

# IRRITABLE BOWEL SYNDROME, CHRONIC GASTRITIS, SMOKING, DEPRESSION, HAEMORRHOIDS AND UROLITHIASIS

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## Abstract

**Background:** We tried to understand whether or not there are some significant relationships between irritable bowel syndrome (IBS), chronic gastritis (CG), smoking, depression, haemorrhoids, and urolithiasis in the present study.

**Method:** IBS is diagnosed according to Rome II criteria in the absence of red flag symptoms including pain and diarrhea that awakens/interferes with sleep, weight loss, fever, and abnormal physical examination findings which are not compatible with IBS.

**Results:** The study included 647 patients with the IBS and 340 control cases. Mean age of the IBS patients was  $41.4 \pm 14.4$  (15-86) years. Interestingly, 64.2% of the IBS patients were female. Prevalence of CG (78.3% versus 15.0%), history of antidepressant use (48.0% versus 15.5%), smoking (36.4% versus 20.5%), haemorrhoids (36.1% versus 7.0%), and urolithiasis (23.3% versus 9.4%) were all significantly higher in the IBS group ( $p < 0.001$  for all).

**Conclusion:** IBS may be a low-grade inflammatory process being initiated with infection, inflammation, smoking, anxiety, depression, sleep disorders, cancer fear, or death fear-like stresses, and eventually terminates with dysfunctions of the gastrointestinal and genitourinary tracts of the body. Probably there are highly significant relationships between IBS, CG, smoking, depression, haemorrhoids, and urolithiasis.

**Key words:** Irritable bowel syndrome, chronic gastritis, smoking, depression, haemorrhoids, urolithiasis

## Introduction

Recurrent upper abdominal discomfort may be the cause of nearly half of applications to Internal Medicine Polyclinics (1). Although gastroesophageal reflux disease, esophagitis, duodenal or gastric ulcers, erosive gastritis or duodenitis, celiac disease, chronic pancreatitis, and malignancies are found among possible causes, irritable bowel syndrome (IBS) and chronic gastritis (CG) may be two of the most frequently diagnosed disorders among all. Flatulence, periods of diarrhea or 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 IBS cases. According to literature, 10-20% of general population have IBS, and it is more common in females with yet unknown reasons (2). Although many patients relate onset of symptoms to intake of food, and often incriminate specific food items, a meaningful dietary role is doubtful both in the IBS and CG. Although smoking is more common in males (3), psychological factors and smoking seem to precede onset or exacerbation of gut symptoms, and many potentially psychiatric disorders including anxiety, depression, sleep disorders, cancer fear, or death fear frequently coexist with the IBS (4, 5). For example, 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 the IBS patients (6). So although IBS is described as a physical instead of a psychological disorder according to Rome II guidelines, psychological factors, cancer fear, death fear, and smoking may be crucial for triggering of the 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 with a low-grade inflammatory process (7). For example, IBS may even terminate with CG, haemorrhoids, and urolithiasis in a significant proportion of patients (8-10). Similarly, some authors studied the role of inflammation via colonic biopsies in 77 patients with the IBS (11). 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 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 killers. All of these 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 (11). A direct link between the immunologic activation and IBS symptoms was provided by work of some other authors (12). They demonstrated not only an increased incidence of mast cell degranulation in the colon but also a direct correlation between proximity of mast cells to neuronal elements and pain severity in the IBS (12). In addition to these findings,

there is some evidence for extension of the inflammatory process behind the mucosa. Some authors addressed this issue in 10 patients with severe IBS by examining full-thickness jejunal biopsies obtained via laparoscopy (13). 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. Nine patients had hypertrophy of longitudinal muscles and seven had abnormalities in number and size of interstitial cells of Cajal. The finding of intraepithelial lymphocytosis was consistent with some other reports in the colon (11) and duodenum (14). On the other hand, smoking is a well-known cause of chronic vascular endothelial inflammation even in the gastrointestinal and genitourinary tracts of the body. We tried to understand whether or not there are some significant relationships between IBS, CG, smoking, depression, haemorrhoids, and urolithiasis 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 upper abdominal discomfort were taken into the study. Their medical histories including smoking habit, alcohol consumption, urolithiasis, and already used medications including antidepressants at least for a period of six-month were learned. Patients with devastating illnesses including eating disorders, malignancies, acute or chronic renal failure, cirrhosis, hyper- or hypothyroidism, and heart failure were excluded. Current daily smokers at least for six months and cases with a history of five pack-year were accepted as smokers. Patients with regular alcohol intake (one drink a day) were accepted as drinkers. A routine check up procedure including C-reactive protein, serum albumin, serum creatinine, thyroid function tests, hepatic function tests, markers of hepatitis A virus, hepatitis B virus, hepatitis C virus, and human immunodeficiency virus, serum IgA, urinalysis, fresh fecal sample examination, a posterior-anterior chest X-ray film, an electrocardiogram, an abdominal ultrasonography, an abdominal X-ray graphy in supine position, recto-sigmoidoscopy in cases symptomatic for haemorrhoids, and a questionnaire for IBS was performed. IBS is diagnosed according to Rome II criteria in the absence of red flag symptoms including pain and diarrhea that awakens/interferes with sleep, weight loss, fever, and abnormal physical examination findings which are not compatible with IBS. An upper gastrointestinal endoscopy was performed, and sample biopsies were taken in case of requirement. CG is diagnosed histologically, and infiltration of neutrophils and monocytes into gastric mucosa is the hallmark of CG (15). Additionally, microscopic examination shows stereotypical changes in epithelium such as degeneration, focal intestinal metaplasia, dysplasia, and glandular atrophy (15). An intravenous pyelography was performed just in suspected cases from presenting urolithiasis as a result of urinalysis and abdominal X-ray graphy. So urolithiasis was diagnosed either by medical history or as a result of current findings. Because of highly variable

clinical severity of celiac disease and high sensitivity and specificity of endomysial antibody (EMA), EMA was used as a screening test for celiac disease and jejunal biopsy was planned just for EMA positive cases to be able to see absence of villi and elongated crypts. Eventually, all patients with the IBS were collected into the first, and age and sex-matched controls were collected into the second groups. Prevalence of smoking, antidepressant use, CG, haemorrhoids, and urolithiasis 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 647 patients with the IBS and 340 control cases, totally. The mean age of the IBS patients was  $41.4 \pm 14.4$  (15-86) years. Interestingly, 64.2% (416) of the IBS cases were female. Prevalence of CG (78.3% versus 15.0%), history of antidepressant use (48.0% versus 15.5%), smoking (36.4% versus 20.5%), haemorrhoids (36.1% versus 7.0%), and urolithiasis (23.3% versus 9.4%) were all significantly higher in the IBS patients ( $p < 0.001$  for all) (Table 1). Although the presence of some social drinkers, there was not any patient with regular alcohol intake among the study cases. Additionally, we were not able to detect any patient with EMA positivity.

## Discussion

Gastric acid is probably not involved in the etiology of CG but psychological factors and smoking seem to be crucial for the development. The highly significant relationship between IBS, CG, and smoking in the present study and already known importance of psychological factors in the development of IBS and CG also support this hypothesis. Additionally, a meaningful dietary role in CG is doubtful. Although some dietary habits may trigger CG, these relationships may not always be seen even in the same patients. The most important etiologic factor of CG is

chronic infection by bacillus *Helicobacter pylori* (*H pylori*). Although *H pylori* is linked to CG, peptic ulcer, gastric carcinoma, and mucosa-associated lymphoid tissue-lymphoma (16), and it is recognised as a class I gastric carcinogen (17), and it affects more than 50% of world population, just a small subset of affected individuals experience *H pylori*-associated disorders. Some possible symbiotic relationships may take role between *H pylori* and the human body. In another definition, *H pylori* infection may be beneficial for the human body to some extent. This hypothesis is based on increased prevalence of gastroesophageal reflux disease, Barrett's esophagus, and adenocarcinoma of esophagus after eradication of *H pylori* in some countries (18). A recent study showed that *H pylori* infection protects against gastroesophageal reflux and esophageal carcinoma (18). So there may be a nearly symbiotic and balanced relationship between the bacterium and the human body. The colonization may either be beneficial or with a low biological cost to the host. Eventually, the role of *H pylori* in CG is obvious but 'why every patient with CG does not need to visit a doctor?' or 'why the patients are not always symptomatic during the infection?' are unknown. We think that CG may actually be just one of the several end-points of the IBS (9, 10). Although there is absence of a meaningful dietary role in IBS, many patients relate onset of symptoms to intake of food and often incriminate specific food items, which may actually be a result of the significant association of IBS with CG.

Urolithiasis is also an extremely common pathology in society. For example, lifetime risk of urolithiasis is around 15% for a white man and around 6% for a white woman with a lifetime recurrence rate of up to 50% (19). Approximately 80% of stones are composed of calcium oxalate (CaOx) and calcium phosphate, and CaOx is their main constituent. the remaining 10% of stones are struvite and 9% are uric acid stones. The majority of CaOx stone formers do not suffer from any systemic disease (20). It is often thought that oxalate is the primary problem in these

**Table 1: Comparison of patients with irritable bowel syndrome and control cases**

Variables	Patients with IBS*	p-value	Control cases
Number	647		340
<u>Mean age (year)</u>	<u>41.4 ± 14.4 (15-86)</u>	Ns†	41.6 ± 14.4 (15-82)
<u>Female ratio</u>	<u>64.2% (416)</u>	Ns	64.1% (218)
<u>Prevalence of smoking</u>	<u>36.4% (236)</u>	<u>&lt;0.001</u>	<u>20.5% (70)</u>
<u>Prevalence of antidepressants use</u>	<u>48.0% (311)</u>	<u>&lt;0.001</u>	<u>15.5% (53)</u>
<u>Prevalence of chronic gastritis</u>	<u>78.3% (507)</u>	<u>&lt;0.001</u>	<u>15.0% (51)</u>
<u>Prevalence of hemorrhoids</u>	<u>36.1% (234)</u>	<u>&lt;0.001</u>	<u>7.0% (24)</u>
<u>Prevalence of urolithiasis</u>	<u>23.3% (151)</u>	<u>&lt;0.001</u>	<u>9.4% (32)</u>

\*Irritable bowel syndrome †Nonsignificant ( $p > 0.05$ )

patients since excess oxalate is absorbed through the inflamed bowel wall. Similarly, low-grade vascular endothelial inflammation-induced increased absorption rate of oxalate may be one of the development mechanisms of urolithiasis in the IBS. Since although indirectly, increased oxalate absorption-induced urolithiasis was also shown, previously (21, 22). We detected ratios of urolithiasis as 15% in men and 13% in women prior (8). Interestingly, some authors reported that relative risk of developing IBS was detected as 2.48 times higher in patients with urinary stone disease, and urinary stone disease should be considered as an etiological factor of IBS (23). But actually we think of IBS as a cause of urolithiasis instead of a result due to its prolonged nature and frequently reported accompanying urinary and gynecological symptoms (8). Although there is male predominance of urolithiasis (19) against the female predominance of IBS (2), the relationship between IBS and urolithiasis may still be significant (8), and IBS may actually be a cascade of many physiological events, being initiated with infection, inflammation, smoking, and psychological disturbances like many stresses, and eventually terminating with gut dysfunction. So urolithiasis may be one of the several end-points of the physiological events' cascade, IBS. By this way, the huge gap about the underlying etiologies of most of urolithiasis cases may be explained by the high prevalence of IBS in society. On the other hand, haemorrhoids are engorged fibrovascular cushions lining the anal canal. Constipation, increased intra-abdominal pressure, and prolonged straining predispose to haemorrhoids. Almost one-half of Americans older than 50 years experience symptomatic haemorrhoids (24). Bright red, painless rectal bleeding just after defecation is the most common symptom. It was detected that beside bleeding, pain, soiling, and prolapse, many patients with grade 3-4 haemorrhoids have concomitant functional bowel symptoms, possibly associated with IBS (25). The low-grade inflammatory process all over the gastrointestinal tract, smoking, excessive straining, repeated toilet visits, and periods of constipation may be considered among possible causes of haemorrhoids in the IBS patients (9).

Smoking-induced vasculitis may be the most common type in society. Smoking is a major risk factor for the development of atherosclerotic end-points including coronary heart disease (CHD), peripheral artery disease, chronic obstructive pulmonary disease (COPD), cirrhosis, chronic renal disease, and stroke (26). Its atherosclerotic effects are the most obvious in Buerger's disease. Buerger's disease is an obliterative disease characterized by inflammatory changes in small and medium-sized arteries and veins, and it has never been reported in the absence of smoking in the literature. Although there are well-known strong atherosclerotic effects of smoking, some studies reported that smoking in humans and nicotine administration in animals are associated with a decreased body mass index (BMI) (27). Evidence revealed an increased energy expenditure during smoking both on rest and light physical activity (28), and nicotine supplied by patch after smoking cessation decreased caloric intake in a dose-related manner (29). According

to an animal study, nicotine may lengthen intermeal time and simultaneously decrease amount of meal eaten (30). Additionally, BMI seems to be the highest in the former, the lowest in the current and medium in never smokers (31). Smoking may be associated with postcessation weight gain but evidence suggests that risk of weight gain is the highest during the first year after quitting and declines over the years (32). Similarly, although CHD was detected with similar prevalence in both genders in a previous study (33), prevalence of smoking and COPD were higher in males with CHD against the higher prevalence of BMI, white coat hypertension, low density lipoproteins, triglycerides, hypertension, and diabetes mellitus in females with CHD as the other atherosclerotic risk factors. This result may indicate both the strong atherosclerotic and weight decreasing roles of smoking (34). Similarly, the incidence of a myocardial infarction is increased six-fold in women and three-fold in men who smoke at least 20 cigarettes per day (35). In other words, smoking is more dangerous for women regarding the atherosclerotic endpoints probably due to the higher BMI and its consequences in them. Parallel to the above results, the proportion of smokers is consistently higher in men in the literature (3). So smoking is probably a powerful atherosclerotic risk factor with some suppressor effects on appetite. Smoking-induced weight loss may be related to the smoking-induced chronic vascular endothelial inflammation all over the body, since loss of appetite is one of the major symptoms of inflammation in the body. Physicians can even understand healing of their patients from their normalizing appetite. 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 explanation, smoking-induced weight loss is an indicator of being ill instead of being healthy (29-31). After smoking cessation, appetite normalizes with a prominent weight gain in the patients but the returned weight is actually their physiological weight.

There may be several mechanisms terminating with IBS, CG, haemorrhoids, and urolithiasis in smokers (36). First of all, smoking-induced chronic vascular endothelial inflammation all over the body may even disturb epithelial function both for absorption and excretion in the gastrointestinal and genitourinary tracts. These functional problems may terminate with loose stool, diarrhea, constipation, and urolithiasis. Secondly, diarrheal losses-induced urinary changes may even terminate with urolithiasis (8, 9). Thirdly, smoking-induced sympathetic nervous system activation may cause motility disorders in the gastrointestinal and genitourinary tracts. Fourthly, immunosuppression secondary to smoking-induced chronic vascular endothelial inflammation all over the body may even cause 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, prevalence of urolithiasis was significantly higher in the IBS group in the present study (23.3% versus 9.4%,  $p < 0.001$ ).

As a conclusion, IBS may be a low-grade inflammatory process being initiated with infection, inflammation, smoking, anxiety, depression, sleep disorders, cancer fear, or death fear-like stresses, and eventually terminates with dysfunction of the gastrointestinal and genitourinary tracts of the body. Probably there are highly significant relationships between IBS, CG, smoking, depression, haemorrhoids, and urolithiasis.

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