetables may be of benefit as a protection against the development of IBD although conclusions differ [24]. Oral contraceptives might increase the risk of developing CD but the mechanism for this association is unknown [25]. Perinatal and childhood factors, such as breastfeeding, domestic hygiene or perinatal infections in the child or mother, have been studied. Infectious aetiologies like measles infection or measles vaccination, and mycobacterias' have all been discussed. Furthermore, non steroid anti-inflammatory drugs (NSAIDs) are suggested to either cause IBD or to trigger flares [26].

Disease characteristics and treatments

The inflammatory bowel diseases are characterized by remitting diseases with acute exacerbations, “flares” and periods of remission. Up to 20% of the patients suffer from chronic continuous disease.

Crohn's Disease is characterized by a transmural and segmental inflammation, and could involve any part of the gastrointestinal tract including the perianal area. A classical endoscopic feature is the cobblestone pattern, caused by longitudinal and transverse linear ulcerations of the bowel wall. The transmural inflammation may lead to stricture development. The disease is typically discontinuous, with affected segments and unaffected parts in between. The small bowel, particularly the terminal ileum, is the most common location in CD. Forty to 50 % of the patients have ileocolitis, 30 to 40% have pure ileitis, the colon is affected in 15-30% and jejunum is involved in 6-7% [27]. Rectum sparing is classically associated with CD but rectal disease is present in 60% of patients having Crohn's colitis. CD is compared to UC, more often complicated by fistulas, abscesses, strictures and perianal disease. Fistulas can be perianal, rectovaginal, enterocutaneous, enterourinary, enterocolic and/or enteroenteric [27] and have obvious impact on the patients' HRQOL.

Ulcerative colitis is a mucosal ulcerating process of the colon and/or rectum. A limited inflammation of only the rectum; *proctitis*, occurs in 25% of the patients, and about 55% of the patients have *proctosigmoiditis* involving the rectum and the sigmoid colon. Left-sided inflammation extends proximally to the sigmoid but not beyond the splenic flexure.

Patients with *extensive colitis* have inflammation involving rectum and colon up to the splenic flexure, and in 20% of the patients the entire colon is involved, *pan colitis*.

A loss of vascular pattern and a sand-paper like appearance with contact bleeding dominates the endoscopy picture at early stages. In more severe cases erosions develop into deep ulcerations and pseudopolyps or inflammatory polyps may be present. Toxic megacolon is one of the most feared complication in severely ill patients with fever and tachycardia and abdominal distension. It may occur in both UC and CD but is more commonly associated with UC. In longstanding UC the colon presents a “hose” like appearance due to colonic shortening with loss of haustral folds [28, 29].

Symptoms

The main symptoms in *UC* are loose stools with blood, urgency, pus and mucous discharge. *Diarrhoea* is usually frequent in number and small in volume if the patient has proctitis or colitis. Bleeding is present in almost all UC patients. *Urgency* is often the most troublesome symptom as it sometimes may lead to incontinence and makes the patient dependent of bathrooms facilities. *Tenesmi* may be painful and explained by sensation of a full rectum, rectal pressure and the desire to defecate but only with small amounts of gas, mucous or blood that passes. *Abdominal pain* in UC is uncommon but may be located to the left lower quadrant and could be described as an aching, back pain [28, 29].

CD is characterized by recurrent, *abdominal pain or cramps*, which sometimes is similar to appendicitis with right lower quadrant tenderness and occasionally abdominal mass. Nausea, vomiting, fever, fatigue and weight loss are frequently common symptoms. *Diarrhoea* is less severe in isolated ileal disease in comparison to colonic disease and may even be absent in 10 to 15% of the patients. *Malabsorption, malnutrition, anaemia* and *osteoporosis* may be present in longstanding disease [30].

Extraintestinal manifestations

The IBD patient is not only afflicted by bothersome symptoms from the disease, but may also be affected by extraintestinal manifestations and at times these symptoms overshadow the distress caused by the bowel symptoms. The manifestations may correlate with the flares of the underlying IBD and may predict relapses [31].

Examples and localisations:

Mouth Aphthous ulcers or stomatitis, may cause pain

Eyes Uveitis and episcleritis, may cause painful eyes and visual blurring

<i>Skin</i>	Erythema nodosum, painful red nodules Pyoderma gangrenosum, painful ulcers
<i>Joints</i>	Arthritis and artralgia, swelling and joint pain
<i>Liver</i>	Primary sclerosing cholangitis

Medical treatment

Medical therapy for IBD often involves a balance between efficacy and toxicity. The main goal is to induce and maintain remission. Medical treatment comprises anti-inflammatory therapy and immunomodulatory treatment [32].

Sulphasalazine induces remission in mild to moderately active UC in 30-80% of the patients, and may also maintain remission. However, 15% of the patients treated by sulphasalazine experience side effects and intolerance and must discontinue the treatment. Folate supplementation should also be prescribed to patients treated by sulphasalazine as it is known to impair folate absorption.

Aminosalicylic acid (5-ASA) compounds were developed from sulphasalazine due to the toxicity of the sulpha-moiety medication. 5-ASA compounds (mesalamine, olsalazine and balsalazide) have been shown to be superior to placebo in mild to moderately UC but has fewer side effects compared to sulphasalazine. Distal colitis may be treated by *topical* 5-ASAs, administered as enemas, suppositories or rectal foams [32]. An enema allows the medication to reach the splenic flexure and the suppositories may treat disease extending up to 15 to 20 cm from the anal verge. Having to take an enema twice a day may well influence the daily QoL life of the patient.

Glucocorticosteroids (GCS) are very efficacious for the treatment of active UC and CD in order to induce remission regardless of disease distribution. However, GCS have no maintenance benefits in preventing relapse. The side effects of GCS treatment are well-known, e.g. weight-gain, acne, striae, hyperglycemia, cataract, osteoporosis, mood disorders and impaired cognitive function. *Budesonide* ‘the second generation of GCS’ has enhanced anti-inflammatory activity with low steroid-related side effects due to low systemic biologic activity and is a standard drug for ileocolonic CD [33]. Topical GCS are also available for rectal application (enemas, suppositories and rectal foam) and Budesonide is available as an enema. Different *antibiotics* are also used in the management of IBD, - the two most commonly used for the treatment of CD are metronidazole and ciprofloxacin.

The most widely used *immunomodulators* are purine analogues, such as azathioprine and 6-mercaptopurine, which have become increasingly important in the management of steroid-refractory disease. However, these immunomodulators have severe side-effects and may cause leukopenia and pancreatitis, secondary infections and lymphoma are also possible.

Methotrexate, ciclosporine and tacrolimus are sometimes used as third line drugs.

A completely new treatment modality is the use of biological antibodies, which has been introduced the last decade. Infliximab is such a biologic compound, (a chimerical monoclonal antibody directed against tumour necrosis factor alpha) and is administered as i.v. infusions. Infliximab has been proven to be efficacious in CD with or without fistulas [34, 35]. However, there is risk of severe opportunistic infections including tuberculosis, which may limit extensive use of these compounds [32].

Leukocyte Apheresis

It is well appreciated that leukocytes play an important role in the pathogenesis of IBD. Studies have shown that activated leukocytes infiltrate the bowel mucosa and cause extensive tissue injury. The activated granulocytes and monocytes produce large amounts of pro-inflammatory cytokines which are involved in the initiation of chronic inflammation [36]. Patients with active UC have been found to have twice the level of granulocyte count in peripheral blood [37].

Already in the 1980s leukocyte apheresis was proposed as a therapy for IBD [38]. Traditional leukocyte apheresis involves passage of peripheral blood through a leukocyte removal filter and the blood is then re-infused back into the patient [39] and centrifugal systems have also been used [40].

A novel, non-pharmacological way to treat chronic inflammatory disorders is *selective* leukocyte apheresis. The Adacolumn is a EU-certified medical device approved for the use in UC [41]. The Adacolumn system provides selective depletion of phagocytic leukocytes (granulocytes, monocytes/macrophages) via passage through cellulose acetate beads that adhere to the cells. The Adacolumn device has a capacity of 335 mL, filled with 35 000 cellulose acetate beads of 2 mm diameter as the column adsorptive carriers, bathed in physiologic saline. The system was originally developed in Japan, for extracorporeal selective depletion of phagocytic leukocytes in cancer patients [42]. Selective leukocyte apheresis has been considered as an alternative therapy to induce remission, reduce drug use and eliminate side effects of standard medication in patients

with UC. The Adacolumn system was studied in Paper III and is currently investigated in long sham controlled studies in IBD patients.

Complementary and Alternative Medicine

Complementary and alternative medicine (CAM) includes a wide range of therapies. A variety of terms, ('unconventional', 'unproven', 'unorthodox') have been used to describe therapies that are not considered part of standard medical practice in the Western World [43]. CAM includes an array of systemic and comprehensive concepts of health and disease as well as diagnostic procedures e.g. herbalism, homeopathy, acupuncture, chiropractic, spiritual healing, massage, aromatherapy, counselling, reflexology etc. The healing effects of these interventions cannot be fully understood by basic science and are argued to be akin to placebo [44]. A definition of what is and is not CAM may be difficult, but one definition often used is

Medical interventions which are neither taught widely
in medical schools nor generally available in hospitals

CAM has been described as maintaining focus on health, with illness regarded as a deviation from health (similar to Antonovsky's salutogenetic view which will be discussed later) while conventional medicine has been more focused on illness and disease and may be described as regarding health as a deviation from disease [45]. Nevertheless the focus has changed and HRQOL is now a more important component integrated in conventional medicine. Traditionally the complementary approach is a more holistic view of the patient, and the patients play a more active role in the healing process, and tend to be more passive in conventional treatment. In CAM therapy the diagnostic process, the therapy, the therapist and the patient all *interact* to achieve the outcome, to treat the patient as a 'whole person' rather than as a 'diseased organ'.

Patients may seek alternative medicine for symptomatic relief and as a novel approach when dissatisfied with how conventional medicine has (not) met their health care needs or failed to provide them with some sense of control of their disease and its management. The patients may be disappointed with their physicians or with conventional medicine in general, they may find it too complex, they might find the treatments difficult to approach or could have experienced treatment failure or adverse side effects. The longer the disease duration, the more often IBD patients used CAM, independent of their perceived

level of information of IBD [46]. Langmead et al [47] proposed that the use of CAM in IBD patients may indicate psychosocial distress similarly to Moser et al who earlier showed that IBD patients who used unconventional medicine had greater IBD-related concerns, e.g. about having surgery, being treated as different and about feeling out of control [46].

In general, up to 50% of IBD patients use some kind of CAM. Recently a study showed that the most commonly used CAM in Canadian IBD patients was herbal or plant-based therapy such as flax seed, aloe vera and garlic [48]. Homeopathy, acupuncture and traditional Chinese medicine was most common in IBD patients from Switzerland [49] and patients in Austria used homeopathy, special diets and acupuncture [46]. Herbal therapy was the most popular CAM in IBD patients in the UK; aloe vera, St Johns wort, and Slippery Elm was used the most [47]. There is an abundance of different CAM treatments that may be of interest for IBD patients, (for an overview see the review article by Langmead et al [50]).

The patients' safety may be at risk if the patients are combining different alternative and medical therapies. Verhoef et al [43] showed that IBD patients who seek complementary and alternative therapies are confronted with an array of treatments and often inconsistent advice regarding disease management from self-treatment guides, practitioners and health food store employees. In 1993 Eisenberg et al reported that 72% of a national sample who used CAM did not inform their medical doctors of their use [51]. A considerable emphasis was put on patient-physician communication in a qualitative interview study regarding IBD patients' decisions to use CAM [52], where one third of the patients did not discuss the use of CAM with their physicians. Yet in another study 71% of the patients had discussed their use of CAM with their gastroenterologist and only 13% believed that their doctor was not supportive of the CAM treatment they used [48]. Communication seems to be improving but the need of increased physician knowledge is obvious. The risk of side effects or interactions between CAM and conventional medicine makes it crucial that physicians caring for IBD patients are informed of all the therapies that a patient is using. In addition, as emphasized by Langmead et al in a recent overview, [50] "doctors in general, and gastroenterologists in particular can no longer ignore the potential benefits and dangers of CAM". Lately, sessions about CAM have become more regular features of major digestive disease meetings in the US [48].

Surgical treatment

Surgical removal of the entire colon and rectum is the only cure for UC, whilst CD is not surgically curable. Surgery in UC usually implies a total proctocolectomy with permanent ileostomy or with an ileal pouch-anal anastomosis where the colon and rectum is removed and an ileal pouch is made out of the terminal ileum and attached to the anal canal. Another method is a total colectomy with ileorectal anastomosis, but then there is a risk of developing cancer in the remaining rectum.

Patients with CD may require various surgical techniques for the management of the disease, such as ileocecal resection, segmental colectomy, total proctocolectomy with ileostomy or strictureplasty and also various fistula surgery [53].

Studies have shown that medically treated patients in remission had significantly worse anxiety, depression scores and emotional function compared to patients who had undergone restorative proctocolectomy [54, 55] and moreover, patients with conventional or continent ileostomy appear to have an excellent QoL [56].

Colorectal cancer

The risk of carcinoma development in longstanding extensive UC is associated with an increased risk of developing colorectal cancer (CRC). The cumulative CRC-risk is 10-14%, after 25 years of disease [57, 58]. Karlén et al reported a standardized morbidity ratio of CRC in UC patients of 4.1 (95% CI, 2.7-5.8) compared to the general population [59]. CD has also been shown to be associated with an increased risk of CRC [57] particularly in patients with extensive CD, colonic distribution but data is inconstant as CD has limited colonic disease and ileal disease seems to have less risk of developing cancer.

The risk of developing CRC in UC is correlated with increased disease duration and increased disease extent. After approximately 8 years of duration dysplasia is more likely to occur in patients with pan colitis than in those with left-sided colitis and when/if the cancer occurs in UC patients it is more common in the rectosigmoid colon [60]. Concomitant primary sclerosing cholangitis (PSC), early disease onset and family history of sporadic CRC additionally increase the risk of developing CRC [61-63]. The CRC risk appears to be increased when the UC debut is at a younger ages compared to those who have developed their disease at an older age, thus there is a difference in having had the disease in 20 years already at 30 years of age compared to 50 years of age.

Surveillance in longstanding UC

Due to the substantially increased CRC-risk, patients with extensive colitis were previously recommended a prophylactic colectomy after 3-15 years of disease duration regardless of symptoms [57]. However, today most UC patients with extensive/total disease and a duration exceeding 8 years are today offered to participate in long-term follow-up colonoscopic cancer surveillance programmes [64]. The first prospective colonoscopic cancer surveillance programme for patients with longstanding UC was initiated at St. Mark's Hospital in London in 1966 [65] and South Hospital and Huddinge Hospital in Stockholm, started similar programmes shortly thereafter.

By performing colonoscopies with multiple biopsies the colorectal mucosa is screened for detection of early precancerous changes, i.e. dysplasia and DNA aneuploidy in order to detect the high-risk patients. If two negative results are obtained from surveillance colonoscopy within one year of each other, then the surveillance interval may be spread out to every three years until 20 years of disease duration. After 20 years the colonoscopies should be conducted annually [64, 66]. Even if multiple (20-40) biopsies are taken, still less than 0.1% of the colorectal mucosa is covered, additionally the dysplasia is often unevenly distributed in the colon. Nevertheless, experience from several surveillance programmes indicates that biopsies taken from 6-10 different sites throughout the colon and rectum are sufficient to detect dysplasia and that the risk of missing an incurable CRC is therefore low [64, 67, 68].

Dysplasia

Dysplasia is defined as epithelial changes of the mucosa that are unequivocally neoplastic and may therefore be associated to invasive carcinoma. Any grade of dysplasia can be associated with concurrent cancer, sometimes in advanced stage [69]. In 1983 a system was developed for grading of dysplasia which was classified as negative for dysplasia (ND), low-grade dysplasia (LGD), high-grade dysplasia (HGD) and indefinite dysplasia (ID) and has since then been adopted by most clinicians [70]. The appearance of macroscopic mucosal lesions such as sessile polyps or dysplasia associated lesion or mass (DALM) was found to be an additional risk factor in the development of CRC [71]. Dysplasia is not always found in association with CRC [67, 72]. Unequivocal HGD in flat mucosa or dysplasia of any grade on the surface of an elevated area of the mucosa and LGD at more than one site or at repeated occasions are indications for colectomy.

It is of outmost importance that the IBD patient is well informed at an early stage of the increased risk of CRC and about the possible consequences of dysplasia findings. Compliance is of major importance for a successful surveillance programme. A study at St Mark's Hospital showed that 10% of patients who abandoned the dysplasia surveillance programme later presented a CRC, of which 60% were fatal [72]. In another study by Karlén et al dysplasia surveillance was suggested to lead to earlier cancer diagnosis and less cancer associated mortality [73]. Robinson et al demonstrated that many UC patients had inadequate knowledge of the cancer risk and the cancer screening and emphasized that patient education and information would contribute to a better compliance to surveillance programmes [74].

Surveillance programmes have been criticized for being ineffective and costly and that instead ‘routine clinical control’ colonoscopy when symptoms of CRC occurs has been advocated [75, 76]. Advanced malignancies have been reported in some programmes despite surveillance, and the incidence of CRC in others has been so small that the cost-effectiveness has been questioned [72]. Controlled studies will never be performed as it would not be ethical to enrol high risk patients in a study arm that includes less or no surveillance colonoscopies, nevertheless case control studies show protective effects of surveillance programmes [73, 77].

HEALTH RELATED QUALITY OF LIFE

The World Health Organisation, WHO, defined *health* in 1948 as

“....a state of complete physical, mental and social well-being
and not merely the absence of disease or infirmity”

“Quality of Life” became an official search term in Medline in 1977. The same year Engel presented the biopsychosocial model – where chronic diseases are not merely of chemical and physiology nature, but a more holistic view of the patients should be considered [18]. QoL has been defined differently in different studies and a complete consensus has not been reached. However, QoL is understood as multidimensional and each dimension changes over time. The concept of HRQOL is more narrow and focuses on the disease itself.

The five major domains that most authors describe in their research was outlined by Spilker:

- Physical status and functional well-being
- Psychological status and well-being
- Social interactions
- Economic and/or occupational status and factors
- Religious and/or spiritual status

He suggests that all domains should be assessed and many components of each domain need to be measured to capture the full range of QoL characteristics. But all domains may not be of significance in all studies, e.g. religion is seldom assessed in clinical trials [78].

Over the past decade the measuring of HRQOL has been understood to be an important component in various medical conditions and has increased in usage in IBD. There has been a shift from the mechanic physiologic view of chronic diseases to a more holistic view regarding the patient as a subject. More emphasize is now focused on the patient's perception rather than measured physiological values. HRQOL is complimentary to clinical and biological measures, e.g. endoscopy and laboratory parameters. It is important to realize that not merely the disease activity predicts the overall HRQOL but also psychological problems, coping with the disease and the information level that an IBD patient has must be accounted for [79].

According to Drossman HRQOL could be defined as [80]

“a global measure of the patient’s perceptions, illness experience and functional status that incorporates social, cultural, psychological and disease related factors”.

Questionnaire assessments

In order to measure HRQOL such as functional health status, coping or anxiety, different types of self-administered questionnaires are usually utilized. A *questionnaire* (or instrument or index) is a collection of one or several *items* (questions), which can be grouped into different *dimensions*, measuring e.g. physical symptoms or psychological symptoms. All items together may form a *sum score* or can be presented as dimensional

scores or single item scores. The patients give their responses on a *scale*. There are different kinds of instruments and scales which are presented below.

General or generic instruments are designed for the use in general populations, and can be used to compare differences in different diseases and studies. These questionnaires describe HRQOL in a general way but may not detect small clinical changes in specific disease conditions or patient populations. Normative data are often available for other diseases and the background population [81]. One example of a generic instrument is the Sickness Impact Profile (SIP) for assessing functional health status. The SIP was used in Paper II.

Disease-specific instruments are appropriate for studying the disease for which they were designed and validated for, targeting a specific patient group. Such questionnaires are highly responsive to changes within the disease, sensitive to small changes in disease-specific parameters and provide useful descriptive information to help clinicians in patient care, but cannot be used for comparison between different conditions [81-83]. The Inflammatory Bowel Disease Questionnaire (IBDQ) is a disease specific instrument, which we used in Papers III and IV.

Domain specific instruments are specialized in one specific domain, addressing a particular aspect but are still of general character, e.g. measuring anxiety. The State Trait Anxiety Inventory, (STAI) S-Anxiety, is a domain specific instrument. This instrument was used in Paper II.

Study-specific instruments for detecting a special interest, e.g. the questionnaire about the use of and attitudes towards complimentary and alternative medication, which was used in Paper I.

The *Likert Scale* is the most commonly used scale in questionnaires. The Likert is a category scale and contains a series of opinion statements, usually comprising from four up to seven categories. There is no assumption of equal intervals on the scale. The responses are often divided numerically into a series of ordered responses. The Likert can indicate the ordering of different people's attitudes but not precisely how far apart or close these attitudes are – how much is the difference between 'very much so' and 'moderately'? Is it the same as between 'somewhat' and 'moderately'? There has been a

lot of discussion of how to interpret the answers. Still, the most often used method is to calculate mean values as in an interval scale [84, 85]. The IBDQ (Papers III and IV), Health Index (HI) and STAI (Paper II) are examples of questionnaires with Likert scales. An example of a four-category scale follows:

Not at all	Somewhat	Moderately	Very much so
1	2	3	4

The *Visual Analogue Scale (VAS)* is a kind of Likert scale. This scale is a line of defined length –usually 10 cm and horizontal. The line is anchored at each end by a descriptive word representing the extremes of a health status or an opinion “worst” and “best”. The respondent is asked to place a mark on the line to indicate the point that best reflects his or her response to the question being asked. The line may also have numerical regular values along the line, it is then known as a numerical scale. A VAS was used in Paper IV.

The *Thurstone scale* was the first major method of measurement that was developed [86]. The scale is constructed by choosing an ‘attitude object’ to be measured. One scale consists of several items and the respondent is asked to agree to the items that they are sure describe their status that day i.e. is in concordance with their current health status. The importance of each item is weighed in relation to the others. It is time consuming to construct a Thurstone scale, and usually these questionnaires comprise many items, such as the SIP (Paper II) [86].

Combinations of disease specific and generic questionnaires are seen as the best way to cover a holistic view of the patient’s perception of HRQOL. In the current studies we used a range of general, disease-specific, domain-specific and study-specific questionnaires.

Measuring functional health status

The *Sickness Impact Profile (SIP)* was one of the first measures of overall health available to researchers. The questionnaire was developed by Bergner et al [87], and it is a behaviourally based measure of health-related limitations in the daily living of both acutely and chronically diseased subjects [87]. The SIP measures a physical dimension which includes ambulation, mobility and body care/movement, a psychosocial dimension

including social interaction, emotional behaviour, alertness behaviour, communication and five independent scales: sleep and rest, home management, eating, recreation and pastimes and work. Impacts of sickness are manifested in the individual's behaviour and, therefore serve as the basis for response to SIP [88]. Hjortswang et al have previously showed, using the SIP, that UC-patients who experienced a relapse had an impaired functional status, particularly regarding the psychosocial dimension, compared with those in remission [89]. The reliability and the validity of the Swedish version of the SIP have been considered appropriate and comparable with the original American version [90, 91]. The *Health Index* (HI) is used to measure the general state of health. The HI was developed by Hansagi and Rosenquist [92] inspired from the Nottingham Health Profile, part I. The HI measures experienced general state of health divided in two dimensions: emotional well being (EWB), and physical well-being (PWB). A single item concerns general health.

HRQOL in IBD

Living with a chronic disease such as CD or UC has a profound psychosocial impact on the patients' HRQOL. Moreover, is it possible to measure HRQOL?

“Assessing quality of life in (IBD) patients is difficult, since even the patient themselves do not know how life would be without the disease”.... [6].

Up to 90% of IBD patients are able to live almost normal working and social lives although it has been shown that 54% of patients with CD felt that their disease strained their professional and personal life. Mayberry et al reported that 30% of CD patients actively concealed their disease from employers [93, 94]. Coping with the disease and its psychosocial problems are fundamental concerns for the patients to deal with in everyday life. Sewitch et al suggest that strategies aimed at improving social support can have a positive impact on psychosocial distress and thereby improve health outcome in IBD patients. Their study showed that patients who were more satisfied with social support were less vulnerable to psychosocial distress [95]. In this context the importance of psychosocial support, education and information emerges.

Several instruments, i.e. questionnaires, both generic and disease-specific, have been developed to measure the psychosocial and physical dimensions of life. One of the first

QoL studies in IBD patients, was a study by Bergman et al [96]. They examined the clinical course of 186 CD patients during 10 years and rated the patients' QoL as "Quality of Life I" (good general health) "Quality of Life II" (reduced ability to work) and "Quality of Life III" (unable to work). Eighty-seven per cent of the patients were considered to have a good QoL. In the Crohns' Disease Activity Index (CDAI) which is used to measure the disease activity, the patients rate their general well-being by responding to a 'global' question, ("generally well", "slightly below par", "poor", "very poor", "terrible") [97]. Today the opinion of the patient is given greater credence and almost all clinical trials include measurement of HRQOL and it is accepted as a valid indicator of whether or not a medical treatment is beneficial. In the (medical) industrialized world the term Patient Reported Outcome (PRO) questionnaires is now being used to stress the importance of the patients' point of view, and has become fundamental.

Currently, there are two important, commonly used IBD-specific instruments, the Inflammatory Bowel Disease Questionnaire (IBDQ), which was used in the present thesis in Papers III and IV [98], and the Rating Form of Inflammatory Bowel Disease Patient Concerns (RFIPC) [99]. The RFIPC covers 25 potential issues related to having IBD, and the patient is told 'Patients often develop concerns or worries related to their disease' and is then asked 'Because of your disease how concerned are you...?' and the patient responds on a visual analogue scale.

The IBDQ is a disease-specific questionnaire and was developed at McMaster University, Ontario, Canada in 1989 [98] and has been further refined and validated [100]. The IBDQ has been widely used internationally to assess HRQOL in patients with IBD, and it was originally developed as an interviewer-administered questionnaire to detect therapeutic efficacy in clinical trials [98, 101] and has also been shown to be reliable when used as a self-administered questionnaire [102].

The IBDQ has been shown to have external validity correlated with other variables measuring the same aspects of health (e.g. IBDQ emotional function versus the Psychological General Well-Being index (PGWB)) and using a 'known group comparison' showed that patients in relapse scored significantly lower on IBDQ sum score and dimensional scores [103] than did patients in remission.

A number of authors have used the IBDQ for assessing HRQOL in IBD patients, a selection is presented in Table 1.

Table 1. Overview of different studies with IBDQ

Author	Year publ	N	IBD	IBDQ before treatm	IBDQ after treatm	Active/remission	Other Q	Comments/treatment
Crossectional studies								
Guyatt [98]	1989	23 19	UC CD	140 135		mixture		Developing the IBDQ
Martin [109]	1990	48	non-IBD	213				Normal subjects
Irvine [110]	1995	45	UC	175 205		mixture	SIP	
Irvine [102]	1996	68 31 37	UC + CD exp. CD novice UC+CD	154 163 146		54% active		
Han [111]	1998	28	UC	174		7% active		validity test
Nordin [112]	2002	331 161	UC CD	188 174		12% active 13% active	SF-36 HAD	
Berneklev [106]	2002	262 190 45	UC+ CD	192 179 143		remission mild moderate/severe	SF-36	5 dimensions
Pallis [116]	2002	81	UC	178		15% active		
Hjortswang [113]	2003	300	UC	188			RFIPC SF-36 PGWB	
Higgins [114]	2005	66	UC	179	181			Survey after 1-14 months
Han [115]	2005	111	UC	182		mixture	SF-36 IPQ	
Treatment or intervention studies								
Martin [109]	1990	50	ileocolonic CD	131		active		5ASA/predn
Can study group	1993	258	CD	127		active		Budesonide
Gordon [117]	2001	18	CD	121	140	active		Natalizumab
Borgaonkar [118]	2002	59	UC CD	168	162	40-48% active	QuICCC	Educational booklets
Irvine[101]	1994	280 193 112	CD CD CD	169 183 146	169	mixture CDAI \leq 150 CDAI>150		Ciclosporin
Probert [119]	2003	43	UC	127		active		Infliximab /prednison
Larsson[120]	2003	26	UC + CD	157	158	mixture	HAD VAS SF-36	Group based Education
Oxelmark (Paper III)	2005	29	UC	138	163	active		Apheresis + GCS
HAD Hospital Anxiety and Depression Scale [121], SF-36 Short Form-36 [122], IPQ Illness Perception Questionnaire [123], VAS visual analogue scale, SIP Sickness Impact Profile, CDAI Crohn's disease activity index, QuICCC Quality Index in Crohn's and Colitis [124], GCS Glucocorticosteroids, mixture = patients with both active and inactive disease Exp CD experienced CD								

During the development of the original IBDQ the 32 items were divided into four dimensions, later there was a 36 item version including five dimensions [104]. Other studies have also discussed five dimensions [105, 106], furthermore, there has been a discussion whether to use the total sum score as a measure of HRQOL or to use the different dimensions. Some concerns about the internal structure of the IBDQ have been found and a factor analysis did not confirm the division of the items into the four dimensions [103]. The IBDQ has also been used as a short form questionnaire, reduced to ten items by using regression analysis technique [107] and recently to nine items by using a Rasch analysis [108].

Coping and the concept of Sense of Coherence

In our lives we are more or less constantly being confronted with stressful situations, life stressors, which may threaten or influence our daily life and quality of life. To a routine stimulus the organism can respond more or less automatically but a *stressor* is a stimulus which poses a demand by the internal or external environment to which the individual has no ready-made immediately available and adequate response. The response to a stressor is followed by a state of tension and the way the stress related situation is handled is defined as *coping* [125].

- ❖ Chronic stressors *are beyond anyone's control* and *affects a large number of persons* such as the historical era or culture in which we live, a natural disaster, man-made catastrophes such as war
- ❖ Major life events *affecting one or a few persons* such as: the death of a family member, a divorce, suffering from a disease
- ❖ Everyday problem -missing the bus, feeling lonely, having an argument, having too many responsibilities

Coping is equated with adaptional success, - to say that the person coped with the demands of a particular situation suggests that the demands were successfully overcome and to say a person did not cope suggests ineffectiveness or inadequacy. For a successful coping certain coping strategies are essential [126]

There are different coping strategies, *problem focused strategies* are direct actions such as problem seeking, letting someone else solve the problem, discussing the problems and setting goals and *emotion focused strategies* are used to manage emotion related distress and may involve e.g. crying, worrying, humour or drugs [126, 127]. Patients who do not cope well show maladaptive symptoms such as depression, chronic anxiety or pathological denial, social withdrawal and may adopt a dependent ‘sick’ role [79].

The American-Israeli medical sociologist Antonovsky introduced the salutogenic theory “the sense of coherence” in the late seventies [125], and developed the life orientation questionnaire, the Sense of Coherence scale (SOC). The background of this scale is that he discovered that a group of women he was studying had stayed healthy despite experiences from concentration camps of the Second World War. He raised the salutogenic question why these people still stayed healthy and postulated it was because of the way they viewed their life. He defined health as a continuum between ease and dis-ease rather than a health-disease dichotomy. We all have some degree of health and are continuously during our lifetime moving between the two extremes of ease and dis-ease on the health continuum.

He found three components:

- | | |
|--------------------------|--|
| <i>comprehensibility</i> | -the ability for people to understand what happens around them |
| <i>manageability</i> | -to what extent they are able to manage the situation on their own or through significant others in their social network |
| <i>meaningfulness</i> | -the ability to find meaning in the stressful situation |

The three components formed the concept of sense of coherence and from this he developed the SOC questionnaire [128-131]. Antonovsky describes the sense of coherence as [125]

“A global orientation that expresses the extent to which one has a pervasive, enduring though dynamic feeling of confidence that one’s internal and external environments are predictable and that there is a high probability that things will work out as well as reasonably can be expected.”

How do people manage the lack of control in their lives? What factors are available for making movements towards health on the continuum? The essential factor is a strong feeling of meaningfulness and willingness to cope with the stressor that makes the person capable to use and re-use the resources for the intended purpose. The resources may be of a different nature such as material, knowledge/intelligence, ego identity, coping strategy, social support, ties, commitment, cultural stability, magic, religion/philosophy/art and a preventive health orientation.

Having a strong SOC implies that life is experienced as comprehensible, manageable and meaningful, essential is that it is *not* the same as having a particular coping strategy. What persons' with a strong SOC do is to select the coping strategy that is the *most appropriate* to handle the present stressor e.g. the diagnosis of a chronic illness [128]. The SOC construct reflects a person's capacity to respond to life stressors.

A person's SOC is stabilized by the end of young adulthood and seems to be stable at least for people with an initial high SOC, but tends to increase with age over the whole life span, [130] with temporary fluctuations when serious events occur [128]. To use the SOC scale in clinical practice would be one way of finding patients that are in need of extra support.

Coping in IBD

As in other chronic health problems, the IBD patient needs to cope with the long-term effects of the disease and this makes support and education an important part of therapy [132]. Nordström et al described in a pilot study that those persons who had a high SOC also indicate a high acceptance of ostomy surgery [133]. In patients with UC life stress is associated with both objective (rectal inflammation) and subjective (symptoms) features. Levenstein et al found that short-term stress does not trigger exacerbation in UC, but long-term stress increases the risk of exacerbation over a period of months to years. Further, symptoms associated with irritable bowel syndrome could be cause of exacerbation [134]. Additionally, Smith et al demonstrated improved Mental Health scores (a dimension from the Short Form -36 questionnaire) in IBD patients' receiving a nurse-led counselling package including information and stress management, on a short term basis [135].

Measuring Anxiety

For Freud anxiety was “something felt”, he described anxiety as a specific unpleasant emotional state or condition of the human organism that included experiential, physiological and behavioral components [136]. Trait anxiety (T-Anxiety) can be described as a relatively stable personality trait, and state anxiety (S-Anxiety) as an unpleasant emotional state or condition. An emotional state exists at a given moment in time and at a particular level of intensity and is characterized by subjective feelings of tension, apprehension, nervousness and worry and by activation of the autonomic nervous system. T-Anxiety implies to individual relatively stable differences between people in the disposition to respond to stressful situations with varying amounts of S-Anxiety. If a persons’ T-Anxiety is strong, it is more probable that the individual will experience more intense elevations in S-Anxiety in a threatening situation, as such individuals tend to interpret a wider range of situations as dangerous or threatening. S-Anxiety may vary and fluctuate in intensity over time as a function of the amount of stress that impinges upon the person [137].

The most widely used state and trait anxiety scale is the State Trait Anxiety Inventory (STAI) which is a self-administered questionnaire. The STAI was originally developed by Spielberger et al [138, 139], for measuring anxiety levels in high school and college students and adults. The STAI measures self-reported anxiety in two parts, state and trait. The scale has been used extensively to assess the level of S-Anxiety induced by stressful experimental procedures and by imminent real life stressor such as surgery, dental treatment, job interviews and important school tests. The S-Anxiety scale should always be administered first, followed by the trait-anxiety scale. Since the S-anxiety scale was designed to be sensitive to the conditions under which the test is administered, scores on this scale can be influenced by the emotional climate that may be created if the T-Anxiety scale is given first [139].

Anxiety level in IBD patients has been shown to be related to increased disease activity [110, 140, 141], whereas UC-patients with active disease had a higher S-Anxiety level.

Patient Education

Psychosocial, cultural and social factors have an effect on illness behaviour [142] and there may be a risk that ‘under-informed’ patients avoid seeking help when they need or treat themselves inappropriately. Drossman advocated his personal view in 1986 that “the best adjustment to the disorder (CD) occurs in the patient who accomplishes a degree of

control over his illness through education” to minimize patient anxiety about lack of control [142]. Furthermore, disease related concerns such as having surgery, being treated as different and feeling out of control seem to influence the decision to use unconventional therapies [46]. An IBD team working closely together with the patient, including a specialist nurse who is skilled and competent in the management of IBD patients can influence how well these patients accept and understand their disease [135]. In this aspect an educational intervention for IBD patients would be of value.

It has been shown in the literature that a major part of the IBD patients feel insufficiently informed about their disease [143-146]. Schölmerich et al [144] found that IBD-patients regarded their physician as the most important and most desirable source of information but that the actual level of information was insufficient, 75% of the patients wanted further information. Similar results were found by Probert et al [147] and Jones et al [148] who reported that 80% of the IBD-patients in their study felt insufficiently informed about their disease and discussed that an education programme could enhance a sense of control and skill in coping with the relapses of the diseases and its complications.

On the other hand, worsening QoL has been shown after providing disease-related information, using educational booklets, in IBD-patients [118]. Furthermore, Verma et al [149] found a poor correlation between the level of disease-related patient awareness and QoL scores, therefore they thought that a better patient awareness may increase the patients’ worries and concerns and worsen QoL scores. Other studies have shown that neither information programmes or the use of compact discs have had any influence on QoL [150, 151].

Nevertheless, the more information a patient had about IBD, the better the more positive patient reported adapting to living with the disease [17]. A self-management training programme in IBD-patients maintained quality of life and initially reported greater confidence in being able to cope with their disease compared to controls [152]. Nurse-led counselling has demonstrated a short term improvement in psychosocial morbidity in IBD patients [153] and the use of psychosocial interventions have been discussed [95]. Szigethy et al demonstrated an improvement in combined global psychological and social functioning after treating adolescents with IBD for depression by cognitive-behavioural therapy, (in this study coping skills were assessed, but not on a group basis) [154].

Only a few studies in this area have included group treatment. Larsson et al [120] studied a selected group of IBD-patients with high anxiety level and found no improvement in HRQOL or anxiety levels compared to controls, after participating in a group-based

patient education programme. Although another study, which was uncontrolled, did show that a standardized cognitive-behavioural group treatment was effective in reducing psychological distress in IBD patients [155].

IBD-patients often experience their symptoms as embarrassing or stigmatizing and sometimes find it difficult to speak with others of their disease-associated problems. The use of group therapy was one way to facilitate a supportive context to encourage the participating patients to express their emotions and true feelings concerning the disease and to be able to talk openly with other patients in the same situation.

AIMS OF THIS THESIS

The main aims of this study were to assess the use of and the attitudes towards complementary and alternative therapies, and to determine how different interventions and unconventional treatments influences the IBD patients' quality of life, functional health status, general state of health, anxiety and coping in different clinical situations either having active disease or being in remission. The specific aims were

- to study the usage of and attitudes towards complementary alternative medicine in IBD patients in four different centres in North America and in Europe. *Paper I*
- to assess levels of anxiety, functional health status, general state of health and coping ability in patients with UC undergoing colonoscopic surveillance, before as well as after a surveillance colonoscopy (high CRC risk group), in comparison with controls i.e. patients with extensive UC not yet enrolled in a surveillance programme, or patients with only distal involvement (low CRC risk group).
Paper II
- to evaluate if therapy with a selective leukocyte apheresis device may be associated with an improvement of HRQOL in patients with chronic active, steroid refractory UC during a six weeks trial. Furthermore, to study the relationship between HRQOL and clinical disease activity parameters including endoscopy. *Paper III*
- to develop and evaluate a group-based integrated medical and psychological/psychosocial intervention for IBD-patients in order to assess the patients' coping abilities and their HRQOL in a randomised fashion. *Paper IV*

METHODS

PAPER I

Patients

This was an international multicenter prospective survey regarding the usage and attitudes of complementary and alternative medicine (CAM) in IBD patients. Patients included in this study were attending four IBD centres in North America and Europe. The centres were at Cork University Hospital, National University of Ireland, Center for Health Sciences, University of California, Los Angeles, USA, Karolinska University Hospital, Huddinge, Stockholm, Sweden and the Health Science Centre, University of Manitoba, Winnipeg, Canada.

Consecutive patients with a diagnosis of UC and CD were asked to fill out a self-administered, study specific, confidential questionnaire concerning their use and attitudes towards complementary and alternative medicine. If they agreed to participate they were given the anonymous questionnaire, which they filled out sitting in the waiting room before seeing the physician.

In total, 289 patients were included in the study and the patients had both active and quiescent disease.

Questionnaire

Study specific questionnaire concerning CAM

The patients were asked about age, gender, marital status, employment status, annual income and urban versus rural residence. Moreover the questionnaire asked about type of IBD, disease specific data, health status, and number of visits to a practitioner of conventional medicine, sick days, and days in bed at home or at hospital within the past year. A list of alternative therapies were given and the patients were asked to indicate the alternative medicine they used, for which symptom they sought the alternative therapy, the cost of it, if their physician were aware of it and if the alternative practitioner was licensed.

The patients' perceived health status was assessed by the following question:

On a scale of 1 to 5, how do you consider yourself to be?

Very poor health/incapacitated.....	1
Poor health.....	2
Fair health.....	3
Good health.....	4
Perfect health.....	5

Table 2 displays the most common complementary and alternative medical treatments that were listed in the questionnaire. If the patient answered 'yes' in the first column, they were instructed to fill in the other columns in that row, indicating the answers in the boxes across from the other treatment used. In the spaces at the end of the list the patients were asked to indicate any other forms of treatment they had used in the past year.

Table 2 CAM treatments asked for in the survey

	Please indicate if you have received treatment from any of the disciplines listed <u>in the past year</u> (circling either Yes or No)	Please indicate in writing opposite the appropriate treatment the symptoms or conditions you sought attention for	Please indicate opposite the appropriate treatment the approximate total cost of such treatments <u>in the past year</u> , including fees paid to practitioners of alternative medicine and cost of any treatments or drugs	Please indicate whether your medical practitioner was aware you received these treatments	Please indicate whether the practitioner from whom you received treatment was medically qualified
Acupuncture	Yes / No				
Chiropractic	Yes / No				
Homeopathy	Yes / No				
Herbalism	Yes / No				
Osteopathy	Yes / No				
Relaxation therapy	Yes / No				
Massage	Yes / No				
Spiritual healing	Yes / No				
Commercial weight-loss programmes	Yes / No				
Self-help groups	Yes / No				
Hypnotherapy	Yes / No				
Folk remedies	Yes / No				
Exercise	Yes / No				
Prayer	Yes / No				
Meditation	Yes / No				
Aromatherapy	Yes / No				
Reflexology	Yes / No				
Counseling	Yes / No				

Furthermore, the questionnaire comprised 22 statements concerning the respondents' attitudes towards conventional and alternative medicine. The patients were asked to indicate whether they agreed or did not agree to the item on a five graded Likert scale, e.g.:

"Alternative medicine practitioners are as good as physicians"	strongly agree
	agree
	disagree
	strongly disagree
	don't know

The questionnaire took approximately 20 minutes to complete.

PAPER II

Patients

Patients included in this controlled prospective study evaluating colonoscopic surveillance were selected from the out-patient IBD clinic and the endoscopy unit, at Karolinska University Hospital, Huddinge, Stockholm Sweden. The patients had a confirmed diagnosis of UC and were in clinical remission.

The *study group* (A) comprised 41 patients. All patients had longstanding (>8 years of UC duration), extensive/total UC, in remission, undergoing surveillance

- Group A₁ with premalignant changes in the colorectal mucosa (single biopsies with LGD and/or DNA-aneuploidy) at least at one previous colonoscopy
- Group A₂, without premalignant changes of the colorectal mucosa

The *control group* (B) consisted of 39 patients

- Group B₁ with extensive/total UC who had not yet started surveillance
- Group B₂ with only distal disease (proctitis or proctosigmoiditis) not being planned for surveillance

Procedure

Four different self-administered questionnaires were used to assess functional health status, general state of health, anxiety and coping. A study specific question whether the patients knew the reason for performing the surveillance colonoscopy was addressed to the patients in group A. Disease and demographic data were collected from the patients' medical records. The patients were initially contacted by telephone or directly at the clinic explaining the aims of the study. Written information together with the questionnaires was sent home to the patients together with a pre-addressed and stamped reply envelope.

Patients in group A were instructed to fill out the questionnaires before any colonoscopy preparation was started. They attended the clinic to undergo a planned surveillance colonoscopy. The second set of questionnaires was sent out to the patients a few weeks after the colonoscopy was performed and the patient had received information from the physician about the outcome of colonoscopy, i.e. the results of the biopsies taken. The patients in group B responded to the questionnaires at one occasion. A reminder was sent out twice.

Questionnaires

Sickness Impact Profile

The SIP comprises 136 items (statements) that describe activities associated with everyday living. The items are grouped into 12 multi-item subscales, three of these aggregate into a physical dimension (ambulation, mobility and body care/movement) and four into a psychosocial dimension (social interaction, emotional behaviour, alertness behaviour, communication). The remaining five subscales (sleep and rest, home management, eating, recreation and pastimes and work) are independent scales. The patients' indicate, by placing a check, only those statements that they believe describe their present functional health status. For example, a respondent is instructed to endorse an item such as "I sit during much of the day" only if he sits much of that day because of his health, not if he has a job that entails sitting all day [87].

A sample of statements from each dimension is presented in Table 2. The scores on the SIP scales are expressed as percentages of the total score of possible dysfunction, ranging from 0 to 100%. The lower the score the lesser perceived dysfunction. A score above ten is considered to indicate a clinically significant dysfunction, a score of more than zero and up to ten is considered to indicate a slight dysfunction without clinical importance and a score of zero indicates no dysfunction.

Table 3. Sample of SIP items

Dimension	Category	Statement
Physical	Ambulation	I walk shorter distances or stop to rest often I do not walk at all
	Mobility	I stay within the room I am not going into town
	Body care and Movement	I do not bathe myself at all, but I am bathed by someone else I change positions frequently
Psychosocial	Social interaction	I am going out less to visit people I am doing fewer social activities with groups of people
	Alertness behaviour	I do not keep my attention on any activity for long I have difficulty reasoning and solving problems, for example, making plans, making decisions, learning new things
	Emotional behaviour	I act nervous or restless I laugh or cry suddenly
Independent categories	Communication	I don't write except to sign my name I don't speak clearly when I'm under stress
	Sleep and rest	I sit during much of the day I sleep or nap during the day
	Eating	I am eating much less than usual I am eating special or different food
	Work	I am not working at all I often act irritable toward my work associates
	Home management	I am not doing any of the clothes washing I usually do I am not doing heavy work around the house
	Recreation and pastimes	I am going out for entertainment less I am not doing any of my usual physical recreation or activities

Health Index

The Health Index (HI) was used to measure the general state of health. The HI measures experienced general state of health comprising questions concerning energy, temper, fatigue, loneliness, sleep, vertigo, bowel function, pain, mobility, and one item concerning general health. The index includes ten items with a four graded Likert scale. The response categories are “Very poor”, “Fairly poor”, “Fairly good” and “Very good”.

The higher the score the better the perceived health. Nine of the ten items form two subscales, emotional well being, EWB, (energy, temper, fatigue, and loneliness) and physical well-being, PWB, (sleep, vertigo, bowel function and pain and mobility). The tenth item concerns general health and can be used as a single item. The Health Index has been tested for reliability and validity in different patient populations with satisfactory results [156, 157]. Cronbach's alpha was 0.84 in the present study.

State Trait Anxiety Inventory

The S-Anxiety from the STAI was used to measure anxiety. The S-Anxiety scale consists of 20 items. The patients rate their answers on a four-graded Likert scale, below are two examples of items from the scale:

Not at all Somewhat Moderately Very much so

Item number 12.

I feel nervous..... 1 2 3 4

Item number 20

I feel pleasant..... 1 2 3 4

Each item is given a weighted score of one to four. A rating score of four represents the presence of a high level of anxiety for ten of the items (e.g. item number 12), the remaining ten items represents absence of anxiety (e.g. item number 20), and therefore the scoring weights for those items must be reversed when calculating the total score. The lowest score is 20 and the highest 80, the higher the score the higher the level of perceived anxiety [137, 138, 157]. The STAI has shown to be both reliable and valid [157, 158]. Cronbach's alpha in this study was 0.93 for the S-Anxiety scale.

Sense of Coherence

The SOC measures the overall coping capacity in stressful life situations. The questionnaire comprise 29 items in which the patient is asked to choose a number on a Likert scale graded from 1-7 with the two anchoring responses “Never” and “Very often”. The minimum score is 29 and the maximum score is 203. Thirteen of the item scores must be reversed before calculating the total score. One item from each of the three dimensions is given as examples below:

Manageability

When something unpleasant happened in the past your tendency was...

Comprehensibility

When you face a difficult problem, the choice of a solution is...



Meaningfulness

When you think about your life, you very often...



Patients identified as having a high SOC better cope with the effects of life stressors, and tend to perceive demands as challenges, worthy of engagement, rather than as threats or stressors. Antonovsky recommended the SOC concept to be examined without dividing the sum of the item values into high or low SOC, he never expressed the level of a normal SOC [128]. However, several studies report divisions into high, low and moderate SOC, but no general consensus has been stated [130]. Langius suggested a score below 140 as “Low SOC” a score between 141-165 as “medium SOC” and above 165 as “high SOC” [159]. The SOC has been validated in several Swedish population groups, and shown to be highly reliable and valid [130, 160]. Coefficient Cronbach’s alpha was 0.87 in the present this study.

Ethical Considerations

Ethical approval for the study was obtained from the local Ethic’s Committee Karolinska Institutet, and the patients gave their informed consent to participate.

PAPER III

Patients

Twenty-nine patients attending five different IBD centres in Sweden and Germany were included in this prospective, open-labeled study. The different centres were the IBD-unit, Sophiahemmet, Stockholm, Sweden, and in Germany: the Campus Virchow, University Clinic Charité Berlin, the Medical Clinic, University Clinic, Leipzig, the Department of Internal Medicine, University Clinic, Kiel and the Department of Internal Medicine Ev. Krankenhaus-Kalk, Cologne.

Eligible for inclusion were patients aged between 18-75 years with a steroid refractory UC defined as having had at least one previous attack of UC with an unsuccessful attempt to taper GCS (i.e. a minimum total dose of 400 mg prednisolone, or equivalent, within the last four weeks; and with the doses of steroid unchanged two weeks prior to study start). Immunomodulators were kept at a constant dose three months prior to study start and 5-aminosalicylates were kept at a constant dose four weeks prior to study start and stable throughout the study. The patients were eligible only if they had filled in the correct version of the IBDQ.

Procedure

The patients were contacted directly at the clinic and consecutively included. The patients were treated with one selective leukocyte apheresis treatment once weekly for five consecutive weeks. The Adacolumn apheresis system was used and a total amount of 1800 ml of blood was typically filtered during 60 minutes, using a flow rate of 30 mL per minute.

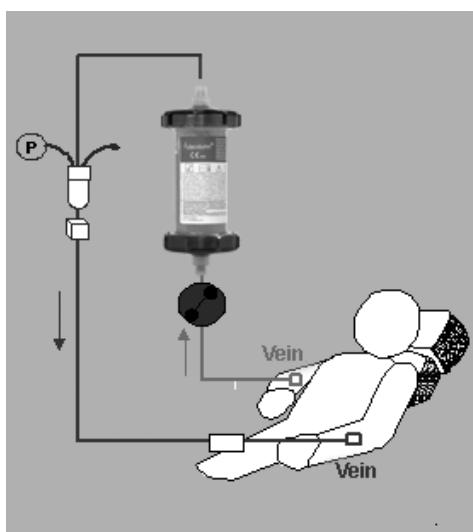


Figure 1. Apheresis procedure

The apheresis procedure is conveniently administered at an out-patient clinic with especially skilled nurses. The patient lies in a recumbent position during the procedure and the blood is led from a vein in one arm via a pump through the column and then back a vein in the other arm. An anticoagulant (Heparin) is used to avoid clotting the system and lines. The procedure is presented in Figure 1.

HRQOL was measured by the IBDQ before treatment start (week 1) during (week 3) and after treatment (week 6). The patients filled out the questionnaire before any other study related procedures were started. Colonoscopy was performed at study start and at the end of the study.

The clinical activity was measured by the Clinical Activity Index (CAI), which is the sum score of seven items comprising the investigators' global assessment of symptomatic state, the patients' rating of abdominal pain/cramps, weekly stool frequency and presence of blood in stools [161]. The score also includes temperature due to colitis, extraintestinal manifestations, and presence of certain laboratory findings. Clinical remission was defined as CAI-score of < 4 and a clinical response as a drop of CAI > 3.

Questionnaire

The Inflammatory Bowel Disease Questionnaire

The IBDQ covers a broad perspective of health, evaluating general activities of daily living, specific intestinal function such as bowel habits and abdominal pain, as well as social performance, personal interactions and emotional status [98]. The scale has 32 items grouped into four dimensions, bowel symptoms, (10 items measuring bowel movements and abdominal pain), systemic symptoms (5 items: fatigue and sleep), emotional factors (12 items: irritation, depression and aggression) and social factors (5 items: ability to work and participate in social activities). The patient responds on a 7-graded Likert scale ranging from "7" representing 'best function' and "1" representing 'worst function'. The dimensional scores are the sum score of the items included in each dimension. Total scores range from 32 to 224 with a higher score indicating a better quality of life there are no reversed items in the questionnaire. The internal consistency, the coefficient Cronbach's alpha, was 0.91 for the total IBDQ.

Examples of items are

Bowel dimension:

How much of the time during the last 2 weeks have your bowel movements been loose?
Please choose an option from

Social dimension

How often during the last 2 weeks have you been unable to attend school or do your work because of your bowel problem? Please choose an option from

Emotional dimension

How often during the last 2 weeks have you been troubled because of fear of not finding washroom (bathroom, toilet)? Please choose an option from

1. ALL OF THE TIME
2. MOST OF THE TIME
3. A GOOD BIT OF THE TIME
4. SOME OF THE TIME
5. A LITTLE OF THE TIME
6. HARDLY ANY OF THE TIME
7. NONE OF THE TIME

Systemic dimension

How much energy have you had during the last 2 weeks? Please choose an option from

1. NO ENERGY AT ALL
2. VERY LITTLE ENERGY
3. A LITTLE ENERGY
4. SOME ENERGY
5. A MODERATE AMOUNT OF ENERGY
6. A LOT OF ENERGY
7. FULL OF ENERGY

Ethical Considerations

Ethical approval for the study was obtained from the local Ethic's Committee Karolinska Institutet, and from each hospital's local IRB. Informed consent was obtained from each patient.

PAPER IV

Patients

Patients from the IBD-outpatient clinic at Karolinska University Hospital, Huddinge, Stockholm, Sweden were invited to participate in this group based intervention study. Patients were eligible if they had a diagnosis of UC or CD, had had at least one serious flare and had been at least once treated with glucocorticosteroids (GCS) orally or intravenously. All patients were in remission or had only mild disease activity at inclusion, with no high dose steroid treatment, (less than 10 mg prednisolone or equivalent) and had had no previous bowel surgery. The patients were initially contacted directly at the clinic or by telephone and if they gave informed consent they were

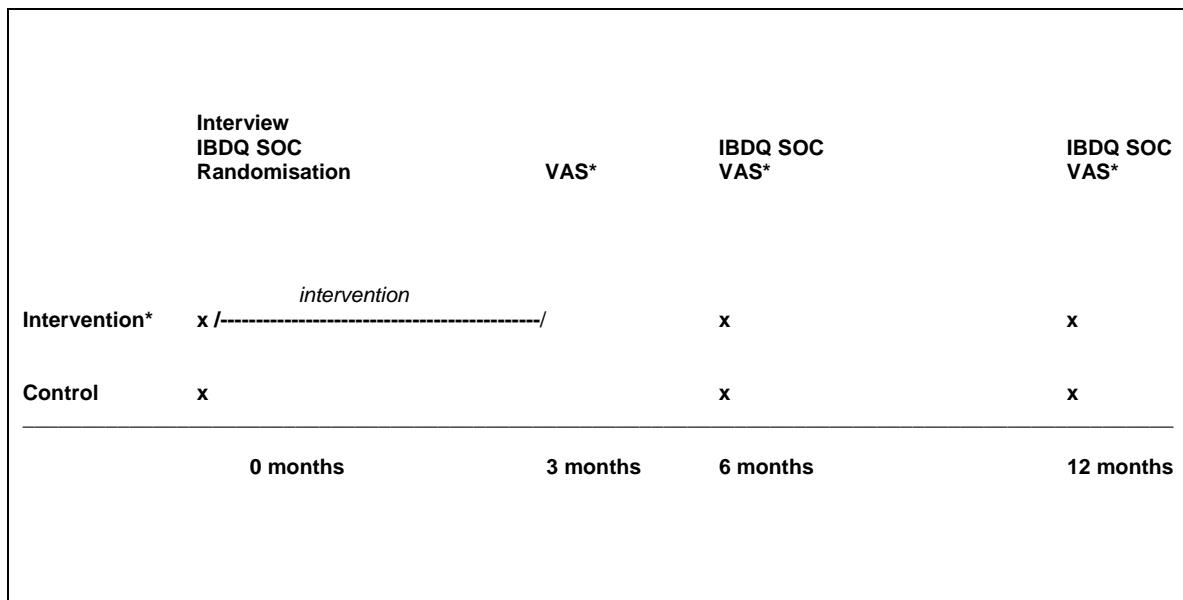
scheduled for semi-structured interviews and initial questionnaires procedures. Patients were then randomized to either intervention group or control group.

Questionnaires

HRQOL was measured by the IBDQ, and coping ability with the SOC, which are described earlier (Papers III and II). All participants filled out the questionnaires at 0, 6 and 12 months. A VAS was used to evaluate the intervention at immediately after the intervention, at six months and at 12 months. The first set of questionnaires was filled out at the clinic after the interview, the following two sets of questionnaires were sent home to the patients together with a preaddressed and stamped reply envelope. A reminder was sent out twice to those patients who did not respond at first. The patients in the control group received conventional “on demand” medical and psychosocial/psychological treatment during the study period and filled out the questionnaires at corresponding times. Cronbach’s alpha was 0.95 for the IBDQ and 0.90 for the SOC in this study.

The intervention programme comprised nine different sessions (once weekly) during approximately three months with lectures alternating with group therapy. The lectures comprised IBD-related information about the aetiology, diagnostic procedures, medical and surgical treatment and research in IBD, anatomy and physiology of the bowel and endoscopy procedures. The significance of diet and food intake was also discussed. The lectures were given by medical gastroenterologists, a specialist nurse (LO), a colorectal surgeons and dieticians. The group therapy was conducted by the medical social worker (AM) who also is a psychotherapist. During the group sessions the following topics were discussed: consequences of the disease, psychological reactions, receiving information about a chronic diagnosis, coping, stress management – positive and negative stress, disease and self-image. The study plan is outlined in Figure 2.

Figure 2. Study plan of the group-based intervention in IBD patients



*The patients in the intervention group evaluated the intervention on a VAS at 3, 6 and 12 months. IBDQ Inflammatory Bowel Disease Questionnaire, SOC Sense of Coherence Scale, VAS Visual Analogue Scale

Ethical Considerations

Ethical approval for the study was obtained from the local Ethic's Committee Karolinska Institutet, and all patients gave informed consent to participate.

STATISTICAL ANALYSES

Quantitative methods

The data in Paper I, was analyzed using the Statistical Analysis System (SAS) logistic regression analysis, χ^2 , and *t*-test scores. A univariate analysis was used for the 10 demographic items and a multivariate logistic regression analysis was used to model any alternative therapy use. As all scales in Papers II, III and IV did not fulfill the assumption of normal distribution, non-parametric methods were used. For comparison of scores between study groups and control groups the Mann-Whitney U-test was used. For group comparisons before and after intervention the Wilcoxon Signed Rank Test was used. P-values lower than 0.05 were considered statistically significant. However, in Paper III, P-values lower than 0.01 were considered statistical significant in order to compensate for multiple comparisons.

Internal consistency reliability was calculated by the means of Cronbach's alpha coefficient. This is a measure of how strongly the items within a scale correlate with each other, and is an indicative of the extent to which the items reflect the same, underlying phenomenon. A value above 0.7 indicates a high level of internal consistency.

A qualitative approach - Content analysis

Content analysis is a systematic qualitative research method of handling qualitative material. The method has a long history back in Scandinavia [162]. Initially researchers used the method as either a quantitative or a qualitative method [163], but later it was mainly used as a quantitative research method i.e. text data was coded into categories and then analysed statistically, sometimes referred to quantitative analysis of qualitative data. In recent years content analysis has been used widely in health studies. Researchers regard content analysis as a flexible method for analysing text data [164]. Text data may be in verbal, print or electronic format and may have been obtained from responses to open-ended questions, interviews, focus groups, observations or print media [165].

The basic coding process in content analysis is to organize large quantities of text into much fewer content categories [166]. Categories directly express themselves in the text or are derived from the text through analysis. The researcher starts with reading through the text several times to achieve immersion and obtain a sense of the whole [167]. The text is then read word by word to derive codes by highlighting the exact words from the text to capture key words or concepts -an inductive category development. Codes are then sorted into the different categories which have emerged from the text [168]. The way of presenting the results is either to report the incidence of codes in a descriptive way, *conventional content analysis*, or by quantifying certain words or content in a text using a *summative content analysis*. In the summative content analysis the keywords are identified before and during the analysis. Another approach is the *directed content analysis*, where the data is collected by targeted questions about predetermined categories which the researcher has obtained from an existing theory or prior research [168].

In Study IV we used a conventional content analysis for the responses to the open-ended questions.

RESULTS AND COMMENTS

A summary of the patients included in the four studies in this thesis is presented in Table 4. Two of the studies were controlled (Papers II and IV). Patients with both UC and CD were studied in Papers I and IV and Papers II and III comprised only UC patients. The SOC was used in Papers II and IV and the IBDQ was used in Papers III and IV.

Table 4. Summary of the studies in this thesis

	Paper I	Paper II	Paper III	Paper IV
Number of patients	289	80	29	44
UC (N)	146	80	29	17
CD (N)	143			27
Study group / Control group	Uncontrolled	41 / 39 *	Uncontrolled	24 / 20 *
Disease activity	Mixture	Remission	Active, steroid resistant	Remission or low activity
Intervention	Complementary or alternative medicine	Surveillance colonoscopy	Selective leukocyte apheresis	Group based education
Questionnaire	Study specific questionnaire	SIP SOC HI STAI	IBDQ	IBDQ SOC

SIP Sickness Impact Profile, SOC Sense of Coherence, HI Health Index, STAI State Trait Anxiety Index, IBDQ Inflammatory Bowel Disease Questionnaire.

* N of patients

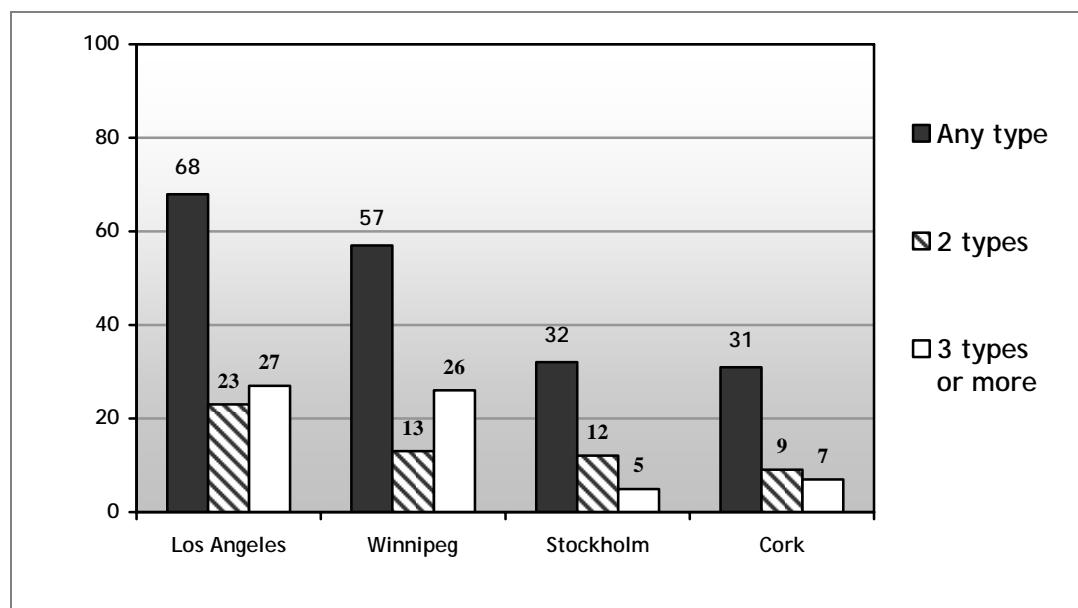
PAPER I

A total of 313 questionnaires were distributed and there were 289 patients who responded, a response rate of 92%. Fifty-one percent of the patient had the diagnosis of CD and 49% of the patients had UC, 134 of the patients were female. The patients had both active and quiescent disease.

CAM questionnaire

Fifty-one percent of the included IBD patients had used some kind of CAM. The usage was greater in the North American sites than in the European sites, 68% of the patients in Los Angeles had used any type of CAM, 57% in Winnipeg, compared to 32% in Stockholm and 31% in Cork. Twenty-seven percent of the US patients and 26% of the Canadian patients had used three or more types of alternative therapies, while for the Irish and Swedish patients the usage of three or more types was 7% and 5% respectively, Figure 3.

Figure 3. The use of any type(s) of alternative medicine by study centres (%).



Seventy-nine per cent (range 77-81%) of the patients considered their health as fair or good, 18% (range 14-21%) perceived their health as very ill or poor. No patient in North America perceived their health as perfect, but 7% of the Swedish patients and 2% of the Irish patients did. Steroids were used by 31% (range 21-37%) of the patients, 60% (range 37-67%) were treated by 5-ASA and 27% (range 12-26%) had immunomodulating therapy.

Exercise was the most commonly used CAM (27%) followed by prayer (18%) and counseling (13%). Massage was used by 11% of the patients, chiropractic services by 11% and relaxation was used by 10%. Seven percent used acupuncture, 7% used homeopathy and 5% used herbal medicine. Exercise and prayer was most frequent in Los Angeles (41% and 25% respectively). There were some cultural differences among the centres studied, e.g. herbalism, self-help groups, spiritual healing, hypnotherapy,

reflexology, osteopathy, folk remedies and aromatherapy were not used at all by the IBD patients at the Swedish centre. Self-help groups and reflexology were most common at the Irish centre. Homeopathy was used the most in Los Angeles and Stockholm.

Reasons for the use of CAM

The reasons for the use of CAM therapies was that the IBD patients'

- ❖ were not satisfied with conventional medicine
- ❖ viewed hospitals as dangerous places
- ❖ thought that CAM practitioners should have a role within the hospitals
- ❖ felt that their medical situation was hopeless

Being single, being a Los Angeles patient, and having an increased number of visits to the physician in the past year were predictive factors for using any form of CAM. Increased degree of ill health and increased number of physician visits were predictive of the use of chiropractic and counseling treatment. Neither patient age, gender, disease diagnosis nor disease duration predicted the use of any type of CAM. The respondents were more likely to use CAM if they were single, lived in an urban area and had a higher income.

Attitudes towards CAM

Patients from Cork were more likely to respond positively toward CAM use and negatively to conventional medicine. Interestingly, the Irish respondents were the ones who had used CAM the least. Those patients that were most satisfied with the conventional treatment were less likely to seek a CAM therapy. Patients in our study responded, in general, that they would consult their conventional physician before they sought an alternative practitioner. Patients who had little faith in CAM would not see a complementary or alternative practitioner, on the other hand if the patient did view the hospitals as a dangerous places, they would more likely use alternative therapies. Particularly the patients who had chosen to use acupuncture considered hospitals as dangerous places.

Comments

It may be possible that the patients in our study were less likely to use CAM as they were all attending special IBD centres and we may therefore have underestimated the use of alternative therapies.

PAPER II

Ninety-two patients were invited to participate in the study, 80 patients (87% response rate) were included, all with confirmed diagnosis of UC in remission. The study group (A) comprised 41 patients with longstanding extensive/total UC (>8 years) participating in a surveillance programme, and who at a previous endoscopy had had premalignant changes in the mucosa (A₁, n=18) or who still had not developed such mucosal changes (A₂, n=23). The control group (B) consisted of 39 patients with either extensive/total UC who had not yet started surveillance (B₁, n=20) or patients with only distal colitis, i.e. proctitis or sigmoiditis (B₂, n=19).

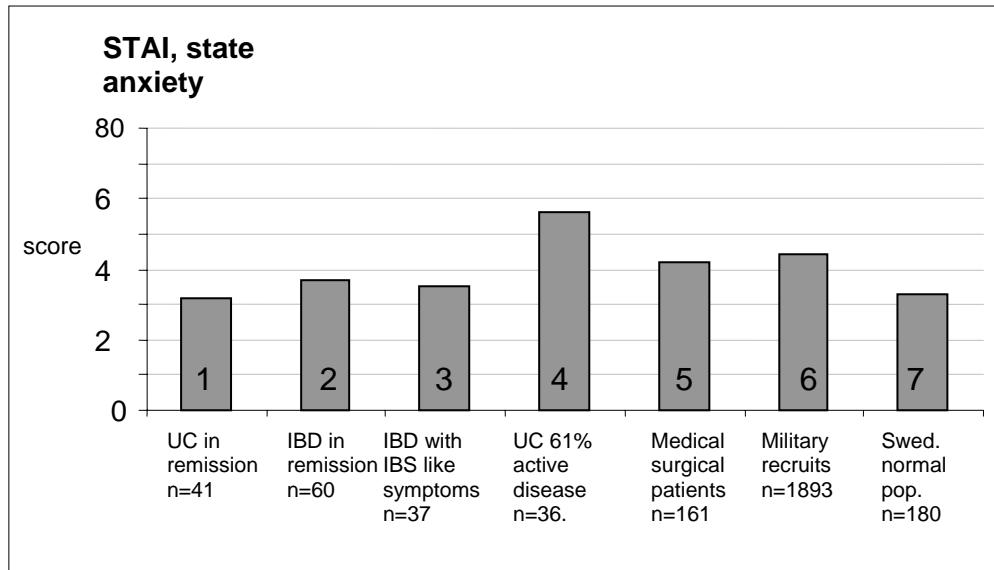
There were 22 female and 19 male in group A, median age was 46.0 (range 28-76) years and median disease duration was 21.0 years (range 9-49). In Group B there were 20 females and 19 males, median age was 30.8 (range 23-83) years, median disease duration was 9.0 years (range 1-18).

State Trait Anxiety Index

The overall anxiety levels in the patients studied were low as measured by the STAI, S-Anxiety scale. The results showed a mean S-Anxiety score of 31.9 (range 20-51) before the colonoscopy in group A compared to 31.6 (range 20-55) after the colonoscopy (NS) and there were no statistically differences compared to group B 31.4 (range 20-57). The results of the S-Anxiety indicate that UC-patients in remission regardless of extent of disease or risk for CRC are in a stable psychological condition which was further elucidated by the SOC scores.

In Figure 4 the patients in group A are compared with other groups of IBD patients; IBD-patients in remission [140], IBD patients with IBS-like symptoms [169] and UC patients where 61% had active disease [141]. A group of general medical and surgical patients and a group of military recruits from the US are also included in the figure [139] and finally a Swedish norm population group [157].

Figure 4. Mean S-Anxiety scores in different IBD groups, US military recruits and a Swedish population norm group.



Filled bars representing, from the left:

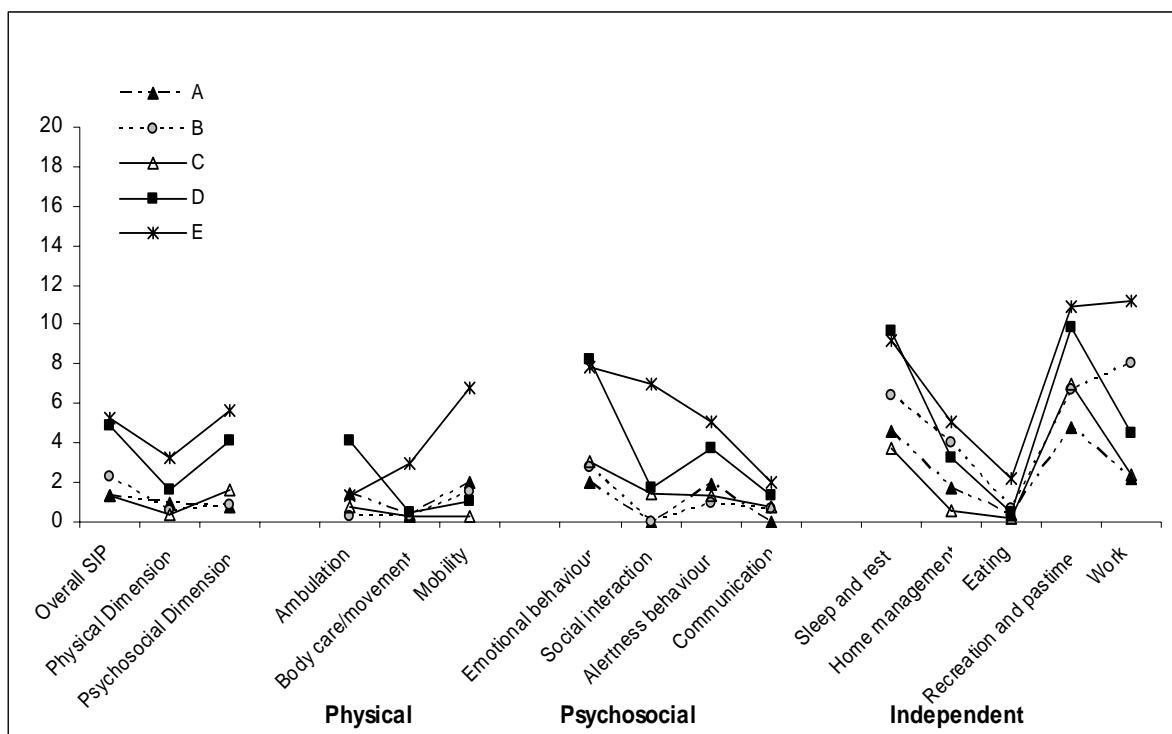
1. UC-patients with longstanding extensive UC in remission, Paper II [170]
2. IBD-patients in remission [140]
3. IBD patients with IBS-like symptoms [169]
4. UC patients with active disease (61%) [141]
5. General medical or surgical patients [139]
6. US military recruits [139]
7. Swedish normal population [157]

Sickness Impact Profile

The results of the overall mean SIP was 1.3 (range 0-10.1) in group A and mean 2.3 (range 0-18.4) in group B. The mean scores in the physical dimension was 1.0 (range 0-11.4) in group A, and the mean scores 1.3 (range 0-5.3) in group B and 0.8 (range 0-20.5) and 0.9 (range 0-6.0) in the psychosocial dimension, respectively. There were no statistically significant differences between the studied groups or in group A before or after the colonoscopy.

The results of the mean SIP scores are displayed in Figure 5. For comparison the mean scores of a group of UC out-patients with active disease are included in the figure. Additionally, a group of patients (n=32) suffering from another chronic disease, asthma, [171] and a Swedish reference group (n=145) [172] are included in the Figure 5 for further comparisons.

Figure 5. Sickness Impact Profile. Results from Paper II compared to other studies



A. UC patients in surveillance, Paper II [170]

B. Control group, Paper II [170]

C. Swedish Reference group, n=145 [172]

D. Patients with asthma, n=32 [171]

E. UC patients mixture of disease activity, n=63 [173]

Health Index

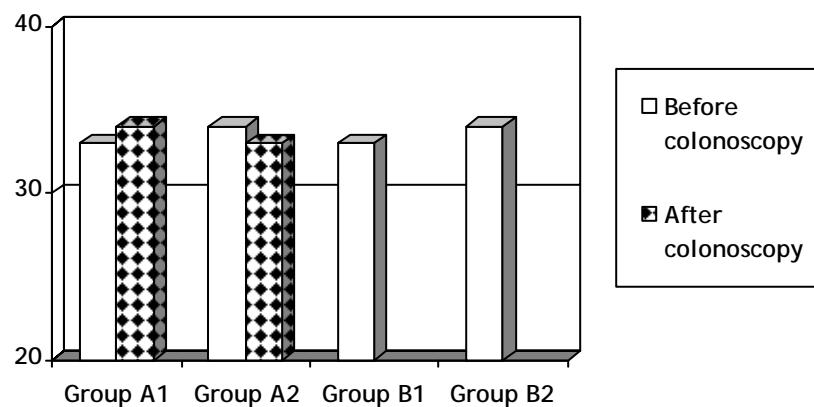
The mean score of the overall HI was 33.1 (range 22-40) in the group A and 32.3 (range 19-38) in group B. The mean EWB score was 12.6 (range 9-16) and 12.6 (range 8-16) respectively. The mean PWB score was 17.2 (range 10-20) and 16.5 (range 0-20) in group A and B respectively and there were no statistically significant differences in any of the groups studied. The HI was significantly correlated the SIP. Furthermore, the PWB was well correlated with the SIP and the EWB was well correlated to the S-Anxiety, Table 5.

The different study groups (A_1 and A_2) showed no significantly differences in HI before or after the surveillance colonoscopy, Figure 6.

Table 5. Spearman rank correlation between different questionnaires/dimensions

Questionnaire	r	P
SIP vs HI	0.52	<0.0001
SIP vs PWB	0.45	<0.0001
S-Anxiety vs EWB	0.61	<0.0001
SOC vs S-Anxiety	0.58	<0.0001

SIP Sickness Impact Profile, HI Health Index, PWB Physical well-being, S-Anxiety state anxiety (STAI), EWB Emotional well-being, SOC Sense of Coherence.

Figure 6. Health Index in UC patients in surveillance compared to controls

A1 Extensive UC with premalignant changes in the colorectal mucosa, in surveillance

A2 Extensive UC without premalignant changes in the colorectal mucosa, in surveillance

B1 Extensive UC not yet started surveillance

B2 Distal UC, proctitis or proctosigmoiditis

Sense of Coherence

The mean SOC score was 158.4 (range 124-186) in the group A and the patients in group B averaged 157.4 (range 126-203). There were no statistically significant differences before or after the colonoscopy in the group A. Furthermore, there was a significant correlation between the SOC and the S-Anxiety, Table 5.

Comments

Patients in groups A₁ and A₂ were analysed together. We had assumed that patients already participating in surveillance, in particular those having previous dysplasia findings (A₁) at an earlier endoscopy, would have an increased anxiety level, but there were no statistically significant differences in any of the questionnaires used between the two groups.

The UC patient group with active disease, included as comparison in Figure 3, demonstrated a higher mean SIP score than our studied groups [173], although the proportion of patients in relapse was not presented. We could see no impairment of functional health status in our study group, presumably because all patients were in remission.

PAPER III

Thirty-four patients with steroid resistant UC were eligible for participation, and 29 remained for final analysis. There were nine patients from Stockholm, six from Cologne, eight from Berlin, three from Leipzig and three from Kiel. There were eight females and 21 males in the study and the mean age was 38.3 (range 20-72) years. The mean disease duration was 7.5 (range 0.8-19.5) years. Twenty of the patients had extensive UC, seven had left-sided disease and two of the patients had proctosigmoiditis. Three patients had chronic continuous disease activity, 23 had gone through two or more episodes of active disease during the last 12 months and three of the patients experienced their first flare.

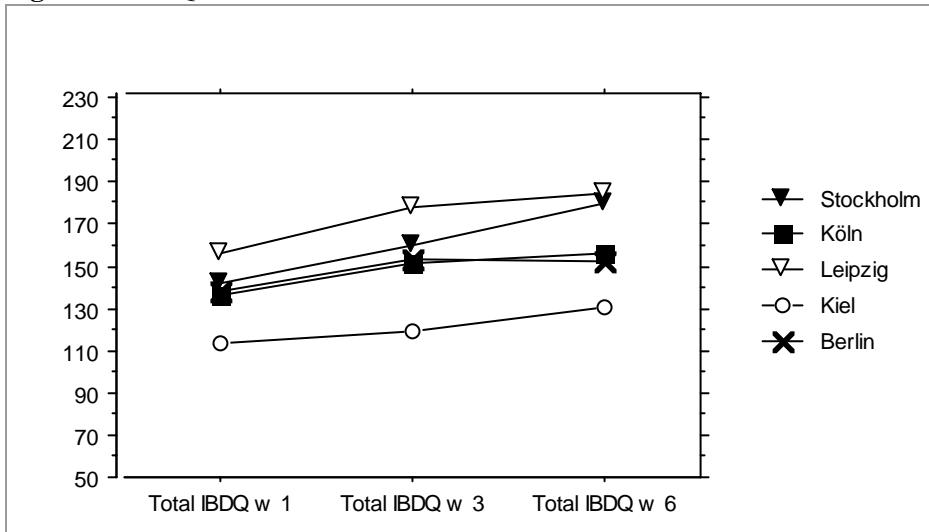
Inflammatory Bowel Disease Questionnaire

The mean IBDQ increased significantly from 138.4 (range 97-208) at study start, to 154.1 (range 95-214) at week 3 and to a score of 162.8 (range 117-216) at week 6.

A majority (n=25, 86%) of the patients showed an increase in total IBDQ scores. Eleven patients had a clinical response to treatment, and these patients had an average increase of total IBDQ of 43.4. Eighteen patients were defined as clinical non-responders and had an average increase of 12.9 in total mean IBDQ. Five of the non responders had an average increase of 51.4 points (range 35-71) in total IBDQ. The systemic dimension score improved with 20% from the first visit (week 1) to the last visit (week 6) ($P = 0.0003$). The other three dimensions, bowel, systemic and emotional, separately showed

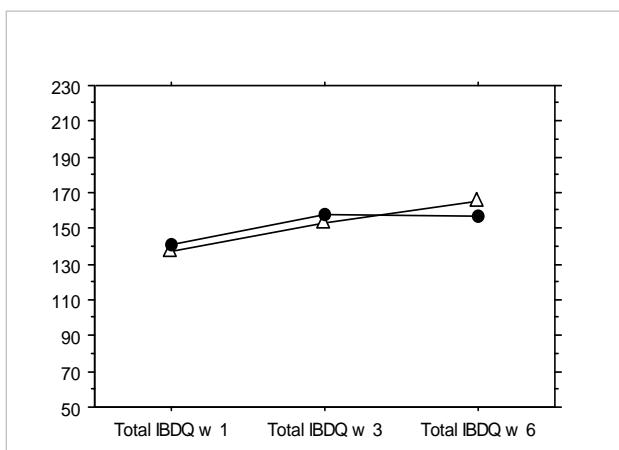
significant improvements from week 1 to week 6. Figure 7 shows the results of the IBDQ from the different participating centres. There were no gender differences, Figure 8.

Figure 7. IBDQ, results from the four different centres.



IBDQ, Inflammatory Bowel Disease Questionnaire, w week

Figure 8. IBDQ and gender



IBDQ, Inflammatory Bowel Disease Questionnaire
Women are represented by ●, and men by △

The clinical parameters improved over time: there was a tendency of decrease in the mean CAI score, from 6.8 (range 4-11) at study start to 5.7 (range 0-14) at week 6 (NS). Two of the patients improved the CAI spontaneously from screening visit to week 1 before treatment. Additionally, there was a statistically significant endoscopic improvement and the oral GCS was tapered from 28.7 mg (range 12.5-80.0) to 19.2 mg (range 2.5-60.0) P<0.001.

A significant correlation ($P<0.001$) was found between low CAI and high IBDQ at week 6, however, there was no correlation at week 1 between low IBDQ and high CAI.

A similar result was seen when correlating a specific item from the CAI with items in the IBDQ; a statistically significant correlation was seen between the clinical parameter “abdominal pain/cramps” and the IBDQ bowel dimension items number 9 and number 13 at week 6, Table 6.

Table 6. Patients' rating of abdominal pain and cramps from the CAI score in correlation with Inflammatory Bowel Disease Questionnaire, item number 9 and number 13

	Week 1		Week 3		Week 6	
	r	P	r	P	r	P
Abdominal Pain vs Item no 9	0.12	>0.20	0.33	0.11	0.54	0.009
Abdominal Pain vs Item no 13	0.24	>0.20	0.32	0.11	0.60	0.003

IBDQ item # 9: "How often during the last weeks have you been troubled by cramps in your abdomen?"

Item # 13 "How often during the last two weeks have you been troubled by pain in the abdomen?"
Spearman rank correlation

Comments

Other studies have shown that a low level of disease activity is associated with better HRQOL [110, 115], yet five of the patients defined as clinical non responders in our study, had an increase in total mean IBDQ. The reason for this may be either a placebo effect or the tapering of GCS.

As far as we know this is the first study, which evaluates HRQOL in UC patients treated with leukocyte apheresis. Randomized controlled trials are now under evaluation in both UC and CD. Recently, Sawada et al showed efficacy of apheresis treatment in UC in a small controlled study [39] using the Cellsorba apheresis device.

PAPER IV

Seventy-two patients were invited to participate in the study. A total of 44 patients were finally included (response rate of 61%), 24 of the patients were randomised to the intervention group and 20 to the control group. Eleven patients in the intervention group had a diagnosis of UC and 13 had CD. In the control group there were six patients with

UC and 14 patients with the diagnosis of CD. The mean IBD duration was 4.6 (range 1-11) years in the intervention group and 5.2 (1-10) years in the control group. The mean age was 36.3 (range 18-71) years and 38.5 (21-59) years respectively. The patients were all in remission or had low disease activity.

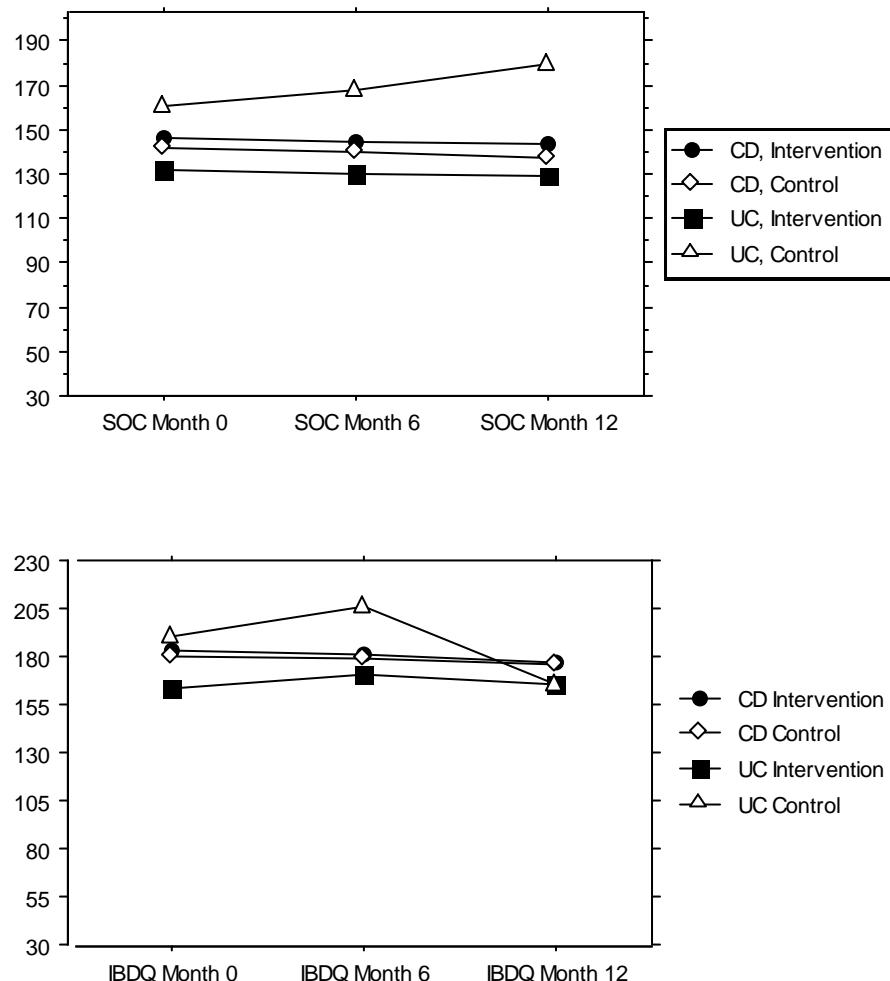
IBDQ and SOC

The mean IBDQ score showed no significant differences before the intervention, 173.9 (range 103-214), or after the intervention at month 6, 175.7 (range 97-221), or at month 12, 171.8 (range 103-202) or when comparing the intervention group, 171.8 (range 103-202) and the control group 173.7 (range 128-215) at month 12.

The mean SOC-score was 139.4 (range 75-170) for the intervention group and 147.6 (range 106-186) for the control group at baseline (NS). There were no statistically significant differences between the groups neither at baseline, nor at 6 or at 12 months. When separately studying the intervention group there were no statistically significant differences when comparing baseline SOC score (139.4) with month 6 (137.6 range 91-167) or with month 12 (137.3, range 76-172) respectively. Neither were there any statistically significant differences regarding the control group. Eleven of the patients in the intervention group and seven in the control group had a low SOC at study start.

The mean SOC score did not indicate any statistically significant improvement when separating patients with UC from patients with CD in the intervention group. However, when specifically studying the different diseases the UC patients in the control group had a tendency to score higher in SOC than the patients in the intervention group (NS). The IBDQ scores in UC patients in the control group had a higher score at month 0 and month 6 (NS) but it decreased at month 12. CD patients had similar IBDQ and SOC scores, both control group and intervention group. The lowest mean SOC and IBDQ scores were seen for UC patients in the intervention group. Figure 9.

Figure 9. SOC and IBDQ mean scores in patients with CD or UC by intervention group and control group.



SOC, Sense of Coherence, IBDQ, Inflammatory Bowel Disease Questionnaire,
UC, ulcerative colitis, CD, Crohn's disease

Visual Analogue Scale and patient comments

The mean VAS score was 11 mm (range 3-33 mm) for the medical lecture, 16 (2-51) mm for the surgical lecture, 19 (3-73) mm for the dietary lecture and 11 (2-48) mm for the group therapy at 3 months. At the follow-up at 6 months the VAS scores were 21 (4-65) mm, 16 (0-47) mm, 37 (4-96) mm and 16 (3-49) mm respectively, and at 12 months: 20 (5-65) mm, 16 (2-65) mm, 32 (2-98) mm and 9 (1-22) mm respectively.

When categorizing the patients' comments from the open ended question five different categories were found:

- ⊕ Meeting other patients in the same situation
- ⊕ Receiving information about the disease
- ⊕ Positive comments of the intervention
- ⊕ Negative comments of the intervention
- ⊕ Other

At month three there were six comments in the category “Meeting other patients in the same situation” and at month 12 there were seven comments, in the same category. “Receiving information about the disease” generated eight comments at month 3 and two after one year. There were eight “Positive comments of the intervention” at three months and five at month 12. The category “Negative comments of the intervention” comprised five comments at month three. There were no negative comments after one year. In total 16 of the patients gave comments at month three and 11 of them commented the intervention month 12. Some of the patients gave more than one comment.

Group Therapy

The participants showed great interest in discussing the different themes, and were both interested in hearing from each other as well as in giving each other feedback. The patients had found it hard to really understand the first information of the diagnosis at the disease onset, the reaction had been gradual. The difficulties of coping with the IBD-diagnosis was discussed, some participants found it easier to cope and accept the diagnosis, medical treatments and interventions than others. Overall the atmosphere developed into a more and more open and supporting group-climate. At conclusion, all patients declared their appreciation of being given the opportunity to meet others in the same situation, to be able to express their emotions and receive feedback which was confirmed by the results from the VAS and the content analysis.

Comments

Education programmes are time consuming to organize, difficult to identify the right patients, finding appropriate times for the sessions. Nowadays many patients have problems to take time off from work, especially as they might already have had time-loss from work due to their disease. A suggestion was raised at the first intervention as to whether other family members should/could attend the sessions. It was decided not to include any relatives considering the delicate and personal issues that would be discussed.

One possibility would have been to have had a separate session with general disease-related information for relatives.

GENERAL DISCUSSION

The need/use of CAM may reflect the disappointment experienced with conventional medicine in IBD patients. Remission is only achieved in 30% of the patients by the use of conventional medicine and in a substantial number of patients the medication has no effect at all.

The most consistent criticism of CAM by conventional practitioners is the lack of scientifically conducted research and randomized controlled trials (RCT), and some physician judges CAM as simply a placebo. On the other hand the appropriateness of RCTs for evaluating CAM is under discussion. CAM practitioners believe that the interaction between the body and mind is vital to achieve a desired treatment outcome, therefore a blinding procedure would be seen as blunting the true effect that could have been achieved without blinding. Additionally, it may be difficult to decide what is truly an alternative therapy compared to a lifestyle approach, e.g. if prayer and exercise CAM therapies have been discussed. Nevertheless, since we conducted our study some RCTs have now been performed concerning CAM treatment [50].

Certainly IBD patients are even more aware of alternative therapies today, as there is definitely more information available now than in 1997 when our study was performed. Several of the CAMs listed in our study, that were used in the US were not used at all in the Swedish centre, and some were not used in Ireland or Canada. Consequently the usage of different CAMs may have changed today in Sweden or in the other studied countries. A new survey would be of interest to perform.

One of the most encouraging findings in Paper II was the result of the STAI, measuring S-Anxiety, showing that UC-patients in remission did not experience anxiety in association to the cancer surveillance procedures. We selected the STAI instrument as this questionnaire has been extensively used for measuring anxiety levels in stressful situations, and we wanted to scrutinize this particular situation, i.e. when the patient is confronted with the potential *cancer* risk and the necessity of undergoing repeated colonoscopy procedures.

However, pharmacological treatment of CRC in longstanding UC seems to be of increasing importance. Significantly reduced CRC risk has been reported in UC patients using 1.2 grams of 5-aminosalicylates per day compared to patients taking less or no 5-ASA. Preliminary data suggests that 5-ASA may be of greater benefit than

sulphasalazine [174]. There is no guarantee of effective cancer prevention if the patient does not comply with its use, however, the realization of the chemo-preventive role of 5-ASAs might enhance patient compliance [175]. Folic acid and ursodeoxycholic acid have also been suggested to decrease the risk of CRC [176, 177]. This may open up for chemo-prevention of CRC and possibly make endoscopic surveillance redundant in the future.

Furthermore, all patients in the study group were well aware of the CRC risk that comes with longstanding disease, and they understood the reason for going through the colonoscopies. Inadequate patient information may account for poor compliance in cancer surveillance programmes [74], but all our patients seemed to be well informed and were all compliant to the surveillance programme.

The patients in surveillance had a SOC score and functional health status comparable to healthy reference groups [160, 172] irrespectively of extensive or distal disease involvement. Compared with other chronic diseases UC-patients are usually younger, are less likely to have important concurrent illnesses [110], and are likely to have fewer problems with mobility and activity of daily living. Although, having co-existing disease has been shown to cause considerable negative impact on HRQOL, a higher overall SIP was seen compared to patients who only suffered from UC [89]. We did not assess the patients for co-existing disease in our study. However, all patients being in remission could well be the explanation of our findings. To further assess the patients' emotional state the disease specific RFIPC questionnaire which is concentrated on patient worries and concerns, would also have been appropriate to use [99]. The SIP instrument is considered as a time consuming questionnaire with 136 items for the patient to fill out, and today we would probably have used another general questionnaire as the trend is toward shorter scales. Preferably we could have used the SF 36 [122].

Nevertheless, the patients in all four studies were not at all reluctant to fill in all the questionnaires, on the contrary they willingly completed them. One patient declared when he had filled out his first questionnaire (the IBDQ), that "this is astonishing; somebody must really have thought about us patients with IBD and understood how it is. All these questions are exactly on the spot how I feel!"

When patients are participating in special projects such as clinical trials, interventions or studies of any kind there is always a risk of a placebo effect. The word placebo derives from the Latin 'I shall please' and was first used in the 14th century and referring to hired mourners at funerals where the professional mourners were often stand-ins for

members of the family of the deceased. There are three necessary components for a placebo effect [178]:

- ❖ positive beliefs and expectations on the part of the *patient*
- ❖ positive beliefs and expectations on the part of the *physician or health care professional*
- ❖ a good relationship between both parties

In all our studies the placebo effect must be considered, as already discussed in the CAM study, further the patients in surveillance were given extra attention as well as the patients in the group based intervention. There is a special situation created between the patient and the caregivers concerning the selective leukocyte apheresis treatment. Positive beliefs and expectations of the novel ‘drug-free’ treatment and the extracorporeal treatment of the patient’s blood may all have influenced the results. The patients studied were all steroid resistant and had experienced treatment failure or side effects, and might have been disappointed with their physicians or with conventional medicine in general, and found the treatment attractive as an alternative therapy.

Some of our patients described the apheresis treatment as the best treatment they had ever tried, ‘a feeling of purification’- although being ‘tied’ to the bed without being able to move their arms. In general, despite being an invasive method and sometimes also cumbersome and time consuming for the patients the apheresis procedures were well tolerated and appreciated by the patients in our study.

A study by Ilnyckyj et al showed that patients with UC were more likely to respond to placebo in randomised controlled trials if they had more than three clinic visits than if they had fewer than three visits [179]. Moreover, a subject’s performance could simply be changed because he or she is being studied, a phenomena referred to as “the Hawthorne effect”, which very well could be relevant in the present intervention studies. [180].

The group-based intervention study was a controlled study, i.e. the patients were informed before the randomisation that they were either going to participate in an intervention or as controls without intervention. It is possible that a certain disappointment was felt by the patients who were randomised to the control group might have influenced the results. Presumably the most ethical design would have been to have the possibility to offer the patients in the control group participation in the intervention group at a later occasion, but

we wanted to avoid a potential anticipation bias “placebo effect” in patients who knew they would soon be a part of the intervention.

To know or not to know, or not want to know - *that* is the question. Does the IBD patient want all the IBD-related information, e.g. long term complications, cancer risk, surgery, intensive medical treatments, or is ignorance the best defence [181]? My experience during the years as a specialist nurse, meeting the all IBD patients at the clinic, is that they *do* want information, they have numerous questions and different problems to discuss and the lack of time with the physician is often eminent. Naturally, there are individual needs of information; a ‘sensitive ear’ is essential, especially when caring for newly diagnosed patients. An integrated medical psychological/psychosocial group based intervention was one way to help and support the IBD patient to better cope with the symptoms and living a life with a chronic disease.

One limitation of this study was that we did not assess the patients’ disease knowledge before or after the intervention, which would have been of interest. Knowledge questionnaires have been developed: the Crohn’s and colitis knowledge Score (CCKNOW) by Eaden et al and the IBD knowledge questionnaire (KQ) for measuring the patient knowledge of their IBD [148, 182] are available.

From the studies presented in this thesis it may be concluded:

- ⊕ In general, the use of complementary and alternative medicine was greater in North America than in Europe. The interest in CAM in IBD patients may reflect their dissatisfaction with conventional medicine.
- ⊕ UC patients in remission, did not experience an increased anxiety due to cancer surveillance, on the contrary they had excellent functional health status and coping ability.
- ⊕ Patients with steroid resistant UC may increase their HRQOL by selective apheresis treatment, and the treatment was well tolerated.
- ⊕ IBD patients do appreciate a group based medical and psychological/psychosocial intervention but HRQOL did not increase with such an intervention.

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