

Smoking may even cause irritable bowel syndrome

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Received: January 2019; Accepted: February 2019; Published: March 1, 2019

Citation: M.R. Helvaci et al. Smoking may even cause irritable bowel syndrome. World Family Medicine. 2019; 17(3): 28-33

DOI: 10.5742/MEWFM.2019.93629

Abstract

Background: Smoking induced chronic vascular endothelial inflammation may even cause irritable bowel syndrome (IBS).

Method: IBS is diagnosed according to Rome II criteria in the absence of red flag symptoms.

Results: The study included 647 patients with IBS and 340 control cases. Mean age of the IBS patients was 41.4 years. Interestingly, 64.2% of the IBS patients were female. Prevalence of smoking was higher in the IBS cases (36.4% versus 20.5%, $p < 0.001$). Similarly, prevalence of antidepressants use was higher in the IBS patients (48.0% versus 15.5%, $p < 0.001$). Additionally, prevalence of urolithiasis was also higher in the IBS group (23.3% versus 9.4%, $p < 0.001$). Mean body mass index values were similar in the IBS and control groups (27.5 versus 27.7 kg/m², $p > 0.05$, respectively). Prevalence of white coat hypertension was also similar in them (29.3% versus 31.4%, $p > 0.05$, respectively). Although prevalence of hypertension and diabetes mellitus and mean values of total cholesterol, triglycerides, low density lipoproteins, and high density lipoproteins were all similar in them, mean value of fasting plasma glucose (FPG) was significantly higher in the IBS group (110.1 versus 105.6 mg/dL, $p = 0.013$).

Conclusion: IBS may be a low-grade inflammatory process being initiated with infection, inflammation, psychological disturbances-like stresses, and eventually terminates with dysfunctions of gastrointestinal and genitourinary tracts and other systems of the body. Although there may be several possible causes of IBS, smoking induced chronic vascular endothelial inflammation may even cause IBS. The higher FPG in the IBS patients should be researched with further studies.

Key words: Smoking, irritable bowel syndrome, metabolic syndrome, fasting plasma glucose

Introduction

One of most frequent applications to Internal Medicine Polyclinics are due to recurrent upper abdominal discomfort (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) may be one of the most frequently diagnosed diseases, clinically. 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 patients. 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, 10-20% of the general population have IBS, and it is more common among females with unknown causes (2). Psychological factors seem to precede onset or exacerbation of gut symptoms, and many potentially psychiatric disorders including anxiety, depression, or sleep disorders frequently coexist with the IBS (3). 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 cases (4). So although IBS is described as a physical instead of a psychological disorder according to Rome II guidelines, psychological factors 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 state (5). For example, IBS may even terminate with chronic gastritis, urolithiasis, and hemorrhoid in a significant proportion of patients (6-8). Similarly, some authors studied the role of inflammation via colonic biopsies in 77 patients with IBS (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 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 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 (9). A direct link between the immunologic activation and IBS symptoms was provided by work of some other authors (10). 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 (10). 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 (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. 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 (9) and duodenum (12). On the other hand, smoking is a well-known cause of chronic vascular endothelial inflammation all over the body. We tried to understand whether or not smoking induced chronic vascular endothelial inflammation all over the body is found among one of the possible causes of the IBS.

Material and methods

The study was performed in the Internal Medicine Polyclinic of the Dumrupinar University between August 2005 and March 2007. Consecutive patients with upper abdominal discomfort were taken into the study. Their medical histories including smoking habit, hypertension (HT), diabetes mellitus (DM), and already used medications including antidepressants at least for a period of six months were learned. A routine check up procedure including fasting plasma glucose (FPG), triglycerides, low density lipoproteins (LDL), high density lipoproteins (HDL), erythrocyte sedimentation rate, C-reactive protein, albumin, thyroid function tests, creatinine, urinalysis, hepatic function tests, markers of hepatitis A virus, hepatitis B virus, hepatitis C virus, and human immunodeficiency virus, a posterior-anterior chest x-ray film, an electrocardiogram, a Doppler echocardiogram in case of requirement, an abdominal ultrasonography, an abdominal X-ray graphy in supine position, 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. An additional intravenous pyelography was performed just in suspected cases from presenting urolithiasis as a result of the urinalysis and abdominal X-ray graphy. So urolithiasis was diagnosed either by medical history or as a result of clinical findings. Patients with a history of eating disorders including anorexia nervosa, bulimia nervosa, compulsive overeating, or binge eating disorder, insulin using diabetics, and patients with devastating illnesses including malignancies, acute or chronic renal failure, cirrhosis, hyper- or hypothyroidism, and heart failure were excluded to avoid their possible effects on weight. Current daily smokers at least for six months and cases with a history of five pack-year were accepted as smokers. Body mass index (BMI) of each case was calculated by the measurements of the same physician instead of verbal expressions. Weight in kilograms is divided by height in meters squared (13). Cases with an overnight FPG level of 126 mg/dL or higher on two occasions or already using antidiabetic medications were defined as diabetics. An oral glucose tolerance test with 75 grams glucose was performed in cases with FPG levels between 100 and

126 mg/dL, and diagnosis of cases with 2-hour plasma glucose levels of 200 mg/dL or higher is DM (13). Office blood pressure (OBP) was checked after a 5-minute rest in seated position with mercury sphygmomanometer on three visits, and no smoking was permitted during the previous 2 hours. Ten-day twice daily measurements of blood pressure at home (HBP) were obtained in all cases, even in normotensives in the office due to the risk of masked HT after a 10-minute education session about proper blood pressure (BP) measurement techniques (14). The education included recommendation of upper arm while discouraging wrist and finger devices, using a standard adult cuff with bladder sizes of 12 x 26 cm for arm circumferences up to 33 cm in length and a large adult cuff with bladder sizes of 12 x 40 cm for arm circumferences up to 50 cm in length, and taking a rest at least for a period of 5 minutes in the seated position before measurements. An additional 24-hour ambulatory blood pressure monitoring (ABP) was not required due to an equal efficacy of the method with HBP measurement to diagnose HT (15). Eventually, HT is defined as a mean BP of 140/90 mmHg or higher on HBP measurements and white coat hypertension (WCH) is defined as an OBP of 140/90 mmHg or higher, but a mean HBP value of lower than 140/90 mmHg (14). Eventually, all patients with the IBS were collected into the first and age and sex-matched controls were collected into the second, groups. Mean BMI, FPG, total cholesterol (TC), triglycerides, LDL, and HDL values and prevalences of smoking, antidepressants use, urolithiasis, WCH, HT, and DM 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 ± 14.4 (15-86) years. Interestingly, 64.2% (416) of the IBS patients were female. Prevalence of smoking was significantly higher in cases with the IBS (36.4% versus 20.5%, $p < 0.001$). Similarly, prevalence of antidepressants use was higher in cases with the IBS (48.0% versus 15.5%, $p < 0.001$). Beside that prevalence of urolithiasis was also higher in the IBS group (23.3% versus 9.4%, $p < 0.001$). Mean BMI values were similar both in the IBS and control groups (27.5 versus 27.7 kg/m², $p > 0.05$, respectively). Additionally, prevalence of WCH was similar in both groups, too (29.3% versus 31.4%, $p > 0.05$, respectively). Although prevalence of HT and DM and mean values of TC, triglycerides, LDL, and HDL were all similar in both groups ($p > 0.05$ for all), mean value of FPG was significantly higher in the IBS group with unknown reasons, yet (110.1 versus 105.6 mg/dL, $p = 0.013$) (Table 1).

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

Variables	Patients with IBS*	p-value	Control cases
Number	647		340
Mean age (year)	41.4 ± 14.4 (15-86)	Ns†	41.6 ± 14.4 (15-82)
Female ratio	64.2% (416)	Ns	64.1% (218)
Prevalence of smoking	36.4% (236)	<0.001	20.5% (70)
Prevalence of antidepressants use	48.0% (311)	<0.001	15.5% (53)
Prevalence of urolithiasis	23.3% (151)	<0.001	9.4% (32)
Mean BMI‡ (kg/m ²)	27.5 ± 5.7 (15.0-51.1)	Ns	27.7 ± 5.9 (16.5-49.0)
Prevalence of WCH§	29.3% (190)	Ns	31.4% (107)
Prevalence of HT	13.9% (90)	Ns	14.7% (50)
Mean FPG** (mg/dL)	110.1 ± 38.2 (66-338)	0.013	105.6 ± 33.0 (70-323)
Prevalence of DM***	8.6% (56)	Ns	10.0% (34)
Mean TC**** (mg/dL)	198.7 ± 41.7 (105-352)	Ns	198.3 ± 42.5 (110-296)
Mean triglycerides (mg/dL)	159.9 ± 96.4 (20-622)	Ns	147.6 ± 103.7 (27-857)
Mean LDL***** (mg/dL)	125.3 ± 34.7 (10-282)	Ns	125.0 ± 32.4 (54-231)
Mean HDL***** (mg/dL)	46.8 ± 13.5 (24-124)	Ns	46.1 ± 10.2 (26-72)

*Irritable bowel syndrome †Nonsignificant ($p > 0.05$) ‡Body mass index §White coat hypertension ||Hypertension
 Fasting plasma glucose *Diabetes mellitus ****Total cholesterol *****Low density lipoproteins *****High density lipoproteins

Discussion

Smoking may be found among one of the most common causes of vasculitis all over the world. It is a major risk factor for the development of atherosclerotic endpoints including coronary heart disease (CHD), peripheral artery disease (PAD), chronic obstructive pulmonary disease (COPD), cirrhosis, chronic renal disease (CRD), and stroke (16, 17). 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 the well-known strong atherosclerotic effects of smoking, some studies reported that smoking in humans and nicotine administration in animals are associated with a decreased BMI (18). Evidence revealed an increased energy expenditure during smoking both on rest and light physical activity (19), and nicotine supplied by patch after smoking cessation decreased caloric intake in a dose-related manner (20). According to an animal study, nicotine may lengthen intermeal time and simultaneously decreases amount of meal eaten (21). Additionally, BMI seems to be the highest in the former, the lowest in the current and medium in never smokers (22). 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 (23). Similarly, although CHD was detected with similar prevalence in both genders in a previous study (24), prevalence of smoking and COPD were higher in male patients with CHD against the higher prevalences of BMI, WCH, LDL, triglycerides, HT, and DM in female patients with CHD as the other atherosclerotic risk factor. This result may indicate both the strong atherosclerotic and weight decreasing roles of smoking (25). Similarly, the incidence of a myocardial infarction is increased sixfold in women and threefold in men who smoke at least 20 cigarettes per day compared to the never smoked cases (26). 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 (17). So smoking is probably a powerful atherosclerotic risk factor with some suppressor effects on appetite. Smoking induced loss of weight gain may be related with 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 its 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 (20-22). After smoking cessation, appetite normalizes with a prominent

weight gain in the patients but the returned weights are their physiological weights, actually.

There may be several underlying mechanisms terminating with the symptoms of IBS in smokers. First of all, smoking induced chronic vascular endothelial inflammation all over the body may even disturb epithelial functions both for absorption and excretion in the gastrointestinal and genitourinary tracts. These functional problems may terminate with the symptoms and signs of IBS including loose stool, diarrhea, constipation, and urolithiasis. Secondly, diarrheal losses induced urinary changes may even terminate with the urolithiasis (6, 7). Thirdly, smoking induced sympathetic nervous system activation may cause motility disorders in the gastrointestinal and genitourinary tracts. Lastly, immunosuppression secondary to the 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%, $p < 0.001$).

Chronic endothelial damage may be the leading cause of aging by causing tissue hypoxia all over the body. Probably whole afferent vasculature including capillaries are mainly involved in the process since much higher BP of the afferent vasculature may be the major underlying cause via recurrent endothelial injuries. Thus the term of venosclerosis is not as famous as atherosclerosis in the literature. Secondary to the chronic endothelial damage, inflammation, edema, and fibrosis, vascular walls become thickened, their lumens are narrowed, and they lose their elastic nature which reduces blood flow and increases BP further. Some of the well-known accelerators of the disseminated atherosclerotic process are physical inactivity, excess weight, smoking, alcohol, and chronic inflammatory or infectious processes including sickle cell diseases, rheumatologic disorders, tuberculosis, and cancers for the development of terminal endpoints including obesity, HT, DM, PAD, COPD, pulmonary hypertension (PHT), CRD, CHD, cirrhosis, mesenteric ischemia, osteoporosis, and stroke, all of which terminate with early aging and premature death. They were researched under the title of metabolic syndrome, extensively (27, 28). Although early withdrawal of the causative factors may delay development of the endpoints, the endothelial changes cannot be reversed completely after the development of obesity, HT, DM, PAD, COPD, PHT, CRD, CHD, or stroke due to their fibrotic nature (29, 30).

Obesity may be found among one of the endpoints of the metabolic syndrome, since after development of obesity, nonpharmaceutical approaches provide limited benefit either to heal obesity or to prevent its complications.

Overweight and obesity may lead to a chronic low-grade inflammatory process on vascular endothelium, and risk of death from all causes including cardiovascular diseases and cancers that increase parallel to the range of excess weight in all age groups (31). The low-grade chronic inflammatory process may cause genetic changes on the epithelial cells, and the systemic atherosclerotic process may decrease clearance of malignant cells by the immune system, effectively (16). The effects of excess weight on BP were shown by several studies (32) in that the prevalence of sustained normotension (NT) was significantly higher in the underweight (80.3%) than the normal weight (64.0%, $p < 0.05$) and overweight cases (31.5%, $p < 0.05$), and 52.8% of cases with HT had obesity against 14.5% of cases with t NT ($p < 0.001$) (33). So the dominant underlying cause of the metabolic syndrome appears as gaining weight, which is probably the major cause of insulin resistance, hyperlipoproteinemias, impaired fasting glucose, impaired glucose tolerance, and WCH via a chronic low-grade inflammatory process on vascular endothelium all over the body (34). Even prevention of the accelerated trend of gaining weight with exercise, even in the absence of a prominent weight loss, will probably result with resolution of many parameters of the metabolic syndrome (35-38). But according to our experience, excess weight may actually be a consequence of physical inactivity instead of an excessive eating habit thus prevention of gaining weight cannot be achieved by diet alone (39). Additionally, limitation of excess weight as an excessive fat tissue around the abdomen under the heading of abdominal obesity is meaningless, instead it should be defined as overweight or obesity by means of BMI since adipocytes function as an endocrine organ, and they produce a variety of cytokines and hormones anywhere in 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 have a large muscular mass, most of them have excessive fat tissue predisposing to hyperlipoproteinemias, HT, DM, CHD, and stroke (13).

As a conclusion, IBS may be a low-grade inflammatory process being initiated with infection, inflammation, psychological disturbances-like stresses, and eventually terminated with dysfunctions of the gastrointestinal and genitourinary tracts, and other systems of the body. Although there may be several possible causes of IBS, smoking induced chronic vascular endothelial inflammation all over the body may even cause IBS. The higher FPG in the IBS patients should be researched with further studies.

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