Irritable bowel syndrome and metabolic parameters

Mehmet Rami Helvaci (1)
Mustafa Yaprak (1)
Yusuf Aydin (1)
Abdulrazak Abyad (2)
Lesley Pocock (3)

(1) Specialist of Internal Medicine, MD
(2) Middle-East Academy for Medicine of Aging, MD
(3) medi+WORLD International

Corresponding author:
Mehmet Rami Helvaci, MD
07400, ALANYA, Turkey
Phone: 00-90-506-4708759
Email: mramihelvaci@hotmail.com

Abstract

Background: We tried to understand whether or not there are some significant relationships between irritable bowel syndrome (IBS) and parameters of the metabolic syndrome.

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

Results: The study included 331 patients with 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 IBS (37.7% versus 20.6%, p<0.001). Mean values of body mass index were similar in both groups (27.6 versus 27.7 kg/m2, p>0.05). As an important component of the metabolic syndrome, prevalence of white coat hypertension was significantly lower among the IBS patients (26.5% versus 31.7%, p<0.05). Although prevalence of hypertension and diabetes mellitus and mean values of fasting plasma glucose and total cholesterol were all similar in both groups (p>0.05 for all), mean values of triglycerides (p= 0.011) and low density lipoproteins (p<0.05) were significantly lower and mean value of high density lipoproteins was significantly higher in the IBS patients (p<0.05).

Conclusion: IBS may be a low-grade inflammatory process being initiated with infections, inflammation, psychological disturbances-like stresses, and eventually terminated with dysfunction of the gastrointestinal and genitourinary tracts, and many other systems of the body. Although there may be a direct relationship between IBS and smoking, there may be some inverse relationships between IBS and parameters of the metabolic syndrome with some unknown mechanisms yet.

Key words: Irritable bowel syndrome, metabolic syndrome, body mass index, white coat hypertension, hyperlipoproteinemias

Citation: Received: September 2018; Accepted: October 2018; Published: December 1, 2018. Citation: Helvaci M.R. et al. Irritable bowel syndrome and metabolic parameters. Middle East Journal of Psychiatry and Alzheimers. 2018; 9(2): 15-20. DOI: 10.5742MEPA.2018.93588

Introduction

One of the 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 general population have IBS, and it is more common among females with yet 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 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 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 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, metabolic syndrome is a well-known cause of chronic vascular endothelial inflammation all over the body, and there are several reports about its components (13). We tried to understand whether or not there are some significant relationships between the IBS and some parameters of the metabolic syndrome.

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 already used medications were learnt. 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 devastating illnesses including type 1 DM, malignancies, acute or chronic renal failure, chronic liver disease, hyper- or hypothyroidism, and heart failure were excluded to avoid their possible effect 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 (14). 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 (14). 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 about proper blood pressure (BP) measurement techniques (15). 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 (16). 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 (15). 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, 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 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). 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).

Discussion

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 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 and as such reduce blood flow and increase 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, peripheric artery disease (PAD), chronic obstructive pulmonary disease (COPD), pulmonary hypertension (PHT), chronic renal disease (CRD), coronary heart disease (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 (17, 18). Although early withdrawal of the causative factors may delay development of the terminal endpoints, the endothelial changes cannot be reversed completely after

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)***
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

the development of obesity, HT, DM, PAD, COPD, PHT, CRD, CHD, or stroke due to their fibrotic nature (19, 20). 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 (21). 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 (22). The effects of excess weight on BP were shown by several studies (23) 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 (24). So the dominant underlying cause of the metabolic syndrome appears as weight gain, which is probably the major cause of insulin resistance, hyperlipoproteinemias, impaired fasting glucose (IFG), impaired glucose tolerance (IGT), and WCH via a chronic low-grade inflammatory process on vascular endothelium (25). Even prevention of the accelerated trend of weight gain 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 (26, 27). 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 (25). The eventual hyperactivity 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 a large muscular mass, most of them also have excess fat tissue, and excess weight does not only predispose to CHD, stroke, and other endpoints, it also has a high burden for other CHD risk factors including hyperlipoproteinemias, HT, and DM (14).

WCH is a condition characterized by elevated BP in medical settings combined with normal ABP or self-measured HBP. As already detected in some other studies (16, 28), both methods were equally effective for the diagnosis of WCH and HT. Similarly, recent HT guidelines propose self-measurement of HBP as an important technique to evaluate response to antihypertensive therapy, to improve compliance with therapy, and as an alternative to ABP to confirm or refute the WCH (29). In the above study (16), we observed very high prevalence of WCH in society, 33.3% in the second, 46.6% in the third, 50.0% in the fourth, 48.9% in the fifth, 36.9% in the sixth, 19.2% in the seventh, and 8.3% in the eighth decade of life, and prevalence of HT initially started to be higher than 40% in the sixth decade, and it reached up to 75.0% in the eighth decade of life. On the other hand, the prevalence of HT was detected as just 3.0% in the third, 8.0% in the fourth, and 21.2% in the fifth decade of life (16). The high prevalence of WCH in society was also shown in some other reports (30, 31). So as a hypothesis, we come to the result that all HT cases, 75.0% in the eighth decade of life (16), may arise from the previous WCH cases but WCH may actually be an acute phase reactant alarming several consequences other than increased BP alone. Although it was postulated in a recent review that patients with WCH are characterized by absence of target organ damage induced by HT, absence of risk of future cardiovascular disease related to HT, and absence of lowering of BP from antihypertensive treatment (32), we evaluated WCH not as a cause of HT alone but as an acute phase reactant mainly alarming excess weight and many associated disorders in the future (23). When we compared the underweight, normal weight, and overweight groups according to BP variability, beside the significantly decreased prevalence of sustained NT from the underweight towards the normal weight and overweight groups, the prevalence of WCH increased in the same direction, significantly (23). Eventually, the prevalence of WCH reached up to 68.4% in the overweight group, and only 31.5% of the overweight group had sustained NT although the very young mean age of them (24.8 ± 4.3 years) (23). Similarly, we detected the prevalence of WCH as 33.3% even in the second and 46.6% in the third decades of life, although the lower prevalence of overweight and obesity in these age groups in the other study (16). On the other hand, when we compared the sustained NT, WCH, and HT groups in another study (28), WCH cases were found in between according to the frequencies of almost all of the following disorders including obesity, IFG, IGT, DM, hypertriglyceridemia, hyperbetalipoproteinemia, and dyslipidemia, and nearly all of the disorders showed a gradual and significant progression in frequencies from the sustained NT towards the WCH and HT cases. As a surprising result of the above study (28), the prevalence of smoking significantly decreased from the sustained NT towards HT and WCH groups, but actually 38.8% of the sustained NT, 65.1% of the WCH, and 55.1% of the HT cases were female and we totally studied 45 smokers, 39 of those were male. So the highest the female ratio of the WCH group showed the lowest the smoking ratio and the lowest the female ratio of the sustained NT group showed the highest smoking ratio. On the other hand, 19.6%, 35.6%, and 68.4% of WCH cases in the underweight, normal weight, and overweight groups, respectively, may indicate that WCH may be a significant component of the metabolic syndrome (13, 18, 23).

Probably plasma lipoprotein levels are under dynamic control, and they may act as acute phase reactants indicating inflammation anywhere in the body. Physical inactivity, increased BMI, smoking, alcohol, elevated BP, increased plasma glucose, prolonged infection or inflammations, and cancers may cause overproduction of very low density lipoproteins (VLDL) in the liver. VLDL

carry endogenous triglycerides from liver to peripheric tissues both to use and store. In capillaries of adipocytes and muscular tissues, 90% of triglycerides are removed by a specific group of lipases. These lipases degrade VLDL into intermediate density lipoproteins (IDL), and IDL are then degraded into LDL by removal of more triglycerides. The fate of LDL is uncertain but liver removes about 70%. A small amount of LDL in circulation is uptaken by scavenger receptors on macrophages that may migrate into arterial walls, where they become the foam cells of atherosclerotic plaques. Hyperlipoproteinemias may result from overproduction or defective clearance of VLDL or increased conversion of VLDL into LDL. The hyperlipoproteinemias by aging may actually be caused by physical inactivity, excess weight, elevated BP, or increased plasma glucose levels induced disseminated endothelial damage, inflammation, fibrosis, and eventual atherosclerosis all over the body. Eventually, high TC and LDL levels are independently associated with CHD. Familial hypobeta- and alphalipoproteinemias are associated with decreased prevalence of CHD and other atherosclerotic sequelae, and they have been referred to as the Longevity syndromes. Similarly, lower HDL values of vegetarian populations may also terminate with lower LDL values and CHD rates, too.

Although the IBS may be a low-grade inflammatory process mainly affecting the gastrointestinal and genitourinary tracts with a higher prevalence in females (6-8), and although there may be a direct relationship between IBS and smoking (33), the significantly lower prevalence of WCH, the significantly lower mean values of triglycerides and LDL, and the significantly higher mean value of HDL in patients with the IBS may be explained by the great attention of such patients on their health due to their prominent disease fear or cancer fear . On the other hand, the significantly higher prevalence of smoking in them may also be explained by some antidepressive properties of smoking.

As a conclusion, IBS may be a low-grade inflammatory process being initiated with infections, inflammation, psychological disturbances-like stresses, and eventually terminated with dysfunction of the gastrointestinal and genitourinary tracts, and many other systems of the body. Although there may be a direct relationship between IBS and smoking, there may be some inverse relationships between IBS and parameters of the metabolic syndrome with some yet unknown mechanisms.

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