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Inflammatory cytokines and oxidative stress biomarkers in irritable bowel syndrome: Association with digestive symptoms and quality of life

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ABSTRACT

A growing body of evidence suggests a possible role for low-grade inflammation in the pathogenesis of irritable bowel syndrome (IBS). The objectives of this study were to measure serum levels of tumor necrosis factor (TNF)-α, interleukin (IL)-17, interleukin (IL)-10, malondialdehyde (MDA) and total antioxidant capacity (TAC) in IBS patients and healthy controls (HCs), and to evaluate possible correlations of such markers with gastrointestinal (GI) symptoms and quality of life (QoL). Ninety Rome III positive IBS patients and 90 sex and age matched HCs were recruited. GI symptoms, IBS-QoL, IBS severity score system (IBSSS), and the serum levels of inflammatory cytokines and oxidative stress biomarkers were evaluated. In IBS patients, TNFα, IL-17 and MDA cytokines were significantly ($P < 0.05$) higher, and IL-10 cytokine and TAC were significantly ($P < 0.05$) lower vs. HCs. When comparing IBS subtypes, TNFα and IL-17 were significantly ($P < 0.05$) higher, and IL-10 was significantly ($P < 0.05$) lower in diarrhea predominant IBS (IBS-D) compared to HCs, whereas the inflammatory cytokine profile of other subtypes more closely resembled that of HCs. The serum levels of MDA and TAC were significantly different ($P < 0.05$) in all the subtypes vs. HCs. All the inflammatory cytokines had significant ($P < 0.05$) correlations with GI symptoms, IBSSS and IBS-QoL, whereas no significant association was found between oxidative stress biomarkers and these symptoms. IBS-D patients display increased pro-inflammatory cytokines and decreased anti-inflammatory cytokines. Present study demonstrated a correlation between inflammatory cytokines and both IBS symptoms and QoL.

1. Introduction

The irritable bowel syndrome (IBS) is a painful chronic functional bowel disorder which is usually associated with altered bowel habit [1]. Recent studies have provided evidence of immune cell infiltration and activation in the intestinal mucosa of IBS patients, and suggest a possible role for low-grade inflammation in the pathogenesis of IBS [1]. Inflammation or injury to tissues leads to the visceral hypersensitivity which is thought to play an important role in the development of chronic pain and discomfort in IBS patients [2]. There is a growing body of evidence demonstrating that IBS patients show altered cytokine profiles as compared to healthy groups [3]. Pro-inflammatory cytokines such as tumor necrosis factor α (TNFα), interleukin (IL)-6 and IL-8 have been shown to be elevated in IBS patients [3,4]. Previously, it has been shown that IBS patients may be genetically predisposed to produce lower amounts of the anti-inflammatory cytokine interleukin 10 [5]. Furthermore, pro-inflammatory cytokines directly affect the hypothalamus, and activate hypothalamic-pituitaryadrenal axis (HPA), the core endocrine stress system [6]. Corticotropin-releasing hormone (CRH), is the primary regulatory peptide produced in the hypothalamus in response to the inflammation [7,8]. There is an exaggerated HPA response to the inflammation, accompanied by an increased intestinal response to CRH in IBS patients, which results in generating digestive symptoms [9]. Nevertheless, a limited number of studies have assessed the relationships between inflammation and clinical symptoms of IBS. In addition, Psychological stressors have a role in activation of the HPA [10]. Psychiatric comorbidities seem to be common in IBS patients, which results in impaired quality of life (QoL), and there is an association between IBS symptoms and these comorbidities [2].

Abbreviations: IBS, irritable bowel syndrome; QoL, quality of life; IBSSS, IBS severity score system; IBS-QoL, IBS specific QoL; GI, gastrointestinal; IBS-D, diarrhea-predominant; IBS-C, constipation-predominant; IBS-A, alternating bowel habits; TNFα, tumor necrosis factor α; IL-10, interleukin 10; IL-17, interleukin 17; SD, standard deviation; VAS, visual analogue scale

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It is well documented that oxidative stress and inflammation are inevitably linked together, as leukocytes activation can produce a reactive oxygen species (ROS) by resident cells such as vascular smooth muscle and endothelial cells [11]. Enzymatic and nonenzymatic antioxidant's defense system can regulate ROS-initiated oxidative stress [12]. In 2013, a study indicated that antioxidant status against ROS is impaired in IBS patients, and alterations in the oxidant-antioxidant enzymatic system may play a role in the pathogenesis of IBS and its symptoms [12].

In the present study, inflammatory cytokines such as IL-10, IL-17 and TNFα were assessed in IBS patients. IL-17 members have an important role in inflammatory and autoimmune diseases and are potential targets for future pharmacotherapy [13]. IL-17 induces several genes associated with inflammation and mediates inflammatory responses in various tissues [14]. Moreover, we assessed oxidative stress biomarkers such as serum malondialdehyde (MDA) levels and total antioxidant capacity (TAC). The aim of the current study was to compare the inflammatory cytokines and oxidative stress biomarkers in IBS patients with healthy controls and in different subtypes of IBS. Furthermore, the relationships between inflammation and clinical symptoms were evaluated.

2. Materials and methods

2.1. Subject population

A total of 90 IBS patients consist of both genders aged between 18 to 70 were recruited by an attendant gastroenterologist through medical examination based on the Rome III Diagnostic Criteria for Functional GI Disorders for the diagnosis of IBS [15]. All the participants were elicited from the outpatient Clinic of the Jundishapur University Hospital, in February and March 2015. Patients with IBS were sub-classified as diarrhea-predominant (IBS-D), constipation-predominant (IBS-C), and those with alternating bowel habits (IBS-A) [16].

Any evidence of abdominal surgery, celiac disease, or other primary GI illnesses, GI infection, pregnancy, lactation and alcohol consumption were considered as exclusion criteria. Additional exclusion criteria consist of concurrent chronic diseases such as diabetes and diagnosed and/or treated malignancy in the past 5 years and any usage of anti-inflammatory drugs (including nonsteroids, steroids, antihistaminics, and mast cell stabilizers). A total of 90 sex and age matched healthy controls (HCs) were used for comparison. After allocation, all participants were asked to refer to the lab for blood sampling the next day.

Anthropometric measures, clinical history, demographic data and a complete physical examination of each subject were assessed. The study protocol was approved by the Medical Ethics Committee at the Jundishapur University of Medical Sciences (Registration No. ir.ajums.rec.1394.306). Approved informed consent was obtained from all the patients involved in the study.

2.2. Laboratory analyses

Blood samples were collected after an 8–12 h overnight fasting. For each sample, 5 mL of blood was drawn. Serums were frozen at −20 °C immediately and then stored at −80 °C until further laboratory analyses were carried out. Serum levels of TNFα, IL-10 and IL-17 were measured using an enzyme-linked immunosorbent assay (ELISA) (BOSTER BIOLOGICAL TECHNOLOGY Co., Ltd., USA). Tiobarbituric acid method was used for measuring serum malondialdehyde (MDA) levels [17]. For analyzing the serum total antioxidant capacity (TAC), the ferric reducing ability of plasma (FRAP) method was used [18].

2.3. Digestive symptoms, severity and quality of life

For evaluating clinical symptoms, patients' abdominal pain, dissatisfaction with bowel habits and overall GI symptoms were assessed, using a self-reporting 100-mm visual analogue scale (VAS), where 0 indicated no symptoms and 100 represented the worst symptoms ever experienced. The IBS severity score system (IBSSS) [19] was used for evaluating IBS severity. The IBSSS, which has been accredited for IBS patients, included 5 clinically applicable items over a 10-day period: (1) severity of abdominal pain, (2) frequency of abdominal pain, (3) severity of abdominal distention or tightness, (4) dissatisfaction with bowel habits, and (5) interference of IBS with life in general [19]. Each item was scored on a scale from 0 to 100, and the sum of the 5 items was considered as the rate of IBS severity (range 0–500). Quality of life was assessed via a self-report measure specific to IBS (IBS-QoL) with 34 items [20]. The individual responses to 34 items were summed and averaged for a total score and then transformed to a 0–100 scale. Higher scores indicating better IBS specific quality of life [20].

2.4. Statistical analysis

All statistical analyses were carried out using SPSS version 16 statistical software (SPSS Inc., Chicago, Ill). For all tests, two-sided P values < 0.05 were considered statistically significant unless otherwise stated. The normal distribution of data related to normality was assessed using the Kolmogorov–Smirnov test. Data were reported as mean ± standard deviation or median (25th, 75th percentile) for parametric and nonparametric data, respectively. Student's t test, χ^2-test, or Fisher's exact test were used for between the groups comparisons, when appropriate. One-way analysis of variance (ANOVA) was used for comparison of the biochemical factors in different IBS subtypes. Linear regression was used for determining the possible correlation between biochemical factors and clinical symptoms and IBS-QoL.

3. Results

3.1. Baseline Characteristics

The mean age of the subjects in the IBS group and the HCs were 37.66 (range, 21–59) and 38.69 (range, 23–59), respectively (Table 1). Among the 90 IBS patients enrolled in the study, 33.3% were IBS-C, 26.7% were IBS-D and 40% were IBS-A (Table 1). As Table 1 indicates, there were no significant differences between the IBS and HCs groups regarding the age, education, smoking, anthropometric measures and daily energy intake.

Table 1
Subject characteristics.

Characteristics	IBS patients (n = 90)	Healthy controls (n = 90)	P value
Age, years	37.66 ± 8.84	38.69 ± 9.21	0.44
Female, n (%)	61 (67.8)	61 (67.8)	
IBS subtypes, n (%): [a]			
IBS-C	30 (33.3)	–	
IBS-D	24 (26.7)	–	
IBS-A	36 (40)	–	
Education level, n (%): [a]			0.36
None/Primary	20 (22.2)	28 (31.1)	
Middle/High school	39 (43.3)	37 (41.1)	
University or higher	31 (34.4)	25 (27.8)	
Smoking status, n (%): [a]			0.12
Never	61 (67.8)	69 (76.7)	
Smoking/Ex-Smoker	29 (32.2)	21 (23.3)	
BMI, kg/m^2	25.12 ± 2.78	24.56 ± 3	0.2
Body fat percentage	28.13 ± 6.38	27.33 ± 6.1	0.4
Daily Energy Intake	1804.11 ± 188.321	1782.08 ± 187.31	0.43

IBS, irritable bowel syndrome; BMI, body mass index; IBS- C, constipation subtype; IBS-D, diarrhea subtype; IBS-A, alternating subtype.
All data are shown as mean ± standard deviation, and analyzed by two-sample t test unless otherwise indicated. P values < 0.05 were considered statistically significant.
[a] Data are numbers (%), and were analyzed by χ^2 test or Fisher's exact test. P values < 0.05 were considered statistically significant.