

The effect of irritable bowel syndrome on carotid intima-media thickness, pulse wave velocity, and heart rate variability

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ABSTRACT

Objective: Irritable bowel syndrome (IBS), a subgroup of functional somatic disorders, may be associated with autonomic dysfunction (AD). Heart rate variability (HRV), a measure of autonomic dysfunction, may predict survival. The aim of this study was to investigate the effect of IBS on HRV parameters, carotid intima-media thickness (CIMT) and carotid-femoral pulse wave velocity (cf-PWV) as surrogates of AD, subclinical atherosclerosis and arterial stiffness, respectively.

Methods: Our study was cross-sectional and observational. Thirty consecutive patients with IBS and 30 control participants underwent 24-hour Holter monitoring, cf-PWV assessment and CIMT measurement. The diagnosis of IBS was based on Rome III criteria. There were 24 patients with IBS-Constipation (80%), 4 patients with IBS-Diarrhea (13.3%), and 2 patients with IBS-Mixed (6.7%) in IBS group. Student t-test and χ^2 test were utilized in order to compare continuous and categorical variables between two groups, respectively.

Results: Biochemical parameters did not differ between groups except for slightly increased creatinine in patients with IBS. cf-PWV and CIMT values were similar between groups. SDNN index and RMSSD were significantly impaired in patients with IBS compared to controls. Frequency analyses revealed lower LF, HF, and VLF in subjects with IBS.

Conclusion: We demonstrated decreased parasympathetic modulation in patients with constipation predominant IBS. However, we could not demonstrate any changes in vascular structure and functions measured by carotid intima-media thickness and pulse wave velocity. Our results do not support accelerated atherosclerosis in IBS population (*Anadolu Kardiyol Derg 2014; 14: 525-30*).

Key words: atherosclerosis, autonomic dysfunction, arterial stiffness, carotid intima-media thickness, heart rate variability, irritable bowel syndrome

Introduction

Irritable bowel syndrome (IBS) is a functional disorder characterized with recurrent abdominal pain or discomfort which is associated with alterations in frequency or form of stool and improvement after defecation (1). IBS is highly prevalent, affecting nearly 20% of general population. Although the pathophysiology of this syndrome have not been clarified; impaired autonomic regulation, altered intestinal motility and increased visceral sensitivity have been proposed as mediators (2).

Arterial stiffness (AS) due to decreased arterial compliance is one of the major signs of vascular aging (3). Several studies have documented the prognostic importance of arterial stiffness as an independent predictor of all-cause mortality and cardiovascular mortality (4, 5). Carotid-femoral pulse wave velocity

(cf-PWV) has been accepted as the gold standard measurement of arterial stiffness. Carotid-femoral pulse wave velocity is a well-recognized predictor of an adverse cardiovascular outcome with higher predictive value than classical cardiovascular risk factors and requires little technical expertise (6).

Non-invasive measurement of carotid intima-media thickness (CIMT) using B-Mode ultrasonography is a valid surrogate marker of atherosclerotic disease (7). An increase in CIMT is associated with increased cardiovascular risk factors (8) and cardiovascular events (9). CIMT is a reliable, reproducible and quantifiable method for detecting subclinical cardiovascular disease, which is independent of traditional risk factors (10).

Heart rate variability (HRV) is a validated tool in estimating autonomic functions (11). An abnormal HRV predicts mortality in patients after myocardial infarction (12) and is associated with

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coronary artery disease in patients with diabetes mellitus (13). The association of altered HRV and IBS has long been sought. Although, several observational studies has focused on impaired HRV in patients with IBS, the results of these studies are controversial; some found no difference (14-16) whereas others revealed differences in HRV when patient characteristics like predominant bowel patterns (14, 17), pain severity (18), sleep patterns (16), and presence of anxiety or depression (19) were taken into account. To date, the association of HRV and atherosclerosis markers in the setting of IBS has not been evaluated. Since long standing autonomic dysregulation may increase atherosclerosis in certain populations, we planned to investigate whether HRV parameters, CIMT and cf-PWV as surrogates of autonomic dysfunction, subclinical atherosclerosis, and arterial stiffness are impaired in patients with IBS compared to controls.

Methods

Study design

Our study was cross-sectional and observational, consisting of 30 female patients with IBS (mean age: 45±12 yrs) and 30 healthy control women (mean age: 47±10 yrs). Informed consent was obtained from all patients prior to the study. The study was performed in accordance with the principles stated in the Declaration of Helsinki and was approved by the Local Ethics Committee.

Patient selection

Women in the IBS group were diagnosed if they were experiencing symptoms compatible with Rome III criteria (1). Predominant bowel patterns were defined using Bristol stool scale (20) and Rome III criteria (1). Patients with a predominant (>25% of time) Bristol stool scale 1-2 pattern were classified as IBS-Constipation (IBS-C), patients with a predominant 6-7 pattern were acknowledged as IBS-Diarrhea (IBS-D), and the remaining patients were assigned to mixed (IBS-M) group.

Patients with previous cardiovascular disease, inflammatory bowel disease, previous gastrointestinal surgery, chronic renal and liver failure, history of cardiac arrhythmia, and patients taking medications that could interfere with HRV such as beta-blockers, antihistaminic agents, benzodiazepines, or antidepressants were excluded.

Control subjects were recruited among healthy volunteers without a history of cardiovascular disease and symptoms compatible with IBS, who were seen by their family physician for routine annual examination and agreed to join a vascular health-screening study for research purposes.

Baseline characteristics

Baseline characteristics were recorded during interview with the patient. Hypertension was defined as active use of

antihypertensive drugs or documentation of blood pressure more than 140/90 mm Hg (21). Diabetes mellitus was defined as fasting plasma glucose levels over 126 mg/dL or glucose level over 200 mg/dL at any measurement or active use of antidiabetic treatment (22). Patients who were using tobacco products on admission to our hospital and those who quit smoking within the last year were considered as smokers. Body mass index (BMI) was calculated by the following formula: $BMI = \text{weight (kg)} / \text{height}^2 \text{ (m)}$.

Measurement of heart rate variability

All participants underwent a 24-hour Holter recording to assess heart rate variability parameters. Holter evaluations were performed by an experienced physician who was blind to the study population. Holter ECG was performed using a 3-channel digitized recorder (DMS 300-3A, DM Software, Nevada, USA). Data was manually preprocessed before analysis. Recordings lasting for at least 18 h and of sufficient quality for evaluation were included in the analysis. If these criteria were not achieved, the recordings were repeated.

The time domain HR variability indices: SDNN [the standard deviation of all NN (normal to normal) intervals], SDNN index (the mean of the deviation of 5 min NN intervals over the entire recording), SDANN (standard deviation of the average NN intervals calculated over 5 min periods of the entire recording), and RMSSD (the square root of the mean squared differences of successive NN intervals) were measured.

The frequency domain analysis of HR variability included total power, high frequency (HF) component (0.15-0.40 Hz), low frequency (LF) component (0.04-0.15 Hz), and very low frequency (VLF) component (0.003-0.04 Hz). The normalized HF and LF were calculated using the following formula: $HF_{nu} = HF / (\text{total power} - VLF)$ and $LF_{nu} = LF / (\text{Total power} - VLF)$, respectively (11).

Assessment of pulse wave velocity

Carotid-femoral pulse wave velocity was measured as an index of arterial stiffness. Vascular assessments in both patients and controls were performed by a single experienced cardiologist who was blinded to patient data, in the morning after an overnight fast and refraining from cigarette smoking for the prior 8 hours. PWV was calculated from the measurements of pulse transmission time and the distance between the 2 recording sites by a validated non-invasive device (SphygmoCor, AtCor Medical, Sydney, Australia). Carotid and femoral pulses were palpated to confirm measurement localization in the corresponding regions. Straight distances from the strongest point of pulses in the carotid and femoral area to the sternal notch were measured. The distance traveled by the pulse wave over the surface of the body was measured with a tape measure (from the sternal notch to right femoral artery minus the distance from the sternal notch to the right carotid artery) and was divided by the transit time; the result was expressed as meters/second

(m/sec). Resting blood pressure was detected by auscultation using a sphygmomanometer.

Measurement of carotid intima-media thickness

Ultrasonography was performed on all patients using a high-resolution ultrasonography scanner (Xario, Toshiba Medical Systems, Tokyo, Japan) with a PLT-805AT linear array transducer. Measurements were performed on the right and left carotid arteries. The patient was lying supine with the head directed away from the side of interest and the neck slightly extended. The transducer was manipulated so that the near and far walls of the CCA were parallel, and the lumen diameter was maximized in the longitudinal plane. The region 1 cm proximal to the carotid bifurcation was identified, and the CIMT of the far wall was evaluated as the distance between the lumen-intima interface and the media-adventitia interface. The CIMT was measured on the frozen frame of a suitable longitudinal image, with the image magnified to achieve a higher resolution of detail. The CIMT measurement was obtained from 4 contiguous sites at 1-mm intervals on each carotid artery, and the average of all 8 measurements was used for analysis. All measurements were performed by the same radiologist who was blinded to patient data. The intra-observer mean absolute difference in measuring the common carotid intima-media thickness was 0.026 ± 0.043 mm (coefficient of variation: 1.6%, intra-class correlation: 0.95).

Biochemical measurements

Blood samples were drawn by venipuncture to evaluate routine blood parameters after fasting for at least 8 hours. Fasting blood glucose, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglyceride levels were recorded. Glucose and lipid profile were determined by standard methods. Serum CRP was analyzed using a nephelometric technique (Beckman Coulter Immage 800; Fullerton, CA, USA; normal range 0-0.8 mg/dL).

Statistical analysis

Continuous variables were given as mean \pm SD; categorical variables were defined as percentages. Data were tested for normal distribution using the Kolmogorov-Smirnov test. Continuous variables were compared by Student t-test and the χ^2 test was used for the categorical variables between two groups. All tests of significance were two-tailed. Statistical significance was defined as $p < 0.05$. The SPSS statistical software (IBM SPSS Statistics for Windows, Version 20.0, IBM Corp., Armonk, NY, USA) was used for all statistical calculations.

Results

Clinical characteristics

The characteristics of the patients are presented in Table 1. Clinical parameters were similar between groups. There were

Table 1. Demographic and clinical characteristics of study participants

Parameters	IBS group(30)	Control group (30)	P*
Age, years	45 \pm 12	47 \pm 10	NS
BMI, kg/m ²	29.4 \pm 5.9	29.7 \pm 5.9	NS
Hypertension, %	23%	37%	NS
Diabetes mellitus, %	3%	13%	NS
Smoking, n, %	10%	3%	NS
Biochemistry and hematology			
Glucose, mg/dL	100 \pm 17	102 \pm 17	NS
Creatinine, mg/dL	0.72 \pm 0.10	0.65 \pm 0.11	0.045
Total cholesterol, mg/dL	206 \pm 45	206 \pm 48	NS
Triglycerides, mg/dL	136 \pm 108	133 \pm 87	NS
HDL cholesterol, mg/dL	53 \pm 10	50 \pm 7	0.023
LDL cholesterol, mg/dL	123 \pm 32	131 \pm 39	NS
Hemoglobin, mg/dL	12.8 \pm 1.0	13.0 \pm 1.3	NS
Leukocytes, 10 ³ /mm ³	7.09 \pm 2.22	7.40 \pm 1.78	NS
Platelets, 10 ³ /mm ³	288 \pm 58	292 \pm 67	NS
CRP, mg/dL	0.45 \pm 0.23	0.44 \pm 0.37	NS
Continuous variables were given as mean \pm standard deviation; categorical variables were defined as percentages. BMI - body mass index; CRP - C-reactive protein; HDL - high-density lipoprotein; IBS - irritable bowel syndrome; LDL - low-density lipoprotein, NS - not significant. *Continuous variables were compared by Student t test and the χ^2 test was used for the categorical variables between two groups.			

24 patients with IBS-C (80%), 4 patients with IBS-D (13.3%), and 2 patients with IBS-M (6.7%) in IBS group.

Biochemical measurements

Biochemical parameters did not differ between groups except for slightly increased creatinine (0.72 \pm 0.10 vs. 0.65 \pm 0.11 mg/dL, $p=0.045$), and HDL-cholesterol concentrations (53 \pm 10 vs. 50 \pm 7 mg/dL, $p=0.023$) in patients with IBS.

PWV, CIMT and HRV parameters

PWV and CIMT values were similar between groups (Table 2). We found significantly lower SDNN index (51 \pm 12 ms vs. 62 \pm 18 ms, $p=0.010$), and RMSSD (28 \pm 9ms vs. 38 \pm 15 ms, $p=0.002$) in patients with IBS compared to controls.

Frequency analyses revealed lower LF (585 \pm 302 vs. 919 \pm 436, $p=0.002$), HF (228 \pm 177 vs. 405 \pm 275, $p=0.006$), and VLF (1871 \pm 803 vs. 2646 \pm 1461, $p=0.016$) in subjects with IBS. However LF/HF ratio, LFnu, and HFnu were not significantly different between two groups.

Discussion

In this study, we demonstrated impaired HRV as surrogate of autonomic dysfunction in patients with IBS. However, we could

Table 2. Heart rate variability and vascular tests in two groups

N (60)	IBS group (30)	Control group (30)	P value*
HRV measurements			
<i>Time domain HR</i>			
SDNN, ms	136±35	151±39	NS
SDANN, ms	120±27	137±39	0.060
SDNN index, ms	51±12	62±18	0.010
RMSSD, ms	28±9	38±15	0.002
Total power	2718±1201	4004±2112	0.007
<i>Frequency domain HR</i>			
LF	585±302	919±436	0.002
LFnu	0.70±0.12	0.70±0.09	NS
HF	228±177	405±275	0.006
Hfnu	0.26±0.07	0.28±0.08	NS
VLF	1871±803	2646±1461	0.016
LF/HF ratio	3.1±1.6	2.8±1.5	NS
<i>Vascular tests</i>			
CIMT, mean, mm	0.64±0.16	0.70±0.23	NS
cf-PWV, m/s	7.42±2.11	7.8±1.95	NS

cf-PWV - carotid-femoral pulse wave velocity; CIMT - carotid intima-media thickness; HF - high frequency power; IBS - irritable bowel syndrome; HFnu - normalized high frequency power; HRV - heart rate variability; LF - low frequency power; LFnu - normalized low frequency power; NS - not significant; RMSDD - square root of the mean squared differences of successive normal-to-normal intervals; SDNN - standard deviation of all normal-to-normal intervals; SDANN - standard deviation of the average normal-to-normal intervals calculated over 5-minute periods of the entire recording. Continuous variables were given as mean±standard deviation; categorical variables were defined as percentages. *Continuous variables were compared by Student t-test and the χ^2 test was used for the categorical variables between two groups.

not document any difference in PWV and CIMT as surrogates of arterial stiffness and atherosclerosis.

Arterial stiffness, one of the earliest manifestations of adverse structural and functional changes within the arterial wall, is mainly associated with aging and hypertension (23). Pulse wave velocity, the gold-standard measure of arterial stiffness, has been shown to be an independent predictor of mortality and stroke in the general population (4) and in patients with end-stage renal disease (24), hypertension (25), or diabetes (26). PWV is significantly associated with the markers of subclinical target organ damage in the coronary, peripheral arterial, and cerebral vascular beds (27). Carotid intima-media thickness, the surrogate of cardiovascular disease, is associated with conventional cardiovascular risk factors and atherosclerosis (8). Moreover, CIMT relates to several CVD risk scores in the elderly, predicts cardiovascular events, and gives information beyond conventional risk factors (9, 28, 29).

Several studies investigated HRV patterns in patients with IBS compared to healthy controls and failed to demonstrate any difference (14-16). However, current evidence support altered HRV and autonomic functions when predominant bowel pat-

terns (14, 17), pain severity (18), sleep patterns (16), and presence of anxiety or depression (19) are taken into account. A recent meta-analysis comparing 392 IBS patients with 263 healthy control subjects revealed lower HF band and higher LF/HF ratio in patients with IBS. Interestingly they demonstrated decreased HF power in patients with IBS-C while no difference was observed in LF/HF ratio which is in line with our study (30).

We revealed decreased RMSSD, LF and HF in patients with IBS, all of which is in line with decreased parasympathetic modulation of autonomic nervous system (11). Since IBS group mainly had patients with IBS-C subgroup; this result is similar to previous studies that reported reduced parasympathetic tone in constipation predominant bowel pattern (14, 17). However, we did not demonstrate any differences in HFnu, LFnu and LF/HF ratio between two groups. Since HF mainly reflects parasympathetic modulation and LF reflects both sympathetic and parasympathetic influence; LF/HF is a measure of autonomic nervous system rather than sympathovagal imbalance. Moreover, HFnu, LFnu and LF/HF ratio are mathematically close to each other and these parameters per se do not reflect distinct autonomic phenomenon (31).

Decreased heart rate variability may predict atherosclerotic progression of carotid arteries in patients with type 1 diabetes population (32). Similarly, decreased HRV is associated with coronary artery disease, myocardial infarction and cardiovascular mortality in diabetic patients (13). However, this association has not been proven in non-diabetics and currently not known in asymptomatic population.

Even though, autonomic dysfunction and altered HRV is related to accelerated atherosclerosis in certain populations, like patients with diabetes mellitus; we failed to demonstrate any changes in pulse wave velocity and carotid intima-media thickness in this population. Since atherosclerosis is a multifactorial disorder, the influence of autonomic dysfunction solely may not be adequate for accelerated atherosclerosis without strong precipitating factors.

Study limitations

Our study has several limitations; the most important is the small sample size. IBS group mainly had IBS-C patients; therefore, our results only apply to this subgroup. Since patients were recruited from gastroenterology clinic, they may have high degree of pain and severe disease. Moreover, our study is cross-sectional in nature; therefore, our results cannot implicate causality. However, in order to decrease variability in measuring atherosclerotic parameters, we utilized validated end-points, which are the stronger aspects of our study.

Conclusion

We demonstrated decreased parasympathetic modulation in patients with constipation predominant IBS. However, we could

not demonstrate any changes in pulse wave velocity and carotid intima-media thickness. Our results do not support accelerated atherosclerosis in IBS population.

Conflict of interest: None declared.

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