The Role of Stress in the Development and Clinical Course of Inflammatory Bowel Disease: Epidemiological Evidence

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Abstract: *Background*: It is unclear whether psychological stress contributes to the inflammatory process in the inflammatory bowel diseases (IBD), ulcerative colitis (UC) and Crohn's disease (CD). This review assesses the epidemiological evidence regarding a causal link between stress and gut inflammation in IBD.

Methods: A Medline search identified prospective studies of the effects of stress on subsequent disease activity and randomized controlled studies of the effects of psychological interventions on disease course in IBD. Controlled retrospective studies were included in the review of aspects of the stress-inflammatory relationship for which few prospective studies are available (e.g. the link between stress and disease onset). Studies were assessed qualitatively.

Results: Among 9 longitudinal studies of stress or depression and disease course, a significant stress-inflammation relationship has been found when UC and CD are studied independently (4 of 4 studies positive) but studies of mixed samples of CD and UC have mostly had negative results (1 of 5 studies positive). Evidence of a contribution of stress to disease onset is very weak. The results of 5 studies of psychological interventions in IBD have been negative or modestly supportive of benefit. Confidence in therapeutic benefits of psychological interventions results is limited by methodological weaknesses in these studies.

Discussion: There is consistent evidence for a contribution of psychological factors to IBD disease course, especially stress in UC and depressive symptoms in CD. More rigorous tests of psychological interventions in IBD are needed.

Keywords: Stress, depression, Crohn's disease, ulcerative colitis, inflammatory bowel disease, inflammation, psychology.

Clinicians and scientists have studied and debated the contribution of stress to the inflammatory process in inflammatory bowel disease (IBD) since at least 1930 [1] without any definitive resolution. Patients with IBD are nearer reaching a consensus, with 74% believing that psychological factors have played a role in triggering the onset of disease or relapse of their illness [2]. More compellingly, recent studies in animals [3-6] and humans [7-9] have provided stronger evidence for plausible mechanisms by which stress effects could be transduced into gut inflammation, including stress-induced changes in intestinal permeability [10-12] and stress-induced changes in mucosal pro-inflammatory cytokines [7].

In this review of chiefly prospective human studies, we assess the epidemiological evidence addressing the question of whether stress plays a contributing role in Crohn's disease (CD) and ulcerative colitis (UC). The early literature on the relationship between stress and UC (up to 1990) was reviewed by North [13], who found that 8 of 15 adequately controlled studies reported a positive association. The smaller literature on CD was even less conclusive [14]. Since that time methodologically sound longitudinal studies have continued to accumulate, although as recently as 2005, the proportion positively supporting a contribution of stress to IBD remained about 50% [15]. Studies of psychological interventions that should reduce stress have also been reported, providing another method of testing the causal hypothesis.

Testing the hypothesis that stress contributes to inflammation in IBD is difficult because of the complexity of defining and measuring various aspects of stress and the complexity of defining and measuring appropriate disease outcomes. Humans experience stress as the result of a variety of types of stressors, including daily hassles, major life events, and traumatic events. Alternatively, stress can be measured as a composite of the subjective response to these various events, or biologically as a measure of the degree to which the body's stress systems have been activated [16]. Finally investigators may study other constructs which are strongly related to stress, such as depressive symptoms [17,18]. While each of these aspects of stress can be measured validly and each may be appropriate to various research questions, it is not known, prior to empirical testing, which is most relevant to gut inflammation.

Another type of methodological complexity relates to disease outcome. The variables which contribute to the onset of an inflammatory disease in a predisposed person may differ from the variables that cause relapse

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or that aggravate inflammation that is already active. Variations in the phenotypic characteristics of the samples studied may contribute to further complexity. The most obvious source of heterogeneity in studies of stress in IBD has been the tendency to study mixed samples that include both UC and CD patients. It is quite plausible that the role of stress differs between CD and UC, and that studies of mixed samples will provide inconsistent results and underestimates of effect size as a result. Beyond the heterogeneity of IBD diagnoses, more subtle sources of heterogeneity may result from gender differences [19,20], genetic differences in stress responsivity [21] and subclinical subtypes of IBD [22].

A final source of methodological stumbling blocks is the bidirectional nature of the interaction: inflammatory bowel disease can be a severe disease, itself engendering psychological stress and distress in the sick person. This makes retrospective and cross-sectional research particularly suspect, and is the reason why in this review we have emphasized studies with a prospective design; even this restriction is, however, not always a guarantee that subtle disease effects are not affecting the findings.

The consequence of this array of difficulties is that individual studies can test only a small number of the permutations of a complex analytic interaction (type of stress X disease outcome X precise character of sample). This is a recipe for inconsistent results, if "inconsistency" is judged from a simple count of how many studies provide a positive or negative result. It is also a recipe for low effect sizes, due to the dilution of stronger correlations in particular phenotypic groups by weak or absent correlations in other groups when these groups are studied as one. In order to avoid some of the pitfalls of comparing dissimilar studies, in this review we will separately evaluate studies that test different aspects of the stress-IBD relationship.

METHODS

For studies reported before 1990, North's reviews of psychiatric factors in UC [13] and in CD [14] were taken as providing a definitive bibliography. More recent papers were identified by a MEDLINE search from 1990 to 2007 identifying English language articles with subject headings ''Colitis, Ulcerative'' or ''Crohn Disease'' or ''Inflammatory Bowel Diseases'' AND ''Stress, Psychological'' or the MEDLINE subheading ''psychology'' with a few additional studies personally known to the authors. The titles and abstracts of articles in this broad search were examined and included for review if the report was directly related to stress or depressive symptoms and to IBD. References cited in the papers reviewed were checked to identify further relevant studies.

Of the abstracts collected, papers were studied and included in this review if they were prospective studies measuring stress and outcomes related to IBD course, or randomized controlled trials of interventions for IBD

Table 1. Prospective Studies of Stress and IBD Disease Activity

A. Patients entered study in remission			
Study	**Sample**	**Type of Stress**	**Result**
Vidal, 2006	76 UC 79 CD	Life events	No effect over 11 months
Bitton, 2004	60 UC	Life events	Hazards ratio = 1.26/life event in month before relapse
Mittermaier, 2004	13 UC 47 CD	Baseline depressive symptoms	Increased risk of relapse over 18 months
Levenstein, 2000	62 UC	Baseline perceived stress	High stress = hazards ratio 2.8 over 45 months
North, 1991	21 UC 64 CD	Life events	No effect over 3 months
Riley, 1989	84 UC 8 CD	Life events	No effect over 3 months
B. Patients not in remission at study entry			
Study	**Sample**	**Type of Stress**	**Result**
Maunder, 2006	93 UC	Baseline atypical autonomic response to stress	Significant association with disease activity 7 – 37 months later
Persoons, 2005	100 CD	Depressive symptoms	Odds ratio = 0.17 of failure of infliximab to achieve remission
Mardini, 2004	18 CD	Depressive symptoms	Significant association to CDAI score 8-12 weeks later
Duffy, 1991	53 UC 77 CD	Life events	Disease activity related to concurrent health-related stresses

that could reduce stress. For examining the relationship between stress and disease onset, controlled retrospective studies were also included, because disease onset is more difficult to study in IBD and few prospective studies are available. Two older studies [23,24] were excluded because their small sample size (n = 10 and n = 11) and methods made interpretation of findings difficult. Papers were critically assessed qualitatively, but no quantitative meta-analysis was feasible because of the number of studies and divergent patient samples and methodologies used.

RESULTS

Contribution of Stress to Relapse of Inflammation

Six studies prospectively examined the contribution of stress to relapse among IBD patients who entered the study in clinical remission (Table **1**). Only two of these studies examined patients with a single diagnosis, and both of these studies found a significant relationship between stress and relapse in UC [25,26]. These two studies differed in methodology. Levenstein and colleagues found that high chronic perceived stress at baseline increased the risk of relapse over 45 months with a hazards ratio of 2.8 [25]. Bitton and colleagues found that stressful life events prior to relapse increased the risk of relapse with a hazards ration of 1.26/stress event, controlling for age, number of prior relapses, and gender [26]. In an earlier cross-sectional study of UC patients in complete symptom remission, Levenstein found high long-term perceived stress levels to predict the presence of endoscopic inflammation [27].

The three studies of life event stress in mixed samples of UC and CD patients have found no significant risk attributed to stressful life events at lag times of one to three months [28-30]. The study by Levenstein also measured life events periodically and found that this measure of stress did not increase the risk of relapse [25]. One study of baseline stress in a sample of predominantly CD (13 UC, 47 CD) found that depressive symptoms measured at baseline were associated with increased risk of relapse [31].

Contribution of Stress to Worsening of Inflammation and Failure of Treatment Response

Two studies have evaluated the link between stress and worsening of disease activity in patients who are not in remission. Mardini and colleagues found that stress, especially in the form of depressive symptoms, contributed significantly to worsening of CD disease activity with a lag period of 2-3 months [32]. This prospective relationship was independent of the strong concurrent relationship between depressive symptoms and disease activity, but the results could have been confounded by the residual psychological impact of previous disease activity. In a mixed diagnostic group, on the other hand, Duffy and colleagues found an equivocal relationship between life events and disease activity: stressful events were associated with activity only when both occurred during the same month, and only when the events were health-related, leaving the direction of causality in doubt [33].

Persoons and colleagues prospectively studied the relationship between depression symptoms and treatment response in 100 unselected CD patients receiving treatment with infliximab [34]. At 4-week follow-up, remission of CD was achieved in 60%, with the presence of high depressive symptoms predicting a lower remission rate (Odds ratio 0.166, $p = 0.004$). High depressive symptoms also significantly decreased time to retreatment ($p = 0.001$). The effect size found in this study is significant but lower than the effect size in the prospective UC studies.

A cross-sectional study provides support for the hypothesis that the link between stress and inflammation differs in biological subgroups of patients. In 148 UC patients, disease activity was significantly correlated with depressive symptoms (correlation = 0.5, $p < 0.001$) and with health anxiety (correlation = 0.6, $p < 0.001$) in patients who lacked the pANCA antibody, whereas neither correlation was significant in pANCA positive patients [22]. With respect to individual differences in biological stress response, a follow-up study of this cohort found that an atypical autonomic response to a standardized stress (a sluggish response of heart rate variability to stress), which was assumed to represent an enduring biological characteristic of the 29% of patients in whom it was found, was significantly associated with reduced risk of disease activity at a second point in time, 7 – 37 months after the stress test [35].

Contribution of Stress to Disease Onset

The potential for stress to contribute to disease onset is difficult to study, because IBD is too uncommon for it to be practical to prospectively follow a sufficiently large sample of healthy people until a substantial number develop UC or CD. One study used existing prospectively collected data to try to address this question. Using a Danish national register of 21,062 parents who had experienced the death of a child and comparing them to 293,745 matched parents who did not have this experience, then linking this register to a register of cases of UC and CD, Li and colleagues found no additional risk of a new diagnosis or increased hospitalizations for IBD related to this particular traumatic stress. Since they did not compare dates of diagnosis, their study cannot exclude stress-related acceleration of the process of developing IBD [36].

A controlled retrospective study also addressed this question [37]. Life events over the preceding 6-month period were assessed in patients newly diagnosed with CD (n = 167) and UC (n = 74) and compared to events over the same period measured in patients with acute self-limited colitis (n = 69) and blood donors (n = 255). After controlling for smoking status and sociodemographic features, there was an excess of life events during the months before disease onset in CD but not in UC; this association was statistically accounted for

by increased levels of depressive symptoms and anxiety, likely mediators of the life stress.

These recent reports tend to corroborate negative findings regarding newly diagnosed ulcerative colitis in earlier case-control studies [38] and the failure of a small, unpublished study to find any association between MMPI profiles in college freshmen and the development of IBD over the following 30 years [39]. The contribution of stress to the onset of IBD would thus seem to be minor, and limited to CD.

Randomized Controlled Trials of Stress-Reduction Interventions

Five randomized controlled trials met the inclusion criteria, two for UC, two for CD, an one for a mixed diagnostic group (Table **2**). Milne and colleagues [40] compared a package of patient education, stress management and relaxation training with treatment as usual in 40 patients with IBD. Although there was a pre-post intervention improvement in CDAI in the treatment group which was not found in the control group, the groups were not equivalent in CDAI at the pretreatment baseline. The prevalence of remission (CDAI score < 150) improved in the treatment group from 58% at baseline to 70 % at 4-month follow-up. The control group had more patients in remission at both time points (baseline: 85%, follow-up: 84%). Thus, although a statistically significant treatment effect was found, it may have been due to regression to the mean in the treatment group.

In Jantschek *et al*.'s multicentric study, 71 CD patients received psychodynamic psychotherapy and relaxation training for one year. Both the treatment group and a comparison group received a standardized course of glucocorticoid treatment during flares of active disease. A two-year follow-up there was no significant difference from a control group in somatic disease outcome [41]. It is noteworthy, however, that this treatment also failed to produce benefits in depressive symptoms, anxiety symptoms, depression, anxiety, psychosocial-communicative status, and health-related quality of life at one year. While, these results suggest that the intervention was not an effective psychological intervention, a subsequent report did indicate decreased hospital utilization in the treatment group [42].

In another study Garcia-Vega and colleagues randomly assigned 45 CD patients to three conditions, stress management training, self-guided stress management or treatment as usual (15 subjects in each group) [43]. They reported improvements in self-reported CD symptom benefits for both stress management groups at 6- and 12-month follow-up, with greater benefits in the self-guided stress reduction treatment group. However, this study used non-validated measures of CD symptoms and analyzed effects for each symptom individually thus introducing multiple comparisons into the analysis. Improvements were reported as significant if $p < 0.10$. Significant improvements might not have survived correction for multiple comparisons, especially if the more common criteria of significance ($p < 0.05$) had been used. Replication in a larger sample with more rigourous outcome and analytic criteria is needed.

One randomized controlled trial used relaxation to influence pain reduction in UC patients with chronic abdominal pain [44]. Twenty patients received relaxation training and were compared with 20 similar patients who received a phone call once a week as a control for therapist attention. The treatment group reported reduced pain intensity, increased relief from pain, less distress secondary to pain, and lower use of nonsteroidal anti-inflammatory drugs.

Finally, Langhorst's study of a lifestyle modification program randomly assigned 60 UC patients with inactive disease to a 60-hour 10-week intervention or to treatment as usual. The intervention included training in stress management, psychoeducation, exercise, Mediterranean diet, and self-care. The intervention succeeded in anxiety, SF-36 physical scale score and a psychological sum score at 3 month follow-up. However there were no significant effects of the intervention on IBDQ or on clinical disease parameters [45], and the inter-group difference had disappeared at 12 months.

DISCUSSION

The design of studies of the link between stress and inflammation in IBD have improved since North's reviews of the scientifically weak literature in the early 1990s. However, the inconsistency of the evidence remains, and seems unlikely to be entirely attributable to methodological weaknesses. While the studies reviewed here do not speak with a single voice, there are some clear themes. First, all three longitudinal observational studies of patients that were restricted to a single

Table 2. Randomized Controlled Trials of Psychosocial Interventions in IBD with Disease Course Outcome Variables

Study	Sample	Intervention	Disease Outcome	Result
García-Vega, 2004	45 CD	Stress management	CD symptom diary	Equivocal
Keller, 2004	108 CD	Psychodynamic therapy and relaxation training	Clinical course	No effect
Langhorst, 2007	60 UC	Lifestyle modification	IBDQ	No effect
Milne, 1986	40 IBD	Stress management	CDAI	Equivocal
Shaw, 1987	40 UC	Relaxation training	Abdominal pain	Treatment effect

diagnosis supported a link between stress or depressive symptoms and disease course. On the other hand, most studies which employ mixed UC and CD patient groups have produced null results (Table **3**). This only exception to this trend was a mixed diagnosis study which included predominantly (78%) CD patients [31]. Given the substantial differences in clinical course, familial/genetic patterns, neuroimmune response, and subclinical markers between CD and UC [46,47], it seems likely that the failure to find a stress-inflammatory link in mixed diagnosis "apples and oranges" samples is the result of a dilution of effect size that results from combining patients with dissimilar vulnerability to stress. It is strongly recommended that future studies of stress in the course of IBD analyze UC and CD separately.

That the stress-relapse link has been supported more robustly in UC than in CD may in part be due to the difficulty of defining clear criteria for remission and relapse in CD. Visualization of the rectal mucosa in UC allows for definitive determination of the presence or absence of active gut inflammation. Without this visualization, psychological characteristics of patients would greatly bias the determination of UC disease activity [48]. Since identification of disease activity in CD is more highly dependant on self-reported symptoms than it is in UC, the potential for confounding is greater; CD patients are also more likely to experience persistent, though fluctuating, disease symptoms. As a result, studies in which patients enter the study in remission, with relapse as an endpoint, are difficult to accomplish in CD. The one study of a pure CD sample that has examined the role of stress in exacerbation of CD activity measured by CDAI, in patients who were not required to be in remission on entry, found an increase in risk of symptom exacerbation attributed to depressive symptoms [32], while another CD study found depressive symptoms to be a risk factor for failure to achieve remission with infliximab [34]. Thus there is evidence of a link between stress or depressive symptoms and subsequent increase in disease activity for both UC and CD, although the evidence is stronger in UC. There also appears to be some specificity to the link between stress and inflammation, in that measures of depressive symptoms have been linked to disease outcome in CD [31,32,34] whereas direct measures of stress have been more predictive of inflammatory risk in UC [25,26,35]. Since CD is more difficult to study because of uncertainty about objectively determining the extent of active inflammation, one possible strategy which has not been exploited thus far would be to enter CD subjects into a longitudinal follow-up at the time of surgical resection, when it can be ascertained directly from visualization of the surgical specimen that all diseased bowel has been removed.

A second conclusion from this review is that whereas longitudinal studies identify a stress-inflammation link in IBD, intervention studies have been less successful in interrupting this link. The small intervention literature suffers from a lack of consistency in the types of interventions applied, a failure to use standardized treatments, a lack of statistical power in most studies, and a lack of rigour in the disease outcomes which are measured. Several interventions are available which are standardized through treatment manuals and training programs and have been used in other medical conditions to reduce stress and depressive symptoms, including cognitive-behavioral therapy [49,50], interpersonal psychotherapy [51], and mindfulness meditation [52,53]. Future studies in IBD would benefit from the use of these interventions. These studies would also benefit from using standard measures of disease activity (relapse confirmed endoscopically in UC, and CDAI score in CD) as outcome variables. On the whole, the small and flawed evidence on intervention in IBD is insufficient to either support or refute the stress-inflammation hypothesis. The third conclusion is that there is no evidence supporting a link between stress and the initial onset of inflammatory bowel disease.

Evidence supports the idea that some IBD patients are more vulnerable to the effects of stress than others either due to psychological traits [54] or differences in biological phenotype [22,35]. However, there is no evidence from the currently available prospective studies for evaluating individual differences in susceptibility to stress, which remains an important future research direction. Identification of such markers of stress-vulnerability is particularly important to using psycholo-

Table 3. Contrast Between Mixed Diagnosis and Single Diagnosis Studies of Stress and IBD Disease Course

	Number of Studies	
	Total	**Supporting stress-disease link**
Mixed diagnosis	5	1 (20%)
UC	3	3 (100%)
CD	2	2 (100%)
Treatment intervention studies		
Mixed diagnosis	1	0 (0 %)
UC	2	1 (50%)
CD	2	1 (50%)

gical interventions to decrease stress. These interventions are likely to be more effective and more cost-effective if they are targeted towards the patients who can most benefit from them.

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