Research

Effect of Yoga-Based Intervention in Patients with Inflammatory Bowel Disease

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Abstract

Background: Inflammatory bowel disease (IBD) is a chronic illness characterized by gross inflammation in the gastrointestinal tract that can result in symptoms such as abdominal pain, cramping, diarrhea, and bloody stools. IBD is believed to be influenced by psychological factors such as stress and anxiety. Therefore, a yoga intervention that reduces stress and anxiety may be an effective complementary treatment for these disorders.
Material and Methods: A total of 100 IBD patients [ulcerative colitis (UC) n = 60 and Crohn's disease (CD) n = 40] during the clinical remission phase of disease were included in the study. These patients were allocated randomly to either the yoga group that underwent an 8-week yoga intervention (physical postures, pranayama, and meditation) 1-hour/day in addition to standard medical therapy (UC, n = 30; CD, n = 20) or the control group (UC, n = 30; CD n = 20), which continued with standard medical therapy alone. The main outcome measures were cardiovascular autonomic functions, serum eosinophilic cationic protein, interleukin-2 soluble receptors, Speilberger's State Trait Anxiety Inventory (STAI) scores, and clinical symptoms.
Results: Before the intervention, all the outcome measures were comparable in the two groups. After the 8-week yoga intervention, fewer UC patients reported arthralgia. The number of patients reporting intestinal colic pain in the control group was higher. State and trait anxiety levels were significantly reduced in patients with UC. However, no significant changes were observed in cardiovascular autonomic functions, eosinophilic cationic proteins, or interleukin-2 soluble receptors.
Conclusions: A simplified yoga-based regimen is a safe and effective complementary clinical treatment modality for patients with inflammatory bowel disease during the clinical remission phase.

Introduction

Inflammatory bowel disease (IBD) is a chronic gastrointestinal disorder with debilitating symptoms such as abdominal cramps, rectal bleeding, diarrhoea, urgency in bowel movement, weight loss, and extraintestinal manifestations. Ulcerative colitis (UC) and Crohn's disease (CD) are the most studied types of IBD, having the highest prevalence and constituting an important global public health problem with increasing and varied incidence worldwide (Molodecky et al., 2012). The etiology of UC and CD is multifactorial and is mainly driven by an abnormal immune response to gut microbes in a genetically predisposed host (Abraham & Cho, 2009). The increasing incidence and prevalence will consequently translate into higher healthcare expenditure, higher patient costs for the disease, and increasing burden on economy as a whole (Odes, 2008). Additionally, recent mortality data have shown an increase in intermediate and long-term mortality among patients with IBD, with even higher percentage for patients diagnosed during childhood or adolescence (Jess et al., 2013).
Conventional treatment with corticosteroids and immunomodulators (IMMs, step-up strategy) has not been able to reduce the complications of the disease or modify its course. Current therapy is not curative but palliative-mainly supportive or immunosuppressive. Adverse side effects due to therapy and the extraintestinal manifestations of the

disease are often distressing for patients. Obviously, all complaints can have profound effects on everyday activities and may lead to increased psychological concern, stress, and anxiety. Patients with IBD experience a chronic stressful situation and there is evidence that acute psychological stress induces systemic and mucosal cytokine release in patients with UC during remission (Mawdsley et al., 2006) and one such study in patients with CD has indicated that stressful events often predispose to relapses (Duffy et al., 2007).

Complementary and alternative medicine (CAM) is used increasingly by patients with chronic diseases. A national survey in Germany conducted by Langhorst et al. (2007) showed that 51.3% of IBD patients had experience with CAM and that psychological stress is a potential indicator for the use of CAM. Mind-body therapies such as yoga have been suggested in the treatment of gastrointestinal disorders since ancient time. A previous study carried out in patients with irritable bowel syndrome suggested the utility of yoga as an adjuvant to conventional treatment (Taneja et al., 2004).

Although less work has been done with non-pharmacological treatment for IBD, a small number of studies have shown benefits. A randomized controlled trial of a relaxation-training intervention compared to a wait-list control showed decrease anxiety levels and improvements in quality of life and mood, as well as decrease in pain and stress (Mizrahi et al., 2012) and mindfulness-based therapy has some benefits on IBD patients with IBS-like symptoms (Berrill et al., 2014). In addition, a recent pilot study on relaxation response-based mind-body group intervention was associated with improvements in disease-specific measures, anxiety, and pain (Kuo et al., 2015) as well as the management of overall symptoms and improvement in quality of life (Schoultz et al., 2015). Therefore, we intended to study the effect of a yoga intervention as an adjuvant to conventional pharmacological treatment measuring the cardiovascular autonomic functions, immune markers, anxiety levels, and disease-associated clinical symptoms in patients with IBD.

Methods and Design

This parallel-arm, randomized study was undertaken between 2004 and 2008 at the All India Institute of Medical Science (AIIMS) in New Delhi, India. The intervention period was eight weeks and outcome variables were recorded at baseline, one month, and two months after randomization. Patients with UC and CD were separately randomized into two groups: the yoga group (yoga intervention plus standard medical therapy) and the control group (standard medical therapy alone). After baseline testing, the yoga group was given an additional supervised yoga training daily for 60 minutes for one week and followed-up regularly at home for an additional seven weeks. The human ethics committee of AIIMS, New Delhi approved the research protocol. All the patients were fully informed about the aims, objectives, and methods of the study. A written informed consent was obtained from the patients on initial contact.

Group assignment was determined by a randomization scheme devised from computer-generated random number tables. The tables were prepared by other researchers who were not involved in the study. The randomization schedule was concealed in sequentially numbered, sealed opaque envelopes. Participants were randomized by the research assistant.

Participants

The study was carried out on patients with UC (n = 60) and CD (n = 40) during the clinical remission phase to avoid confounding of the results by processes associated with active inflammation (e.g., glucocorticoid release, cytokine production, pain, etc.). No information regarding more than two parameters was found during reviewing the literature and, therefore, considering the feasibility and limitation of patient's availability, only 60 UC and 40 CD patients were considered for statistical analysis. All the diagnosed patients were referred from the Department of Gastroenterology and Human Nutrition at AIIMS, New Delhi. The diagnosis of UC was established on the basis of clinical evidence of large bowel diarrhea, hematochezia and tenesmus; endoscopic evidence of diffuse pattern of involvement of the gastrointestinal mucosa characterized by loss of vascular pattern, erythema, friability, or ulcerations; and histological evidence. The diagnosis of CD was established on the basis of the presence of characteristic clinical manifestations (chronic diarrhea, hematochezia, abdominal pain, and intestinal obstructive manifestations), endoscopic features (skip lesion, asymmetrical involvement, deep ulcers, ileocecal valve involvement, and terminal ileum involvement), together with histological evidence (acute or chronic colitis, presence of inflammation extending beyond muscularis mucosa, lymphoid follicles, and noncaseating granulomas). The involvement of the small intestine was assessed by barium meal follow-through, small bowel enema, and/or retrograde ileoscopy.

Only patients between 16-60 years who were in the clinical remission phase of the disease were included in the study. UC and CD activity was assessed using the criteria of Truelove and Witts (1955) and the Crohn's Disease Activity Index (CDAI; Best et al., 1976), respectively. The inclusion criteria for UC patients in the remission phase were (a) one or two stools a day without blood, (b) no fever, (c) no tachy-

cardia, (d) hemoglobin normal or returning towards normal, and (e) erythrocyte sedimentation rate (ESR) normal or returning towards normal. Patients with a CDAI score ≤150 were considered in remission.

Exclusion criteria were (a) IBD patients with other chronic diseases like diabetes mellitus, hypertension, or cardiovascular diseases, (b) any condition known to affect the cardiovascular autonomic functions such as chronic alcoholism or smoking, (c) patients who have undergone any surgical intervention for IBD, (d) pregnant women, (e) patients on any drug regime affecting autonomic functions, (f) patients on psychiatric medication, and (g) patients who have practiced yoga within at least one year preceding the study.

Patient Recruitment and Grouping

Patients were verbally informed by their physicians about the ongoing study on their visit to the outpatient clinic. Once patients were listed using the recruitment strategy detailed above, they were scheduled for an individual interview with the gastroenterologist to further explain the study, determine eligibility, and provide informed consent. Patients were then requested to visit the clinic. During the interview, patient demographic and clinical variables were recorded and each patient was assessed for eligibility. After determining eligibility and obtaining consent, participants were randomized to groups. Thereafter, participants were assessed for baseline outcome variables.

Interventions

Conventional Treatment Group. The standard pharmacological treatment was used by all the patients for maintenance of disease remission. All patients were treated with maintenance doses of mesalamines and azathioprine, along with multivitamins and calcium supplements.

Yoga Intervention Group. Along with the standard medical therapy, patients assigned to the *yoga group* underwent the yoga intervention, which was comprised of physical postures, pranayama (controlled breathing), and meditation (Table 1). The supervised yoga intervention (one week for one hour daily) was given under the guidance of a certified yoga trainer. The physical postures consisted of preliminary stretching exercises followed by breathing exercises and then by asana in four categories (standing, sitting, prone, and supine). Participants were instructed to follow a specific breathing pattern during each asana and asked to hold each pose in its final position for 10 to 30 seconds without holding the breath. Participants were encouraged to assess their own limits and hold the pose for less time, if necessary. The yoga asana was practiced with awareness focused primarily on their physical movements and respiration. Each posture was followed by an appropriate relaxation posture for 30 seconds to one minute. The session concluded with relaxation (shavasana and meditation) for 15–20 minutes. During meditation, the participants listened to the recorded voice of the yoga teacher to guide them through the relaxation. For relaxation, patients were encouraged to put emphasis on breathing.

S No.	Types of practice	Details of practice	Yoga asana
1.	Loosening Exercise	Dynamic exercise *Sukshma Vyayama* (Joint movements)	Loosening of ankles, knees, hip joints, working towards the head: Toe movement, ankle rotation, knee rotation, waist movements, elbow movements, arm rotations, shoulder rotation, and neck roll. (Repeat 5 times).
		Static and dynamic exercise *Suryanamaskar* (Sun- salutations)	12 postures with slow and rhythmic breathing (Repeat 3 times).
2.	Breathing exercise	Standing posture	Hands-in-out, hands- tretch, ankle-stretch (repeat 5 times).
3.	Yogasanas (Postures)	Standing posture	*Ardhakaticakrasana, Pada hastasana, Ardhacakrasana* (30 seconds each).
		Sitting posture	*Vajrasana, Vakrasana* (10- 30 seconds each).
		Prone position	*Bhujangasana, Salabhasana* (10-30 seconds each).
		Supine position	*Matsyasana*
4.	Relaxation techniques	Supine position	*Shavasana* (7-10 minutes)
		Prone position	*Balasana* (in between asanas)
5.	Breathing practices	Sitting posture	*Pranayama*: alternate nostril breathing (10 minutes).
6.	Meditation	Sitting posture	Concentration on breath (10 minutes).

Table 1. Yoga intervention routine.

Due to feasibility reasons, the supervised yoga training was provided for one week (each session for one hour) followed by a daily practice at home continuously over two months (one hour daily). Standard medical treatment was continued by all the participants.

Follow-Up Schedule

In the yoga group, after one week of supervised yoga training, participants were asked to continue with the yoga practice at home for an additional seven weeks. Compliance during the follow-up period was strictly monitored by a symptom diary, which participants were asked to fill daily and bring along with them during each visit. A single yoga session was offered individually to the participants during the follow-up visits. During the home practice sessions, patients listened to the audio recording for relaxation; an instruction manual on different postures was also provided to all participants. Telephone support was provided to both groups to motivate a high degree of compliance.

Outcome Measures

Assessment of Autonomic Tone and Autonomic Reactivity

Cardiovascular autonomic tone was assessed using heart rate variability (HRV). All participants were advised to refrain from caffeine and have proper restorative sleep on the night before the study. The recording was done after at least two hours of fasting. ECG signals were recorded under standard laboratory conditions in supine position after a rest period of at least 15 minutes between 10.00 AM and 1.00 PM. A 5-minute continuous ECG was recorded from the three standard limbs for the assessment of HRV; the recording device was a PCI 20450P DASport A/D converter. During the recording, participants were requested to fully relax, stay awake, breathe regularly, and not to speak or move. A technician carefully observed the condition of each participant to ensure that the recording period was free of any subjective discomfort and movement artifacts. The ECG was processed to detect the R-R wave interval.

HRV analysis examined the R-R intervals of the ECG signal using dedicated software (Nevrokard, version 6.4.0, Slovenia). HRV analysis was carried out in three domains: time-domain, frequency-domain, and non-linear analysis, which are standard and validated for evaluating autonomic tone of the heart (Task Force, 1996). For detailed interpretations of the time domain, frequency domain, and non linear indices of HRV, refer to Sharma et al. (2009).

To assess autonomic reactivity, a standard battery of cardiovascular autonomic reactivity tests was performed (Nyarko-Adomfeh, 1992). The diagnosis was based on multiple tests (Ziegler et al., 1992). ECG and respiratory tracings were obtained (Polyrite, Recorders and Medicare, India). Blood pressure (BP) was manually recorded during the examination process. Adequate time was given between each test for the BP and HR to come back to normal levels before the next test was started. The following reactivity tests were performed to assess the cardiovascular autonomic functions. **Parasympathetic reactivity:** heart rate (HR) response for lying to standing test (LST), deep breathing test (DBT), and Valsalva maneuver (VM). The '30:15 ratio' assesses the physiological response to active standing; it measures the ratio of the heart rate increase that occurs approximately 15 seconds after active standing to the relative bradycardia that occurs at approximately 30 seconds after active standing. This ratio provides a measure of cardiac vagal function (Freeman, 2006). **Sympathetic reactivity:** blood pressure (BP) response to LST, isometric handgrip test (HGT), and cold pressor test (CPT).

Immune Markers

Serum eosinophilic cationic protein (ECP) and soluble interleukin-2 receptor (sIL-2R) at baseline and after two months were assessed. The blood was allowed to clot at room temperature (22°C) for 1 hour ± 10 minutes and then centrifuged at 4500 rpm for 10 minutes. The serum was separated and aliquots were frozen at -20°C until used for the assay. Serum ECP and sIL-2R levels were assessed by a sandwich ELISA kit (MBL ECP ELISA kit, Japan; Code No. 7618E and Quantikine, R&D Systems, Abingdon, UK, respectively). This ELISA detects human ECP and sIL-2R with a minimum detection limit of 0.125ng/ml and 10pg/ml, respectively. The optical density (OD) of each well was measured at 450 nm using a microplate reader.

Anxiety Assessment

Anxiety levels were assessed by the State and Trait Anxiety Inventory (STAI; Spielberger et al., 1970). It consisted of two 20-item subscales for measuring state and trait anxiety. Patients were asked to mark—not at all, somewhat, moderately, very much, on a scale of 1–4. Scoring was done as the sum of these individual scores. The range of anxiety score was 20–80.

Clinical Symptoms Evaluation

Patients were given a symptom diary at the beginning of the study in which they were asked to record the presence or absence of clinical symptoms. In accordance with the wide range of proposals for indices of clinical activity of IBD, the following symptoms were considered: blood, tenesmus, intestinal colic, peri-anal pain, arthralgia, and anorexia. Participants were asked to fill the self-report form once per day before going to bed.

Statistical Methods

Study variables are summarized as mean ± standard deviation and median (interquartile range). To reduce bias, a midterm analysis of the results was not carried out. We used generalized linear model (GLM) repeated measure analyses for comparing the efficacy of each treatment over a period of two months, followed by Bonferroni adjustment for multiple comparisons. This approach was used to compare mean values of study variables within the group (i.e., intragroup comparisons for yoga and conventional treatment at baseline and post-intervention-after one month and after two months), and to compare mean values between the two groups (intergroup analyses) at different follow-up visits and the difference between two groups and (intergroup analysis) for comparing between disease subtypes (i.e., yogic and conventional). All tests used in the study were two-tailed and a p value ≤ 0.05 was considered statistically significant.

Results

Patient Flow and Dropout Details

Of the 60 UC patients randomized, 51 came for all visits. Five patients from the yoga group and four from the conventional group missed the follow-up visits (Figure 1). Similarly, of the 40 patients with CD, 36 patients completed all the follow-up visits; one from the yoga group and three from the control group missed the follow-up visits (Figure 2). Thus, the patient dropout rate was 10% and 15% for UC and CD, respectively. The dropout rate was not significantly different between the groups and was also not related to any adverse events related to the intervention. The UC and CD patients who completed the 2-month add-on yoga intervention study practiced yoga an average of 76% and 81% of the days, respectively. In UC and CD patients, asana practice lasted for an average of 45 (range 20 to 77) and 56 (range 22 to 100) minutes/day, respectively.

Baseline Variables Between the Groups

In both disease groups, baseline clinical characteristics and other demographics were comparable. As per the study protocol, all patients with CD and UC randomized for the study continued to take standard medical therapy as prescribed by their physicians. There were no significant differences between the medication used by the yoga and control groups. The baseline values of the cardiovascular autonomic tone, immune markers, anxiety levels, and clinical symptoms were comparable in the yoga and control groups in both disease conditions. The yoga group patients with UC were assessed to have a significantly lower 30:15 ratio at baseline as compared to those with the control group. All other cardiovascular reflex variables were comparable.

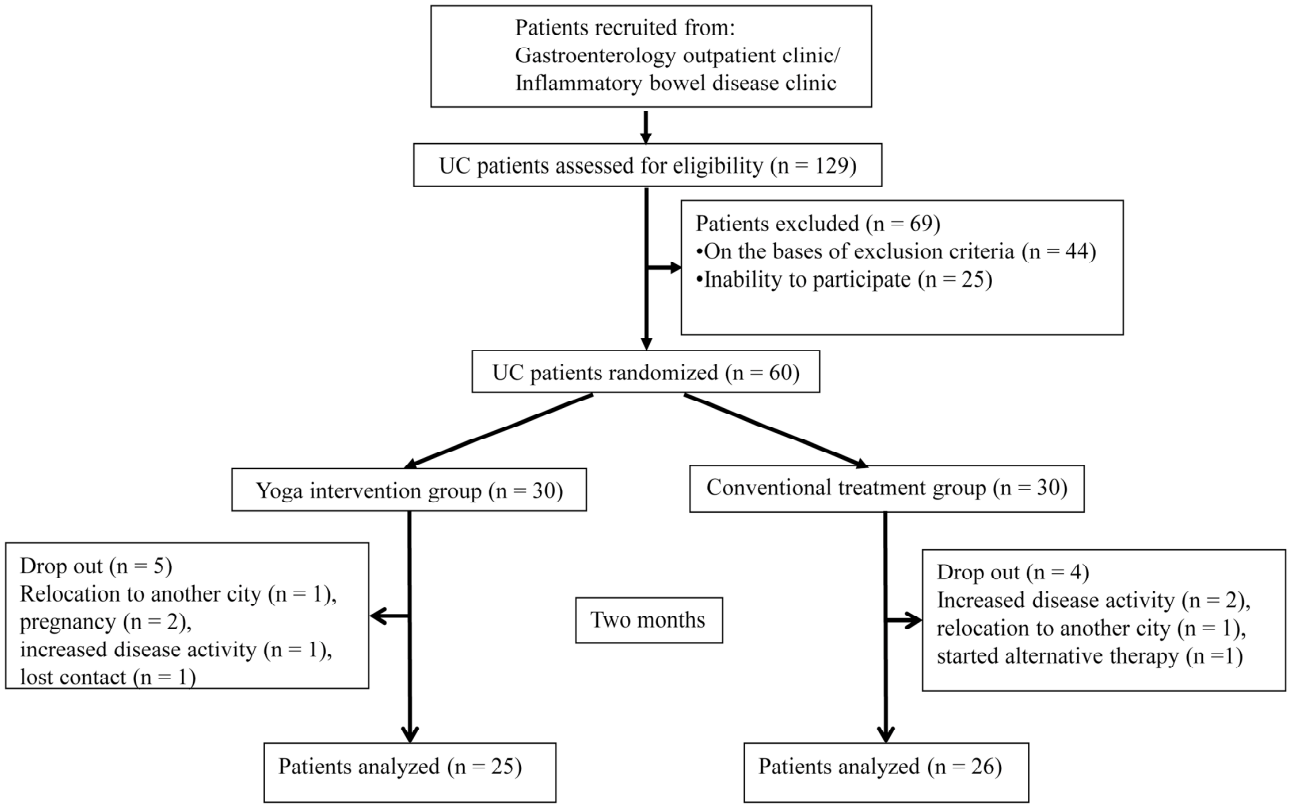

Figure 1. Study flow chart showing recruitment, exclusions, drop outs, and follow-up of the randomized trial in patients with ulcerative colitis (UC).

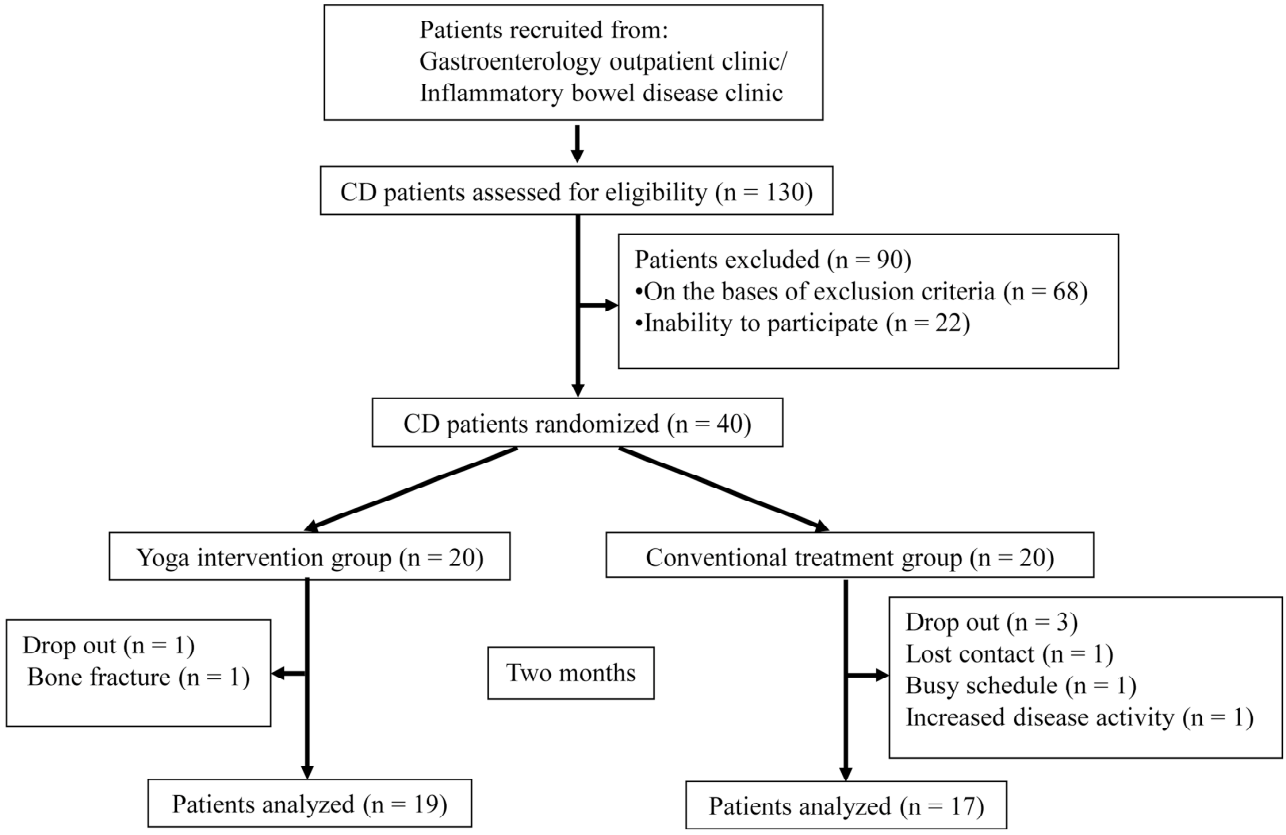

Figure 2. Study flow chart showing recruitment, exclusions, drop outs, and follow-up of the randomized trial in patients with Crohn's disease (CD).

Effect of Yoga on Autonomic Activity

UC: *Within-Group Comparison:* The values of mean R-R interval were not significantly different between the yoga group and the control group ($p = 0.055$). There were no significant differences in the coefficient of variation ($p = 0.46$), standard deviation of the R-R interval (SDNN) ($p = 0.63$), or the total power (ms^2) ($p = 0.16$). *Between-Group Comparison:* There were no significant differences between groups in the mean RR intervals ($p = 0.84$), coefficient of variation ($p = 0.67$), SDNN ($p = 0.92$), or the total power (ms^2) ($p = 0.45$) (Table 2).

Parasympathetic Activity: There were no differences in the RMSSD ($p = 0.69$), *p*NN50 (p = 0.62), HF (ms^2) ($p = 0.46$), HF nu ($p = 0.38$), and SD1nu ($p = 0.71$) with respect to therapy in the yoga intervention group compared with the control group. There were also no significant differences in RMSSD ($p = 0.78$), *p*NN50 (p = 0.83), HF (ms^2) ($p = 0.34$), HF nu ($p = 0.10$), and SD1nu ($p = 0.28$) between UC yoga group and the control group (Table 3).

Sympathetic Activity: There was no difference in the LF power expressed both in absolute values and in normalized units ($p = 0.35$ and $p = 0.5$), respectively, with respect to therapy in the yoga group compared with the control group, and there were no significant differences between the UC yoga group and the control group (Table 4).

CD: *Within-Group Comparison:* There were no significant effects of therapy on the mean RR intervals ($p = 0.43$), coefficient of variation ($p = 0.32$), SDNN ($p = 0.25$), and the total power (ms^2) (expressed in absolute values) ($p = 0.79$) in the yoga group compared with the control group. *Between-Group Comparison:* No significant differences were found in the mean RR intervals ($p = 0.45$), coefficient of variation ($p = 0.30$), standard deviation of the R-R interval (SDNN) ($p = 0.24$) and the total power (ms2) (expressed in absolute values) (p = .15) between patients in the yoga versus control conditions.

Parasympathetic Activity: There were no differences in the RMSSD ($p = 0.2$), pNN50 ($p = 0.38$), HF (ms^2) ($p = 0.33$), HF nu ($p = 0.91$), and SD1 nu ($p = 0.14$) in the yoga intervention group across time. Similarly, no significant differences were observed in RMSSD ($p = 0.56$), *p*NN50 ($p = 0.46$), HF (ms^2) ($p = 0.31$), HF nu ($p = 0.23$), and SD1nu ($p = 0.52$) between CD yoga group and the control group.

Sympathetic Activity: Although there was no statistically significant change in the LF after two months of yoga intervention, there was a strong trend towards a reduction in the LF power in the yoga group [404.95 (145.04, 659.57) vs. 171.54 (72.08, 498.01); $p = 0.052$]. No significant effect of the yoga intervention was detected on the LF:HF ratio ($p = 0.98$) or SD2 (nu) (p = 0.53).

Variables	Follow-up	Study groups		*P* (Intergroup)
		Yoga	Control	
	Baseline	758.66 (721.78, 893.81)	863.41 (789.81, 939.74)	
Mean RR	1 month	771.11 (715.24, 870.51)	873.5 (800.31, 988.89)	0.05
	2 month	776.31 (730.4, 912.61)	862.63 (814.36, 904.06)	
Intragroup		*P* = 0.84		
	Baseline	4.29 (3.31, 5.04)	4.19 (3.02, 5.76)	
COV	1 month	4.68 (3.66, 5.30)	3.99 (3.41, 5.41)	0.46
	2 month	4.59 (3.29, 5.38)	4.28 (3.61, 5.28)	
Intragroup		*P* = 0.67		
	Baseline	34.17 (22.36, 42.23)	34.92 (27.76, 49.54)	
SDNN	1 month	36.53 (32.23, 45.33)	33.61 (28.89, 46.58)	0.63
	2 month	36.43 (24.8, 44.65)	38.9 (29.74, 48.91)	
Intragroup		*P* = 0.92		
	Baseline	962.3 (501.88, 1580.22)	1238.79 (621.7, 2525.29)	
TP (ms^2)	1 month	1322.12 (665.35, 1918.98)	1111.69 (697.25, 3661.91)	0.16
	2 month	1246.14 (639.02, 2163.28)	1467.86 (720.79, 2949.84)	
Intragroup		*P* = 0.45		

Table 2. Cardiovascular autonomic activity in patients with UC during the study in both groups.

P values in (column) are based on group mean differences between yoga and control groups, and in (rows) on the bases of with time effect. R-R interval, time between two successive peak R waves; COV, coefficient of variance; SDNN, standard deviation of the R-R intervals; TP, total power. *P* values were obtained from GLM repeated measures.

Variables	Follow-up	Study groups		*P* (Intergroup)
		Yoga	Control	
	Baseline	26.03 (15.91, 43.23)	26.79 (16, 33.65)	
RMSSD	1 month	29.37 (17.42, 39.94)	26.81 (20.49, 39.94)	0.78
	2 month	27.98 (18.12, 39.58)	28.23 (18.73, 39.54)	
Intragroup		*P* = 0.69		
	Baseline	1.23 (0.10, 9.48)	2.13 (0, 6.4)	
pNN50	1 month	2.71 (0.24, 9.31)	2.79 (0.91, 9.26)	0.83
	2 month	3 (0.26, 9.37)	3.6 (0.53, 8.87)	
Intragroup		*P* = 0.62		
	Baseline	426.46 (110.77, 675.37)	262 (104.99, 750.83)	
HF (ms^2)	1 month	332.17 (118.56, 698.81)	372.27 (136.83, 878.56)	0.34
	2 month	410.99 (141.39, 730.58)	384.16 (126.81, 613.41)	
Intragroup		*P* = 0.46		
	Baseline	43.35 (34.36, 59.10)	44.24 (25.66, 55.49)	
HF (nu)	1 month	47.27 (27.68, 65.59)	44.66 (26.11, 55.52)	0.10
	2 month	52.42 (36.93, 67.35)	37.79 (21.27, 56.29)	
Intragroup		*P* = 0.38		
	Baseline	2.48 (1.58, 3.32)	2.09 (1.46, 2.97)	0.28
SD1 (nu)	1 month	2.54 (1.59, 3.4)	2.25 (1.65, 3.12)	
	2 month	2.46 (1.55, 3.33)	2.39 (1.61, 2.87)	
Intragroup		*P* = 0.71		

Table 3. Cardiovascular parasympathetic activity in patients with ulcerative colitis during the study in both groups.

Values are expressed as median (interquartile range); *P* values in (column) are based on group mean differences between yoga and control groups, and in (rows) on the bases of with time effect. rMSSD, root mean square of successive difference; pNN50, percentage of difference between adjacent R-R intervals that is ≥50 ms; HF high frequency power; HF(nu), high frequency in normalized units; SD1nu, standard deviation of instantaneous beat-to-beat interval variability expressed in normalized units.

Variables	Follow-up	Study groups		*P* (Intergroup)
		Yoga	**Control**	
	Baseline	211.7 (133.53, 409.22)	454.96 (144, 805)	
LF (ms2)	1 month	230.21 (167.51, 499.40)	429. 28 (172.45, 697.58)	0.08
	2 month	217.96 (157.61, 476.13)	444.56 (179.3, 977.34)	
Intragroup		*P* = 0.35		
	Baseline	44.04 (29.88, 59.19)	53.26 (37.62, 67.74)	
LF (nu)	1 month	49.22 (27.40, 63.41)	46.71 (38.17, 70.57)	0.07
	2 month	41.95 (26.88, 55.63)	54.27 (38.54, 72.16)	
Intragroup		*P* = 0.5		
	Baseline	2.48 (1.58, 3.32)	2.09 (1.46, 2.97)	
SD2 (nu)	1 month	6 (4.67, 7.13)	5.21 (4.3, 6.96)	0.65
	2 month	5.97 (4.48, 6.89)	5.79 (4.61, 6.92)	
Intragroup		*P* = 0.53		
	Baseline	1.06 (0.5, 1.61)	1.18 (.73, 2.65)	
LF:HF ratio	1 month	1.04 (0.42, 2.37)	.96 (.73, 2.53)	0.15
	2 month	.76 (.41, 1.54)	1.51 (.68, 3.42)	
Intragroup		*P* = 0.52		

Table 4. Cardiovascular sympathetic activity in patients with ulcerative colitis during the study in both groups.

Values are expressed as median (interquartile range); *P* values in (column) are based on group mean differences between yoga and control groups, and in (rows) on the bases of with time effect. LF, low frequency power; LF(nu), low frequency power in normalized units; LF/HF, ratio of LF to HF; SD^2, standard deviation of continuous beat-to-beat interval variability; nu, normalized unit.

Variables	Follow-up	Study groups		*P* (Intergroup)
		Yoga	**Control**	
	Baseline	22 (14, 30)	21 (15.75, 31)	
DBT Δ HR	1 month	21 (15.50, 30)	21.5 (14.5, 28)	0.69
	2 month	20 (17.50, 31.50)	19.5 (12, 28.25)	
Intragroup		*P* = 0.34		
	Baseline	1.34 (1.19, 1.42)	1.32 (1.22, 1.45)	
E:I ratio	1 month	1.32 (1.23, 1.44)	1.31 (1.21, 1.45)	0.90
	2 month	1.33 (1.25, 1.50)	1.17 (1.29, 1.45)	
Intragroup		*P* = 0.41		
	Baseline	1.7 (1.41, 2)	1.75 (1.5, 1.91)	
Valsalva ratio	1 month	1.8 (1.50, 2.09)	1.76 (1.48, 2)	0.83
	2 month	1.7 (1.44, 2)	1.71 (1.45, 2)	
Intragroup		*P* = 0.17		
	Baseline	1.37 (1.16, 1.47)	1.5 (1.39, 1.60)	
30:15 ratio	1 month	1.31 (1.18, 1.55)	1.42 (1.3, 1.61)	0.1
	2 month	1.38 (1.23, 1.51)	1.41 (1.29, 1.57)	
Intragroup		*P* = 0.09		

Table 5. Heart rate responses in the yoga intervention group and the control group in patients with ulcerative colitis during deep breathing test, the Valsalva ratio and the lying to standing test (30:15 ratio).

The values are presented in median (inter quartile range); *P* values in (column) are based on group mean differences between yoga and control groups, and in (rows) on the bases of with time effect. DBT, deep breathing test; Δ , delta; E:I ratio, maximum RR interval to minimum RR interval; VM, Valsalva maneuver; LST, lying to standing test; 30:15 ratio, RR interval around 30th beat/ RR interval around 15th beat.

Variables	Follow-up	Study groups		*P* (Intergroup)
		Yoga	**Control**	
Isometric	Baseline	14 (10, 20)	14 (8, 18)	0.16
handgrip	1 month	10 (10,15)	12 (10, 14)	
(↑DBP)	2 month	12 (10, 16)	10 (6, 14)	
Intragroup		*P* = 0.5		
Cold	Baseline	10 (10, 20)	13 (8, 20)0.91	
Pressure test	1 month	12 (9, 19)	11 (8, 20)	0.91
(↑DPT)	2 month	14 (9, 21)	12 (9, 20)	
Intragroup		*P* = 0.29		
Lying to	Baseline	4 (0, 10)	0 (0, 6)	
standing	1 month	4 (0, 10)	2 (0, 9)	0.34
(↓SBP)	2 month	4 (0, 8)	4 (0, 10)	
Intragroup		*P* = 0.34		

Table 6. Blood pressure changes (mmHg) in the yoga interventional and control group in patients with ulcerative colitis response to the handgrip test, cold pressure test and the lying to standing tests.

The values are presented in median (inter quartile range); *P* values in (column) are based on group mean differences between yoga and control groups, and in (rows) on the bases of with time effect. HGT, handgrip test; CPT, cold pressure test; ↑, rise; ↓, fall; DBP, diastolic blood pressure; SBP, systolic blood pressure.

Effect of Yoga on Parasympathetic and Sympathetic Reactivity

UC: There were no group differences in patients who underwent the yoga intervention versus patient in the control group in the Δ HR during DBT ($p = 0.69$), E: I ratio ($p = 0.90$), Valsalva ratio ($p = 0.83$), and the 30:15 ratio of the LST ($p = 0.1$) (Table 5).

There were no group differences in patients who underwent the yoga intervention and the control group patients in the rise in DBP in response to isometric HGT ($p = 0.16$) and CPT ($p = 0.91$) and the fall in the SBP in response to the LST ($p = 0.34$) (Table 6).

CD: There were no group differences in patients who underwent the yoga intervention and the control group patients in the Δ HR during DBT ($p = 0.82$), E: I ratio ($p = 0.80$), Valsalva ratio ($p = 0.78$), and the 30:15 ratio of the LST ($p = 0.42$).

CD patients who received the yoga intervention tended to exhibit higher levels of the rise in the DBP in response to the isometric HGT ($p = 0.05$). There was no group difference in patients who underwent yoga intervention and the control group patients in the rise in DBP in response to CPT ($p = 0.29$) and the fall in the SBP in response to the LST ($p = 0.06$).

Effect of Yoga on Immune Markers

In UC patients, there were no significant changes in serum sIL-2R levels during the 8-week study period in either group (yoga group baseline, 1211.5 (857.43, 2236.75) vs 2-month 1689 (1020, 1989); control group baseline 2070 (1421.36, 2645.25) vs 2-month 2396.5 (1311.5, 2831.25). ECP also showed no effect (yoga group baseline, 57 (28.37, 89.68) vs 2-month 67 (37.04, 107.28); control group baseline, 39.97 (11.30, 115.86) vs 2-month 69.95 (14.55, 98.51). The patients with CD showed no significant change in serum sIL-2R and ECP levels after the yoga intervention ($p > 0.05$).

Effect of Yoga on Clinical Symptoms

At one month, the yoga group showed no significant effect on the symptoms and the group was not statistically different from the control group. At two months, fewer participants reported arthralgia in the yoga group. More patients in the control group reported intestinal colicky pain (Table 7).

Effect of Yoga on Anxiety Levels

Compared to baseline levels, in response to therapy UC patients of yoga group showed significantly reduced levels of state ($p = 0.01$) and trait anxiety ($p = 0.001$) (Table 8). However, patients with CD showed no change in anxiety after intervention ($p > 0.05$).

Discussion

In this study, we demonstrated that at the end of an 8-week yoga intervention a significant reduction in anxiety levels in patients with UC was observed. Improvements in anxiety and pain measures occurred in the absence of any significant changes in autonomic functions and immune markers. However, these effects were not detected in the patients with CD. Larsson and colleagues have observed that CD patients have more disease-related anxiety and distress as compared to UC patients (Schwarz et al., 1991; Larsson et

Variable	Group	Follow-up					
		Baseline		After 1 month		After 2 months	
		Present	Absent	Present	Absent	Present	Absent
Blood	Yoga (n = 25)	5	20	5	20	10	15
	Control (n = 26)	3	23	4	22	9	17
Tenesmus	Yoga (n = 25)	10	15	4	21	5	20
	Control (n = 26)	7	20	6	20	5	20
Intestinal colic pain	Yoga (n = 25)	3	22	2	23	5**	20
	Control (n = 26)	4	22	6	20	14*	12
Peri-anal pain	Yoga (n = 25)	3	22	2	23	2	23
	Control (n = 26)	3	23	4	22	7	19
Arthralgia	Yoga (n = 25)	10	15	5	20	3*	22
	Control (n = 26)	5	21	6	20	5	21
Anorexia	Yoga (n = 25)	5	20	5	20	3	22
	Control (n = 26)	7	19	9	17	8	18

Table 7. Comparison of the clinical symptoms in each group and at different follow-up phase in patients with ulcerative colitis.

All the values are the proportion of patients presenting the symptom;
* $P < 0.05$ within group comparison.
** $P < 0.05$ between group comparisons.

Variable	Group	Baseline	2 month	P value
STAI-S	Yoga	38.88 ± 8.85	32.8 ± 8.21	.01
	Control	39.73 ± 8.58	39 ± 9.05	.59
STAI-T	Yoga	49.48 ± 8.7	41.24 ± 8.22	.001
	Control	44 ± 7.88	42.26 ± 8.49	.30

Table 8. State and Trait anxiety (STAI) counts before and after yoga intervention in the patients with ulcerative colitis, compared with the patient control group.

P values are based on Wilcoxon signed rank test between baseline and 2 months.

al., 2003). Our findings of reduced anxiety in UC patients with yoga intervention and no such effect in CD patients suggest three possibilities. First, a prolonged intervention might be helpful for the patients with CD. Second, patients require individualized therapy for the relief of the anxiety that concerns them the most. Third, the tool used for the assessment of anxiety status was not appropriate. We rule out the first possibility because Keller et al. in a full year of psychotherapy was unable to observe any significant change in the anxiety and quality of life in patients with IBD (Keller et al., 2004). The STAI is a standardized tool used to assess the anxiety. Therefore, an intervention focused on the major disease related concerns of the patients with CD need to be further designed.

Previous studies by Larsson (2003) on patients with UC and CD observing the effect of a group-based education intervention for IBD did not indicate any benefits in terms of reduced anxiety or improved health-related quality of life (QOL). Similar to our observations, previous reports have also failed to show changes in the psychological measures in patients with CD (Keller et al., 2004) and in a combined group of patients with IBD (Maunder et al., 2001; Schwarz et al., 1991). On the contrary, Langhorst (2007) observed a positive effect of the stress reduction intervention on anxiety score. The yoga intervention used in this study comprised physical postures, deep breathing exercises, and meditation. Our findings are in consonance with recent reviews published in 2012, which found that a majority of studies had noted a decrease in anxiety and/or stress symptoms when a yoga intervention was implemented (Amber et al., 2012; Sharma, 2014; Pascoe & Bauer, 2015). The foundation of mind-body interventions—eliciting the relaxation—response-has an overall impact on the general well-being of the individual. In patients with IBD, mind-body interventions are found to be effective in combating the negative impact of stress, improvement in depression, trait anxiety, QOL (Schoultz et al., 2015; Kuo et al 2015; Mizrahi et al., 2012), and in reducing clinical symptoms (Berrill et al., 2014). They can be used as an adjunct to conventional pharmacological therapy. Meditation encourages detachment from distressed cognition, improves caregiver's perceived ability to control distressing thoughts, and reduces anxiety and depression (Waelde et al., 2004; Lavretsky et al., 2013). Recent studies demonstrate increased endorphin (Hartle et al., 1995) and dopamine release (Kjaer et al., 2002) in yoga practitioners.

We also hypothesized, based on our own findings from our laboratory in patients with IBS as well as the work of others in the field of cardiovascular disorders, that the approach to stress reduction experienced by yoga intervention can abate or reduce the fight-or-flight reaction characteristic of the sympathetic nervous system, particularly in

stressful or stress prone situations. Deep breathing and meditation are associated with calmness, clarity, and stability of mind, which are associated with one's ability to respond to physiological stress tests with greater effectiveness rather than with hyperactive responses. Patients with UC and CD in our study showed no significant changes in blood pressure, heart rate, respiratory rate, or in cardiovascular reflex tests in the yoga group and the control groups. The results of the previous study by Elsenbruch et al. suggest beneficial effects of a mind-body intervention on quality of life rather than on clinical or physiological parameters (e.g., release of cortisol, noradrenaline, adrenaline) in the remission phase of patients with UC (Elsenbruch et al., 2005). These findings suggest that the effects of a yoga intervention manifest themselves mainly on a psychological rather than at a physiological level. However, it has to be noted that the present study was a pilot study and we did not made any attempt to calculate the sample size beforehand; therefore, sample size in the current study may have been small to allow a more conclusive examination of physiological effects of the yoga intervention, particularly in light of the great inter-individual differences among participants in autonomic tone and other parameters. It is also possible that these greater inter-individual differences may have masked subtle changes due to the intervention. A second possibility is that we only selected patients in the remission phase of the disease or with relatively low disease activity. Moreover, additional consideration needs to be given to how yoga interventions can be delivered in a way that is most feasible and followed by all participants. Despite our efforts, inadequacy in self-reporting of yoga practice at home is possible. A group-based approach may enhance motivation for completing daily yoga practice.

The patients with UC and CD in the yoga intervention and the control group showed no change in the immunological markers in response to therapy. Earlier researchers (Elsenbruch et al., 2005) found that mind-body therapy showed no changes in circulating T cells, helper T cells, cytotoxic/suppressor T cells, NK cells, or B cells. Studies in the past decade have indicated that the immunological abnormalities in patients with IBD play a pivotal role in the pathophysiology of the stress mediated disease activation (e.g., Mawdsley & Rampton, 2005). It is well accepted that the hypothalamus-pituitary-adrenal (HPA) axis represents a major immunoregulatory system that plays an important role in balancing the immune response, especially under stressful conditions. Beside the HPA axis, the hypothalamus-autonomic nervous system (HANS) is also involved (Niijima et al., 1991; Tarao et al., 1994). Activation of both axes leads to local immunosupression, for example, in the spleen (Elenkov et al., 2000). It may be the simultaneous action of the ANS and the HPA axis that works in parallel fashion and possibly produces anti-inflammatory action in the innervated area and dampens inflammation. Straub (2002) observed that there is an uncoupling of these axes in patients with IBD, which may be a possible reason that peripheral inflammation in IBD patients is not sufficiently dampened (Straub et al., 2002). Furthermore, others have also suggested that a blunted adrenocortical response to stress may be a feature of chronic allergic inflammation such as asthma (Buske-Kirschbaum et al., 2003). We speculated that this inadequate functioning of the two anti-inflammatory axes together in patients with IBD might be a significant risk factor for the chronicity and the proper functioning of the anti-inflammatory reflex pathway.

Conclusions

In IBD, treatment goals are usually directed towards the management of digestive and systemic symptoms. Outcome and follow-up measures are typically based on clinical symptoms, laboratory findings, and endoscopic and histological features. However, since these objective measures may not necessarily correspond with patients' subjective experience of illness and health outcomes, current trends point towards improving general wellbeing and to reducing the disease associated concerns. This study suggests that medical treatment plus yoga intervention is more effective than medical treatment alone in reducing the anxiety in patients with UC.

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Competing Interests

The authors declare that they have no competing interests.

References

Abraham, C., & Cho, J. H. (2008). Inflammatory bowel disease. *The New England Journal of Medicine, 36*1(21), 2066-2078.

Berrill, J. W., Sadlier, M., Hood, K., & Green J. T. (2014). Mindfulness-based therapy for inflammatory bowel disease patients with functional abdominal symptoms or high perceived stress levels. *Journal of Chohn's and Colitis, 8*(9), 945-955.

Best, W. R., Becktel, J. M., Singleton, J. W., & Kern, F. Jr. (1976). Development of a Crohn's disease activity index. National cooperative Crohn's disease study. *Gastroenterology, 70*(3), 439-444.

Buske-Kirschbaum, A., Auer, K. V., Krieger, S., Weis, S., Rauh, W., & Hellhammer, D. (2003). Blunted cortisol response to psychological stress in asthmatic children: A general feature of atopic disease? *Psychosomatic Medicine, 65*(5), 806-810.

Duffy L. C., Zielezny, M. A., Marshall, J. R., Byers, T. E., Weiser, M. M., Philips, J. F., Calkins, B. M., Ogra, P. L., & Graham, S. (1991). Relevance of major stress events as an indicator of disease activity prevalence in inflammatory bowel disease. *Behavioral Medicine, 17*(3), 101-110.

Elenkov, I. J., Wilder, R. L., Chrousos, G. P., & Vizi, E. S. (2000). The sympathetic nerve-An integrative interface between two supersystems: the brain and the immune system. *Pharmacological Reviews, 52*(4), 595-638.

Elsenbruch, S., Langhorst, J., Popkirowa, K., Müller, T., Luedtke, R., Franken, U., Paul, A., Spahn, G., Michalsen, A., Janssen, O. E., Schedlowski, M., & Dobos, G. J. (2005). Effects of mind-body therapy on quality of life and neuroendocrine and cellular immune functions in patients with ulcerative colitis. *Psychotherapy and Psychosomatics, 74*(5), 277-287.

Freeman, R. (2006). Assessment of cardiovascular autonomic function. *Clinical Neurophysiology, 117*(4), 716-730.

Hartle, J. L., Eifert, G. H., & Smith, R. (1995). The effects of running and meditation on beta-endorphin, corticotrophin-releasing hormone and cortisol in plasma and on mood. *Biological Psychology, 40*(3), 251-265.

Jess T., Frisch M., & Simonsen J. (2013). Trends in overall and cause-specific mortality among patients with inflammatory bowel disease from 1982 to 2010. *Clinical Gastroenterology and Hepatology, 11*(1), 43-48.

Keller, W., Pritsch, M., Von Wietersheim, J., Scheib, P., Osborn, W., Balck, F., Dilg, R., Schmelz-Schumacher, E., Doppl, W., Jantschek, G., & Deter, H. C. (2004). The German study group on psychosocial intervention in Crohn's Disease. Effect of psychotherapy and relaxation on the psychosocial and somatic course of Crohn's disease: Main results of the german prospective multicenter psychotherapy treatment study on Crohn's disease. *Journal of Psychosomatic Research, 56*(6), 687-696.

Kjaer, T. W., Bertelsen, C., Piccini, P., Brooks, D., Alving, G., & Lou, H. C. (2002). Increased dopamine tone during meditation-induced changes of consciousness. *Cognitive Brain Research, 13*(2), 255-259.

Kuo, B., Bhasin, M., Jacquart, J., Scult, M. A., Slipp, L., Riklin, E. I., Lepoutre, V., Comosa, N., Norton, B. A., Dassatti, A., Rosenblum, J., Thurler, A. H., Surjanhata, B. C., Hasheminejad, N. N., Kagan, L., Slawsby, E., Rao, S. R., Macklin, E. A., Fricchione, G. L., Benson, H., Libermann, T. A., Korzenik, J., & Denninger, J. W. (2015). Genomic and clinical effects associated with a relaxation response mind-body intervention in patients with irritable bowel syndrome and inflammatory bowel disease. *PLoS One, 10*(4):e0123861.

Langhorst, J., Anthonisen, I. B, Steder-Neukamm, U., Luedtke, R., Spahn, G., Michalsen, A., & Dobos, G. J. (2007). Patterns of complementary and alternative medicine (CAM) use in patients with inflammatory bowel disease: Perceived stress is a potential indicator for CAM use. *Complementary Therapies in Medicine, 15*(1), 30-37.

Larsson, K., Sundberg Hjelm, M., Karlbom, U., Nordin, K., Anderberg, U. M., & Lööf, L. (2003). A group-based patient education programme for high-anxiety patients with Crohn's disease or ulcerative colitis. *Scandinavian Journal of Gastroenterology, 38*(7), 763-769.

Lavretsky, H., Epel, E. S., Siddarth, P., Nazarian, N., Cyr, N. S, Khalsa, D. S., Lin, J., Blackburn, E., Irwin, M. R. (2013). A pilot study of yogic meditation for family dementia caregivers with depressive symptoms: effects on mental health, cognition, and telomerase activity. *International Journal of Geriatric Psychiatry, 28*(1), 57-65.

Li A. W., & Goldsmith, C. A. (2012). The effects of yoga on anxiety and stress. *Alternative Medicine Review, 17*(1), 21-35.

Maunder, R. G., & Esplen, M. J. (2001). Supportive-expressive group psychotherapy for persons with inflammatory bowel disease. *Canadian Journal of Psychiatry, 46*(7), 622-626.

Mawdsley, J. E., Macey, M. G., Feakins, R. M., Langmead, L., & Rampton, D. S. (2006). The effect of acute psychological stress on systemic and rectal mucosal measures of inflammation in ulcerative colitis. *Gastroenterology, 131*(2), 410-419.

Mawdsley, J.E. & Rampton, D.S. (2005). Psychological stress in IBD: new insights into pathogenic and therapeutic implications. *Gut, 54*(10), 1481-1491.

Mizrahi, M. C., Reicher-Atir, R., Levy, S., Haramati, S., Wengrower, D., Israeli, E., & Goldin, E. (2012). Effects of guided imagery with relaxation training on anxiety and quality of life among patients with inflammatory bowel disease. *Psychology and Health, 27*(12), 1463-1479.

Molodecky, N. A., Soon, I. S., Rabi, D. M., Ghali, W. A., Ferris, M., Chernoff, G., Benchimol, E. I., Panaccione, R., Ghosh, S., Barkema, H. W., & Kaplan, G. G. (2012). Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. *Gastroenterology, 142*(1), 46-54.

Niijima, A., Hori, T., Aou, S., & Oomura, Y. (1991). The effects of interleukin-1 beta on the activity of adrenal, splenic and renal sympathetic nerves in the rat. *Journal of Autonomic Nervous System, 36*(3), 183-192.

Nyarko-Adomfeh, C. (1992). The long-term reproducibility of clinical tests of autonomic cardiovascular function in normal subjects. *Clinical Autonomic Research, 2*(4), 257-265.

Odes, S. (2008). How expensive is inflammatory bowel disease? A critical analysis. *World Journal of Gastroenterology, 14*(43), 6641-6647.

Pascoe, M. C., & Bauer, I. E. (2015). A systematic review of randomised control trials on the effects of yoga on stress measures and mood. *Journal of Psychiatric Research, 68*, 270-282.

Schoultz, M., Atherton, I., & Watson, A. (2015). Mindfulness-based cognitive therapy for inflammatory bowel disease patients: Findings from an exploratory pilot randomised controlled trial. *Trials, 16*(1), 379.

Schwarz, S. P., & Blanchard, E. B. (1991). Evaluation of a psychological treatment for inflammatory bowel disease. *Behavioral Research and Therapy, 29*(2), 167-171.

Sharma, M. (2014). Yoga as an alternative and complementary approach for stress management: A systematic review. *Journal of Evidence Based Complementary and Alternative Medicine, 19*(1), 59-67.

Sharma, P., Makharia, G. K., Ahuja, V., Dwivedi, S. D., & Deepak, K. K. (2009). Autonomic dysfunctions in patients with inflammatory bowel disease in clinical remission. *Digestive Disease and Science, 54*(4), 853-861.

Spielberger, C. D., Gorsuch, R. L., & Lushene, R. E. (1970). STAI manual for the state-trait anxiety inventory. Palo Alto, CA: Consulting Psychologist Press.

Straub, R. H., Herfarth, H., Falk, W., Andus, T., & Scholmerich, J. (2002). Uncoupling of the sympathetic nervous system and the hypothalamic-pituitary-adrenal axis in inflammatory bowel disease? *Journal of Neuroimmunology, 126*(1-2), 116-125.

Taneja, I., Deepak, K. K., Poojary, G., Acharya, I. N., Pandey, R. M., & Sharma, M. P. (2004). Yogic versus conventional treatment in diarrhea-predominant irritable bowel syndrome: A randomized control study. *Applied Psychophysiology and Biofeedback, 29*(1), 19-33.

Tarao, A., Oikawa, M., & Saita, M. (1994). Tissue-specific increase in norepinephrine turnover by central interleukin-1, but not by interleukin-6, in rats. *American Journal of Physiology, 266*(2), R400-R404.

Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. (1996). Heart rate variability: Standards of measurement, physiological interpretation and clinical use. *Circulation, 93*(5), 1043-1065.

Truelove, S.C., & Witts, L.J. (1955). Cortisone in ulcerative colitis; Final report on a therapeutic trial. *British Medical Journal, 2*(4947), 1041-1048.

Waelde, L.C., Thompson, L., Gallagher-Thompson, D. (2004). A pilot study of a yoga and meditation intervention for dementia caregiver stress. *Journal of Clinical Psychology, 60*(6), 677-87.

Ziegler, D., Dannehl, K., Mühlen, H., Spüler, M., & Gries, F. A. (1992). Prevalence of cardiovascular autonomic dysfunction assessed by spectral analysis, vector analysis, and standard tests of heart rate variation and blood pressure responses at various stages of diabetic neuropathy. *Diabetic Medicine: A Journal of the British Diabetic Association, 9*(9), 806-814.