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Irritable Bowel Syndrome is a Multisystemic Inflammatory Disorder

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Abstract

Background: Irritable bowel syndrome (IBS) is a common cause of recurrent complaints about gastrointestinal and genitourinary tracts in adults.

Method: Consecutive patients with IBS and age and sex-matched controls were studied. IBS was diagnosed according to Rome II criteria in the absence of red flag symptoms including pain, diarrhea interfering with sleep, weight loss, fever, and any pathological finding with physical examination. Current daily smokers, patients with regular alcohol consumption (one drink a day), and patients with inflammatory, infectious, or devastating disorders were excluded.

Results: The study included 291 patients with the IBS (245 females and 46 males) and 186 control cases (156 females and 30 males). Interestingly, mean age of the IBS patients was 42.9±13.9 (17-76) years, and 84.1% of them were female. Although the mean body weight, height, body mass index, systolic and diastolic blood pressures, and hematocrit values were similar in both groups, erythrocyte sedimentation rate (ESR) (16.7 versus 13.5 mm/h, p=0.009) and C-reactive protein (CRP) values (3.1 versus 2.1mg/L, p=0.008) were higher in the IBS patients, significantly.

Conclusion: IBS is a multisystemic inflammatory disorder, probably triggered by smoking, alcohol, infections, inflammations, anxiety, depression, sleep disorders, illness fear, cancer fear, or death fear-like stresses, and eventually terminates with dysfunctions of the gastrointestinal and genitourinary tracts and elevations of ESR and CRP-like acute phase reactants in the plasma. The multisystemic inflammatory process probably induces an associated chronic endothelial damage and an accelerated atherosclerosis all over the body, and a shorthened survival in both genders.

Keywords: Irritable bowel syndrome; Smoking; Alcohol; Erythrocyte sedimentation rate; C-reactive protein; Chronic endothelial damage; atherosclerosis

Abbreviations: IBS: Irritable Bowel Syndrome; CG: Chronic Gastritis; APR: Acute Phase Reactants; ESR: Erythrocyte Sedimentation Rate; CRP: C-Reactive Protein; BP: Blood Pressures; PAD: Peripheric Artery Disease; COPD: Chronic Obstructive Pulmonary Disease; CRD: Chronic Renal Disease; CHD: Coronary Heart Disease; LDL: Low Density Lipoproteins; WCH: White Coat Hypertension; HT: Hypertension; AUD: Alcohol Use Disorder; NAD: Nicotinamide Adenine Dinucleotide; NT: Normotension

Introduction

Recurrent complaints of the gastrointestinal and genitourinary tracts are common causes of applications to the Internal Medicine and Gastroenterology Polyclinics [1]. Although gastroesophageal reflux disease, esophagitis, duodenal and/or gastric ulcers, erosive gastritis and/or duodenitis, celiac disease, chronic pancreatitis, and malignancies are found among possible causes, irritable bowel syndrome (IBS) and chronic gastritis (CG) may be the most common diagnoses. Flatulence, periods of diarrhea and constipation, repeated toilet visits due to urgent evacuation or early filling sensation, excessive straining, feeling of incomplete evacuation, frequency, urgency, reduced feeling of well-being, and eventually disturbed social life are often reported by the patients with IBS. Although many patients relate onset of symptoms to intake of food, and often incriminate specific food items, a meaningful dietary role is doubtful in the IBS. According to literature, nearly 20% of general population have IBS, and it is more common in female gender with unknown reasons, yet [2]. Psychological factors seem to precede onset and exacerbation of gut symptoms, and many potentially psychiatric disorders including anxiety, depression, sleep disorders, illness fear, cancer

fear, or death fear usually coexist with the IBS [3]. For instance, thresholds for sensations of initial filling, evacuation, urgent evacuation, and utmost tolerance recorded via a rectal balloon significantly decreased by focusing the examiners' attention on gastrointestinal stimuli by reading pictures of gastrointestinal malignancies in patients with IBS [4]. In other words, although IBS is described as a physical disorder according to Rome II guidelines, psychological factors may be crucial for triggering of these physical changes in the body. IBS is actually defined as a brain-gut dysfunction according to the Rome II criteria, and it may have more complex mechanisms affecting various systems of the body via a low-grade inflammatory process on vascular endothelium [5]. Eventually, IBS may even terminate with CG, urolithiasis, and hemorrhoids [6-8]. Similarly, some authors studied the role of inflammation in the IBS via colonic biopsies in 77 patients [9]. Although 38 patients had normal histology, 31 patients demonstrated microscopic inflammation, and eight patients fulfilled criteria for lymphocytic colitis. However, immunohistology revealed increased intraepithelial lymphocytes as well as increased CD3 and CD25 positive cells in the lamina propria of the group with "normal" histology. These features were more evident in the microscopic inflammation group who additionally revealed increased neutrophils, mast cells, and natural killer cells. All of the immunopathological abnormalities were the most evident in the lymphocytic colitis group who also demonstrated HLA-DR staining in the crypts and increased CD8 positive cells in the lamina propria [9]. A direct link between the immunological activation and IBS symptoms was shown by some other authors, too [10]. They demonstrated not only an increased mast cell degranulation in the colon but also a direct correlation between proximity of the mast cells to the neuronal elements and severity of pain in the IBS [10]. Additionally, there are some evidence about extension of the inflammatory process behind the mucosa. Some authors addressed this issue in ten patients with severe IBS by examining full thickness jejunal biopsies obtained via laparoscopy [11]. They detected a low-grade infiltration of lymphocytes in myenteric plexus of nine patients, four of whom had an associated increase in intraepithelial lymphocytes and six demonstrated evidence of neuronal degeneration [11]. Nine patients had hypertrophy of longitudinal muscles, and seven had abnormalities in the number and size of interstitial cells of Cajal [11]. The finding of intraepithelial lymphocytosis was consistent with some other reports in the colon and duodenum, too [9,12]. On the other hand, smoking and alcohol are well-known causes of chronic endothelial inflammation terminating with an accelerated atherosclerosis-induced end-organ insufficiencies all over the body [13]. We tried to understand whether or not there are some significant relationships between IBS and acute phase reactants (APR) including erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) in the present study.

Material and Methods

The study was performed in the Internal Medicine Polyclinic of the Dumlupinar University between August 2005 and March 2007. Consecutive patients with recurrent complaints about the gastrointestinal and genitourinary tracts were taken into the study. Their medical histories including smoking habit and alcohol consumption, and already used medications were learned. Patients with inflammatory, infectious, or devastating disorders including eating disorders, malignancies, acute or chronic renal failure, cirrhosis, hyper- or hypothyroidism, and heart failure were excluded. Current daily smokers and patients with regular alcohol consumption (one drink a day) were excluded, too. A routine checkup procedure including hemogram, ESR, CRP, albumin, creatinine, thyroid function tests, hepatic function tests, markers of hepatitis A, B, C, and human immunodeficiency viruses, urinalysis, a posterior-anterior chest x-ray graphy, an electrocardiogram, a Doppler echocardiogram in case of requirement, an abdominal ultrasonography, and a questionnaire for the IBS was performed. IBS was diagnosed according to Rome II criteria in the absence of red flag symptoms including pain, diarrhea interfering with sleep, weight loss, fever, and any pathological finding with physical examination. Body mass index (BMI) of each case was calculated by measurements of the Same Physician instead of verbal expressions. Weight in kilograms is divided by height in meters squared [14]. Office blood pressures (BP) were checked after a 5-minute of rest in seated position with mercury sphygmomanometer. Eventually, all patients with the IBS were collected into the first, and age and sex-matched control cases were collected into the second groups. Mean height, weight, BMI, hematocrit, ESR, CRP, and systolic and diastolic BP were detected in each group and compared in between. Mann-Whitney U test, Independent-Samples T test, and comparison of proportions were used as the methods of statistical analyses.

Results

The study included 291 patients with the IBS (245 females and 46 males) and 186 control cases (156 females and 30 males). Interestingly, mean age of the IBS patients was 42.9±13.9 (17-76) years, and 84.1% of them were female. Although the mean weight, height, BMI, systolic and diastolic BP, and hematocrit values were similar in both groups, ESR (16.7 versus 13.5 mm/h, p=0.009) and CRP values (3.1 versus 2.1 mg/L, p=0.008) were higher in the IBS patients, significantly (Table 1).

Discussion

Just after the excess weight, smoking may be the second common cause of vasculitis all over the world. It is the major risk factor for the atherosclerotic end-organ insufficiencies including coronary heart disease (CHD), peripheric artery disease (PAD), chronic obstructive pulmonary disease (COPD), chronic renal disease (CRD), cirrhosis, and stroke [13,15]. Its atherosclerotic effect is the most obvious in Buerger's disease. Buerger's disease is an obliterative vasculitis characterized by inflammatory changes in small and medium-sized arteries and veins, and it has never been reported in the absence of smoking. Beside the well-known atherosclerotic effects of smoking, some studies reported that smoking in human being and nicotine administration in

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animals are associated with lower BMI values [16]. Some evidence revealed an increased energy expenditure during smoking both on rest and light physical activity [17], and nicotine supplied by patch after smoking cessation decreased caloric intake in a dose-related manner [18]. According to the animal study, nicotine may lengthen intermeal time, and simultaneously decrease amount of meal eaten [19]. Additionally, the BMI seems to be the highest in the former, the lowest in the current, and medium in never smokers [20]. Smoking may be associated with a postcessation weight gain, but evidence suggest that risk of the weight gain is the highest during the first year after quitting and decreases with the following years [21]. Similarly, although the CHD was detected with similar prevalences in both genders, prevalences of smoking and COPD were higher in males against the higher BMI, low density lipoproteins (LDL), triglycerides, white coat hypertension (WCH), hypertension (HT), and diabetes mellitus (DM) in females [22]. This result may indicate both the atherosclerotic and weight decreasing roles of smoking [23]. Similarly, the incidence of myocardial infarctions is increased six-fold in women and three-fold in men who smoked at least 20 cigarettes per day [24]. In another word, smoking may be more harmful for women about the atherosclerotic endpoints probably due to the higher BMI and its consequences in them. Similarly, smoking is consistently higher in men in the literature [15]. So smoking is probably a powerful atherosclerotic risk factor with some suppressor effects on appetite. On the other hand, smoking-induced weight loss may be related with the vascular endothelial inflammation all over the body, since loss of appetite is one of the major symptoms of disseminated inflammation in the body. Clinicians can even understand healing of the patients by means of normalizing appetite of themselves. Several toxic substances found in cigarette smoke get into the circulation via the respiratory tract and cause a vascular endothelial inflammation until their clearance from the circulation. But due to the repeated smoking habit of the individuals, the clearance process never terminates. So, the patients become ill with loss of appetite, permanently. In another definition, smoking-induced weight loss is an indicator of being ill instead of being healthy [18-20]. After smoking cessation, appetite normalizes with a prominent weight gain but the returned weights are their physiological weights, actually. On the other hand, there may be several underlying mechanisms terminating with the IBS in smokers [25]. First of all, smoking-induced vascular endothelial inflammation may disturb epithelial functions for absorption and excretion in the gastrointestinal and genitourinary tracts. These functional problems may terminate with the symptoms and components of the IBS including loose stool, diarrhea, constipation, and urolithiasis. Secondly, diarrheal losses-induced urinary changes may even cause urolithiasis [6,7]. Thirdly, smoking-induced sympathetic nervous system activation may cause motility disorders in the gastrointestinal and genitourinary tracts. Fourthly, smoking-induced loss of appetite may terminate with obstipation. Finally, immunosuppression secondary to smoking-induced vascular endothelial inflammation may even terminate with gastrointestinal and genitourinary tract infections causing loose stool, diarrhea, and urolithiasis since some types of bacteria can provoke urinary supersaturation and modify the environment to form crystal deposits in the urine. In fact, 10% of urinary stones are struvite stones which are built by magnesium ammonium phosphate produced during infection with bacteria that possess the enzyme, urease. Similarly, urolithiasis was detected in 17.9% of cases with the IBS, whereas this ratio was 11.6% in cases without the IBS ($p<0.01$) [6]. Due to the systemic inflammatory effects of smoking, current daily smokers were excluded in the present study.

Table 1: Comparison of patients with irritable bowel syndrome and control cases without the effects of smoking and alcohol.

Variables	Patients with IBS*	p-Value	Control Cases
Number	291		186
Female ratio	84.1% (245)	Ns†	83.8% (156)
Mean age (year)	42.9±13.9 (17-76)	Ns	42.9±13.9 (13-68)
Weight (kg)	73.4±15.1 (42-122)	Ns	73.7±16.3 (44-129)
Height (cm)	161.0±8.1 (142-192)	Ns	162.6±7.8 (145-185)
BMI‡ (kg/m^2)	28.4±6.3 (15.0-51.1)	Ns	27.9±6.1 (17.8-49.0)
Systolic BP§ (mmHg)	130.4±25.2 (80-220)	Ns	134.8±28.8 (90-220)
Diastolic BP (mmHg)	90.0±12.4 (50-120)	Ns	91.1±13.8 (70-140)
ESR‖ (mm/h)	16.7±12.0 (1-87)	0.009	13.5±9.2 (2-46)
CRP** (mg/L)	3.1±3.8 (0-22)	0.008	2.1±2.6 (0-12)
Hematocrit (%)	38.6±3.8 (30-50)	Ns	38.8±4.4 (21-52)

*Irritable Bowel Syndrome; †Nonsignificant ($p>0.05$); ‡Body Mass Index; §Blood Pressures; ‖Erythrocyte Sedimentation Rate; **C-Reactive Protein

After the excess weight and smoking, alcohol may be the third common cause of vasculitis all over the world. Alcohol is the most dangerous drug, and the only drug that mostly damaged the others. It is causally linked to more than 200 different diseases, conditions, and injuries [26]. For example, people hospitalized with alcohol use disorder (AUD) have an average life expectancy of 47-53 years

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in men and 50-58 years in women and die 24-28years earlier than people in the general population [27]. People with AUD have three-fold higher mortality in men and four-fold higher mortality in women than the general population [28]. A very substantial part of the Danish excess mortality and low life expectancy compared to Sweden can be attributed to higher mortality related to alcohol and tobacco consumption [29]. Women are generally more sensitive than men to the harmful effects of alcohol, primarily due to their smaller body weight, lower capacity to metabolize alcohol, and higher proportion of body fat. Alcohol can cause liver damage, brain damage, and its consumption is one of the major leading causes of cancers all over the world [26]. Alcohol may even cause loss of consciousness and death in high amounts. Hepatic alcohol dehydrogenase is the main enzymatic system to metabolize alcohol that requires the cofactor nicotinamide adenine dinucleotide (NAD), and the products are acetaldehyde and reduced NAD. Normally, NAD is used to metabolize fats in the liver but alcohol competes with these fats for the use of NAD in drinkers. In another definition, prolonged exposure of alcohol means that fats accumulate in the liver, leading to the term of fatty liver. Acetaldehyde is subsequently metabolized by the aldehyde dehydrogenase into acetate which in turn is broken down into carbon dioxide and water. Around 5 to 10% of alcohol that is ingested is eliminated unchanged in urine, breath, and sweat. Ethanol is the only type of alcohol that is found in alcoholic beverages. Other alcohols, such as methanol and isopropyl alcohol are significantly more toxic. For example, methanol is lethal in quantities as small as 10 to 15 milliliters. Ethanol crosses biological membranes and blood-brain barrier easily, through a simple process of passive diffusion. Alcohol works in the brain primarily by increasing the effects of the gamma aminobutyric acid. This is the major inhibitory neurotransmitter of the brain. Alcohol produces happiness and euphoria, decreased anxiety, increased sociability, sedation, impairment of cognitive, memory, motor, and sensory functions, and generalized depression of central nervous system. Drinking in pregnancy can result in fetal disorders, since ethanol is classified as a teratogen. Alcohol is addictive to humans, and can result in AUD, dependence, and withdrawal. Continued alcohol consumption leads to cell death in liver, scarring, cirrhosis, and hepatocellular carcinoma. Prolonged heavy consumption of alcohol can cause permanent brain damage. Similarly, alcohol is a major contributing factor of elevated triglycerides levels in the plasma. It is well-known that plasma triglycerides are sensitive APR in the body [30]. Alcohol can also cause nausea, vomiting, peptic ulcer disease, and other gastrointestinal disorders. Similar to the smoking, regular alcohol drinkers were excluded due to the systemic inflammatory effects of alcohol in the present study.

Obesity may be one of the terminal consequences of the metabolic syndrome since after development of the obesity, nonpharmaceutical approaches provide limited benefit either to heal obesity or to prevent its complications. Excess weight may cause a chronic low-grade inflammation on vascular endothelium, and risk of death from all causes including cardiovascular diseases and cancers increases parallel to the range of excess weight in all age groups [31]. The chronic low-grade inflammatory process may even cause genetic changes on the epithelial cells, and the systemic atherosclerotic process may decrease clearance of malignant cells by the immune system. The effects of excess weight on BP were shown in the literature, extensively [32]. For example, incidence of sustained normotension (NT) was higher in the underweight (80.3%) than the normal weight (64.0%, $p<0.05$) and overweight groups (31.5%, $p<0.05$), significantly, and 52.8% of cases with HT had obesity against 14.5% of cases with the NT ($p<0.001$) [33]. So, the dominant underlying cause of the metabolic syndrome appears as weight gain, which is probably the main cause of insulin resistance, hyperlipoproteinemias, impaired fasting glucose, impaired glucose tolerance, and WCH via the prolonged low-grade inflammation on vascular endothelium all over the body [34]. Prevention of the weight gain with physical activity, even in the absence of a prominent weight loss, will probably result with resolution of many parameters of the syndrome [35-38]. According to our experiences, excess weight may actually be a consequence of physical inactivity instead of an excessive eating habit, thus prevention of weight gain cannot be achieved by diet, alone [39]. Additionally, limitation of excess weight as an excessive fat tissue around abdomen under the title of abdominal obesity is meaningless, instead it should be defined as overweight or obesity via the BMI since adipocytes function as an endocrine organ, and they produce a variety of cytokines and hormones all over the body [34]. The eventual hyperactivities of sympathetic nervous system and renin-angiotensin-aldosterone system are probably associated with chronic endothelial inflammation, insulin resistance, and elevated BP. Similarly, the Adult Treatment Panel III reported that although some people classified as overweight with larger muscular masses, most of them also have excessive fat tissue predisposing to HT, DM, CHD, and stroke-like terminal endpoints of the metabolic syndrome [14]. Interestingly, we did not find any significant association between the IBS and weight, height, or BMI in the present study.

Chronic endothelial damage may be the major underlying cause of aging and death by causing end-organ insufficiencies in human being [40]. Much higher BP of the afferent vasculature may be the major accelerating factor by causing recurrent injuries on vascular endothelium. Probably, whole afferent vasculature including capillaries are mainly involved in the process. Thus, the term of venosclerosis is not as famous as atherosclerosis in the literature. Due to the chronic endothelial damage, inflammation, edema, and fibrosis, vascular walls thicken, their lumens narrow, and they lose their elastic natures, those eventually reduce blood supply to the terminal organs, and increase systolic and decrease diastolic BP further. Some of the well-known accelerating factors of the inflammatory process are physical inactivity, sedentary lifestyle, animal-rich diet, excess weight, smoking, alcohol, chronic inflammations, prolonged infections, and cancers for

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the development of terminal consequences including obesity, HT, DM, cirrhosis, PAD, COPD, CHD, CRD, mesenteric ischemia, osteoporosis, stroke, dementia, other end-organ insufficiencies, early aging, and premature death [41]. Although early withdrawal of the accelerating factors can delay terminal consequences, after development of HT, DM, cirrhosis, COPD, CRD, CHD, PAD, mesenteric ischemia, osteoporosis, stroke, dementia, other end-organ insufficiencies, and aging, endothelial changes cannot be reversed completely due to their fibrotic natures. The accelerating factors and terminal consequences are researched under the headings of the metabolic syndrome, aging syndrome, or accelerated endothelial damage syndrome, extensively [42,43].

The acute phase response is a facet of the innate immune system that occurs in response to infections, infarctions, foreign bodies, autoimmune disorders, allergies, neoplasms, traumas, or burns-like stresses of the body. Certain mediators known as APR are increased or decreased during the acute phase response [44,45]. These markers are commonly measured in clinical practice as indicators of acute illnesses. The terms of acute phase proteins and APR are usually used synonymously, although some APR are polypeptides rather than proteins. An acute phase reaction classically presents with fever, tachycardia, and leukocytosis. Positive and negative APR are those whose concentrations increase or decrease during an acute phase response, respectively. The acute phase response is predominantly mediated by the pro-inflammatory cytokines including TNF, IL-1, and IL-6 secreted by the immune cells. In case of inflammations, infections, and tissue damages, neutrophils and macrophages release such cytokines into the circulation. The liver and some other organs respond by producing many positive APR to the cytokines. Some of the well-known positive APR are ESR, CRP, fibrinogen, ferritin, procalcitonin, hepcidin, haptoglobin, ceruloplasmin, complement proteins, and serum amyloid A. CRP is involved in innate immunity, and responsible for activating the complement pathway. Serum CRP rises rapidly, with a maximal concentration reached within two days, and falls quickly once the inflammation has resolved. Measurement of CRP is a useful indicator of inflammations in the clinics. It correlates with ESR, but not always directly. This is due to the ESR being largely dependent on elevation of fibrinogen with a half-life of one week, approximately. Thus, ESR remains higher for a longer period despite the removal of the inflammatory stimulus. Whereas CRP rises with a half-life of 6-8 hours, rapidly, and then returns to normal in case of a successful treatment, quickly. On the other hand, productions of the negative APR are suppressed at the same time. Some of the well-known negative APR are albumin, transferrin, retinol-binding protein, antithrombin, transcortin, and alpha-fetoprotein. The suppression of such proteins is also used as an indicator of inflammations. Suppression of the synthesis of such proteins may be due to the protection of amino acids for the production of positive APR, sufficiently. Due to the same reason, productions of high-density lipoproteins (HDL) and LDL may also be suppressed in the liver during the acute phase responses [46]. For example, although the similar mean age, gender distribution, smoking, and BMI in both groups, triglycerides, DM, and CHD were higher whereas LDL were lower in patients with plasma HDL values of lower than 40 mg/dL, significantly [46]. So HDL and LDL may actually behave as negative APR in the plasma. Similarly, although the lower mean age, BMI, fasting plasma glucose (FPG), and LDL, the highest CHD of the group with HDL values of lower than 40 mg/dL can also be explained by the same hypothesis [30]. Beside that although the mean triglycerides, fibrinogen, CRP, and glucose values were higher in cases with ischemic stroke, the oxidized LDL values did not correlate with the mean age, stroke severity, and outcome in another study [47]. Additionally, significant alterations occurred in the lipid metabolism and compositions of the lipoproteins, and plasma triglycerides increased whereas HDL and LDL decreased during infections [48]. Furthermore, a 10 mg/dL increase of plasma LDL values was associated with a 3% lower risk of hemorrhagic stroke in another study [49]. Similarly, the highest prevalences of HT and DM parallel to the increased values of LDL and HDL, and the highest prevalences of COPD, CHD, and CRD in contrast to the lowest values of LDL and HDL may show initially positive but eventually negative APR behaviors of LDL and HDL in the plasma [50]. So, the most desired values were between 80 and 100 mg/dL for LDL, between 40 and 46 mg/dL for HDL, and lower than 60 mg/dL for triglycerides in the plasma [30]. Parallel to ESR and CRP, plasma triglycerides and FPG may behave as positive APR in the IBS [51].

Conclusion

As a conclusion, IBS is a multisystemic inflammatory disorder, probably triggered by smoking, alcohol, infections, inflammations, anxiety, depression, sleep disorders, illness fear, cancer fear, or death fear-like stresses, and eventually terminates with dysfunctions of the gastrointestinal and genitourinary tracts and elevations of ESR, CRP, triglycerides, and FPG-like APR in the plasma. The multisystemic inflammatory process probably induces an associated chronic endothelial damage and an accelerated atherosclerosis all over the body, and a shortened survival in both genders.

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