SMOKING MAY EVEN TERMINATE WITH IRRITABLE BOWEL SYNDROME

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Abstract

Background: Smoking induced chronic vascular endothelial inflammation may be found among several underlying causes of irritable bowel syndrome (IBS).

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

Results: The study included 331 patients with the IBS and 334 control cases. The mean age of the IBS patients was 41.8 years. Interestingly, 65.2% of the IBS patients were female. Prevalence of smoking was significantly higher in patients with the IBS (37.7% versus 20.6%, $p<0.001$). Similarly, prevalence of antidepressants use was also higher in the IBS cases (51.3% versus 15.8%, $p<0.001$). As an important component of the metabolic syndrome, prevalence of white coat hypertension (WCH) was significantly lower among the IBS patients (26.5% versus 31.7%, $p<0.05$). Similarly, mean values of triglycerides ($p= 0.011$) and low density lipoproteins (LDL) ($p<0.05$) were significantly lower and mean value of high density lipoproteins (HDL) was significantly higher in the IBS patients ($p<0.05$).

Conclusion: IBS may be a low-grade inflammatory process being initiated with infections, inflammations, psychological disturbances-like stresses, and eventually terminated with dysfunctions of the gastrointestinal and genitourinary tracts, and many other systems of the body. Although there may be several underlying causes of IBS, smoking induced chronic vascular endothelial inflammation all over the body may even terminate with IBS. The lower prevalence of WCH, lower values of triglycerides and LDL, and higher value of HDL in the IBS patients may be caused by smoking induced loss of weight gain secondary to chronic endothelial inflammation in the whole body.

Key words: Irritable bowel syndrome, smoking, metabolic syndrome, weight gain, white coat hypertension, hyperlipoproteinemias

Introduction

One of most frequent applications to Internal Medicine Polyclinics is 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 several 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, yet (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, or hemorrhoid in a significant proportion of patients (6-8). Similarly, some authors have studied the role of inflammation via colonic biopsies in 77 patients with the 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 beyond 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 in the whole body is found among several underlying causes of the IBS.

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 included into the study. Their medical histories including smoking habit, hypertension (HT), diabetes mellitus (DM), and 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, 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, 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. 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-years 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-gram 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-minute 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 prevalence of smoking, antidepressants use, 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 331 patients with the IBS and 334 control cases, totally. The mean age of the IBS patients was 41.8 ± 14.8 (17-86) years. Interestingly, 65.2% (216) of the IBS patients were female. Prevalence of smoking was significantly higher in cases with the IBS (37.7% versus 20.6%, p<0.001). Similarly, prevalence of antidepressants use was also higher in cases with the IBS (51.3% versus 15.8%, p<0.001). Mean BMI values were similar both in the IBS and control groups (27.6 versus 27.7 kg/m2, p>0.05, respectively). Interestingly, prevalence of WCH was significantly lower in the IBS group (26.5% versus 31.7%, p<0.05). Although prevalence of HT and DM and mean values of FPG and TC were all similar in both groups (p>0.05 for all), mean values of triglycerides (113.3 versus 147.7 mg/dL, p= 0.011) and LDL (118.4 versus 125.0 mg/dL, p<0.05) were significantly lower and mean value of HDL was significantly higher in the IBS group (50.6 versus 46.1 mg/dL, p<0.05) (Table 1).

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

Variables	Patients with IBS*	*p*-value	Control cases
Number	331		334
Mean age (year)	41.8 ± 14.8 (17-86)	Ns†	41.8 ± 14.4 (15-82)
Female ratio	***65.2% (216)***	Ns	65.2% (218)
Prevalence of smoking	***37.7% (125)***	***<0.001***	***20.6% (69)***
Prevalence of antidepressants use	***51.3% (170)***	***<0.001***	***15.8% (53)***
Mean BMI‡ (kg/m2)	27.6 ± 5.8 (15.0-50.5)	Ns	27.7 ± 5.9 (16.5-49.0)
Prevalence of WCH§	***26.5% (88)***	***<0.05***	***31.7% (106)***
Prevalence of HT‖	15.7% (52)	Ns	14.3% (48)
Mean FPG** (mg/dL)	108.3 ± 35.1 (66-321)	Ns	105.7 ± 33.3 (70-323)
Prevalence of DM***	9.9% (33)	Ns	10.1% (34)
Mean TC**** (mg/dL)	200.9 ± 39.7 (105-337)	Ns	198.3 ± 42.5 (110-296)
Mean triglycerides (mg/dL)	***113.3 ± 42.9 (38-198)***	***0.011***	***147.7 ± 104.0 (27-857)***
Mean LDL** (mg/dL)***	***118.4 ± 28.7 (10-269)***	***<0.05***	***125.0 ± 32.4 (54-231)***
Mean HDL*** (mg/dL)***	***50.6 ± 9.7 (40-80)***	***<0.05***	***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), peripheric 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. It 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 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 former, the lowest in current and medium in never smokers (22). Smoking may be associated with postcessation weight gain but evidence suggests that risk of weight gaining 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 prevalence of BMI, WCH, LDL, triglycerides, HT, and DM in female patients with CHD as the other atherosclerotic risk factors. 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 athersclerotic 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 returning appetite. Several toxic substances found in cigarette smoke get into the circulation by means of 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 (20-22). After smoking cessation, normal appetite comes back with a prominent weight gain in the patients but the returned weight is their physiological or 'normal' weight, 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, or urolithiasis. Additionally, diarrheal losses induced urinary changes may even terminate with the urolithiasis (6, 7). On the other hand, smoking induced sympathetic nervous system activation may cause motility disorders in the gastrointestinal and genitourinary tracts. Thirdly, 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.

Chronic endothelial damage may be the leading cause of aging and associated morbidity and mortalities by causing disseminated 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 by inducing recurrent endothelial injuries. Therefore 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 in the literature, extensively (27, 28). Although early withdrawal of the causative factors may delay development of the terminal endpoints, the endothelial changes cannot be reversed after the development of obesity, HT, DM, PAD, COPD, PHT, CRD, CHD, or stroke due to their fibrotic nature (29, 30).

Obesity is probably found among one of the irreversible 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 increases 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); 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 groups (31.5%, $p<0.05$), and 52.8% of cases with HT had obesity against 14.5% of cases with the NT ($p<0.001$) in another study (33). So the dominant underlying cause of the metabolic syndrome appears as weight gaining, 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 (34). Even prevention of the accelerated trend of weight gaining with diet or exercise, even in the absence of a prominent weight loss, will probably result with resolution of many parameters of the metabolic syndrome (35-37). But according to our opinion, limitation of excess weight as an excessive fat tissue around 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 infections, inflammations, psychological disturbances-like stresses, and eventually terminated with dysfunctions of the gastrointestinal and genitourinary tracts, and many other systems of the body. Although there may be several underlying causes of IBS, smoking induced chronic vascular endothelial inflammation all over the body may even terminate with IBS. The lower prevalence of WCH, lower values of triglycerides and LDL, and higher value of HDL in the IBS patients may be caused by smoking induced loss of weight gain secondary to chronic endothelial inflammation in the whole body.

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