

Evaluation of increased subclinical atherosclerosis risk with carotid intima-media thickness and pulse wave velocity in inflammatory bowel disease

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ABSTRACT

Background/Aims: A significant increase in accelerated atherosclerosis risk have determined in chronic inflammatory diseases. Recent studies have suggested a pathophysiological link between inflammatory bowel disease (IBD) and atherosclerosis; for which carotid intima-media thickness (CIMT) and pulse wave velocity (PWV) has been considered as an early marker. The aim of this study was to determine the presence of early atherosclerosis in IBD patients without clinically diagnosed cardiovascular disease and any coincident risk factors for atherosclerosis.

Materials and Methods: 40 IBD patients who are in remission and without known atherosclerosis and also without any risk factors for atherosclerosis (17 Crohn's disease and 23 ulcerative colitis) and 40 healthy subjects for control group involved in the study. The measurement of bilateral CIMT and carotis-femoral PWV have done in patients and control groups.

Results: Significant differences existed between control subjects and patients with IBD in the values of PWV (5.97 ± 0.54 vs. 7.17 ± 0.92 m/sn; $p < 0.001$), maximum CIMT (0.76 ± 0.06 vs. 0.86 ± 0.11 mm; $p < 0.001$) and mean CIMT (0.66 ± 0.06 vs. 0.74 ± 0.09 mm; $p < 0.001$). In the correlation analysis, a positive correlation has determined between PWV and maximum CIMT and mean CIMT ($p < 0.001$, $r = 0.75$ / $p < 0.001$, $r = 0.74$ respectively).

Conclusion: IBD patients have an increased risk of subclinical atherosclerosis than healthy controls as showed by greater values of CIMT and PWV.

Keywords: Inflammatory bowel disease, pulse wave velocity, carotid intima-media thickness, subclinical atherosclerosis

INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC) are the two major forms of chronic inflammatory bowel disease (IBD). The exact etiology of IBD is unknown. However, IBD is believed to develop when intestinal microvascular endothelial cells are damaged by an abnormal immune response resulting in chronic intestinal inflammation (1).

Early atherosclerosis can lead atherothrombotic complications in many inflammatory diseases. This situation is a very important cause of mortality and morbidity (2,3). Recent studies have focused on the role of inflammation in the development and progression of atherosclerosis (4,5). Accelerated atherosclerosis was found in inflammatory and immune disorders such as systemic

lupus erythematosus and rheumatoid arthritis (3,6). Atherosclerosis is a process which is characterized by vessel wall remodeling that occurs over years. Obesity, aging, hypertension, diabetes, and hyperlipidemia have a major impact on the progression of atherosclerosis. In recent studies, there is an evolving evidence that IBD is an independent factor for development of atherosclerosis (7,8). Carotid intima-media thickness (CIMT) and pulse wave velocity (PWV) measurement methods were used to determine subclinical atherosclerosis in IBD (7-9). Endothelial dysfunction is a marker of vascular damage before development of atherosclerotic plaques. Inhibition of nitric oxide (NO) synthesis by chemical or mechanical stimulation, or inhibition of vascular response to NO are responsible mechanisms for endothelial dysfunction. Endothelial injury precipitates

This study was presented at the 28th National Gastroenterology Congress, 16-20 December 2011, Antalya, Turkey.

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Received: February 21, 2013 **Accepted:** July 26, 2013

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to reduced arterial elasticity and increased arterial stiffness. Arterial stiffness assessed by the degree of increase in PWV. Previous studies demonstrated that increased arterial stiffness is a marker of increased cardiovascular mortality and morbidity (10,11). CIMT increase develops as a result of intimal smooth muscle proliferation and accumulation of atherogenic particles. CIMT can be used in early diagnosis of atherosclerosis, risk classification and evaluation of response to treatment (12).

The aim of this study was to investigate the presence of early signs of atherosclerosis in IBD patients. In our study we excluded the patients with traditional risk factors for atherosclerosis, including hypertension, obesity, smoking, diabetes and hyperlipidemia. We evaluated the early signs of atherosclerosis with the PWV and CIMT measurement methods in IBD patients.

PATIENTS AND METHOD

Patients

The study enrolled 23 ulcerative colitis patients and 17 patients with Crohn's disease who were in remission for at least 6 months and being followed in Department of Internal Medicine, Division of Gastroenterology outpatient clinics between June 2009 and February 2010 with the diagnosis of IBD. UC patients were assessed by using Mayo score for assessing ulcerative colitis activity and CD patients with Crohn's Disease Activity Index (13,14). Those who were found to be remitters were enrolled. Forty healthy subjects were included as control group. The study was approved by the local ethics committee. Each patient was informed about the study and all patients read and signed informed consent.

Cardiovascular system examinations were performed for enrolled patients after 10-minute rest. Blood pressures were obtained from both arms while sitting using a mercury sphygmomanometer with an appropriate cuff, based on Korotkoff phase I and phase V sounds. Body weight, height, waist and hip circumference measurements were performed for patients. Body mass index (BMI) was calculated by dividing the body weight (in kg) by height in meters squared, using Quetlet index. Biochemical analysis and blood counts were conducted on venous blood samples obtained from patients in all groups between 08:00 am and 13:00 pm after 8 hours of fasting.

Study Exclusion Criteria:

Exclusion criteria were as follows: (1) coronary artery disease (defined as having a typical angina pectoris, history of a prior myocardial infarction, presence of a positive stress test or positive coronary angiographic findings) or peripheral artery disease (with atherosclerosis detected by peripheral angiography and Doppler ultrasonography); (2) diabetes mellitus (diabetes mellitus was defined as a fasting blood glucose level > 126 mg/dL or current use of a diet or medication to lower blood glucose); (3) hypertension (those who were previously diagnosed, receiving anti-hypertensive drugs or those who are not on

antihypertensive therapy, with blood measure recordings over 140/90 mmHg during previous examinations and follow-up charts); (4) dyslipidemia (those diagnosed as dyslipidemia, receiving antihyperlipidemic therapy, LDL cholesterol >130 mg/dL and Triglycerides >200 mg/dL); (5) chronic alcoholism and smoking; (6) valvular heart disease, congenital heart disease, left ventricular systolic dysfunction (EF<50%), acute heart failure and cases of acute coronary syndromes, arrhythmias; (7) cerebrovascular diseases, hepatic or renal failure, malignancies, concomitant endocrinologic disorders (hypothyroidism, hyperthyroidism, Cushing syndrome, pheochromocytoma, acromegaly); (8) patients with a disease duration of less than 6 months, patients aged over 45 and non-remitter patients.

Pulse Wave Velocity and Carotid Intima-Media Thickness Measurement

Carotid intima-media thickness measurements of the individuals were performed by a physician blinded to both patient and the obtained PWV value. Both common carotid arteries were visualized by Toshiba Powervision 7500 (Toshiba AG) ultrasound device with a 7.5 MHz linear probe. Maximum and mean thicknesses were calculated with the far edge measurement method by the CIMT measurement program M'ATH[®] standart version 2.0.1.0 (Metris AG, France) from a determined 1 cm segment of common carotid artery, 2-3 cm distal to bulb. This method was applied for the measurement of both common carotid arteries were evaluated based on the average.

For the measurement of PWV, SphygmoCor (Artcore, Sydney, Australia) device was used. Before the procedure, blood pressures were measured in patients. Distance between the palpable point of femoral artery and sternal notch and the distance between the most distal palpable part of carotid pulse and sternal notch were recorded to system. Applanation tonometry of the device was applied through the skin to these points sequentially. Recording have done after the most appropriate waveform amplitude and shape were obtained. Simultaneous ECG records are taken from patients. Pulse transit time, in other words pulse wave velocity (PWV) were calculated automatically by the SphygmoCor device by subtracting the time between the ECG and proximal pulse from the time between the ECG and distal pulse.

Statistical Analysis

Study data were analyzed using SPSS 18.0 software package. Continuous variables were expressed as mean±standard deviation, whereas frequency data were expressed as percentage. Based on distribution features of variables, continuous variables showing normal or non-normal distribution were analyzed using Student's t test and Mann-Whitney U test respectively, for comparison of two independent groups. Normality analysis was done using Kolmogorov-Smirnov test. Pearson's Correlation analysis was used for determining linear association between two variables. All tests were structured as two-sided and critical alpha level was considered as 0.05.

Table 1. Baseline characteristics in IBD and control group

	IBD (mean±sd) (n=40)	Control group (mean±sd) (n=40)	p value
Age (years)	38.4±6.5	38.25±6.4	0.97
Kreatinin (mg/dL)	0.78±0.12	0.79±0.14	0.76
Total cholesterol (mg/dL)	178.2±20.6	170.1±21.8	0.10
LDL cholesterol (mg/dL)	107.5±21.4	99±20.3	0.06
HDL cholesterol (mg/dL)	52.2±12	49.5±10.6	0.41
Triglyceride (mg/dL)	109.4±48.5	117.2±50	0.53
SBP (mmHg)	117.6±10	116.9±10	0.80
DBP (mmHg)	74±7.6	71.2±7.2	0.16
Sedimentation (mm/h)	21.4±12.4	16.1±3	0.18
CRP	0.44±0.37	0.23±0.07	0.002
Fasting blood glucose (mg/dL)	88.3±8.1	84.8±8.4	0.62
BMI (kg/m ²)	23.7±1.94	23.7±1.56	0.76

IBD: inflammatory bowel disease; mean±sd: mean±standart deviation; LDL: low-density lipoprotein; HDL: high-density lipoprotein; SBP: systolic blood pressure; DBP: diastolic blood pressure; CRP: C-reactive protein; BMI: body mass index

Table 2. Comparision of groups in terms of carotis intima media thickness and pulse wave velocity

	IBD (mean±sd) (n=40)	Control group (mean±sd) (n=40)	P value
PWV (m/second)	7.17±0.92	5.97±0.54	<0.001
Maximum CIMT (mm)	0.86±0.11	0.76±0.06	<0.001
Mean CIMT (mm)	0.74±0.09	0.66±0.06	<0.001

IBD: inflammatory bowel disease; mean±sd: mean±standart deviation; PWV: pulse wave velocity; CIMT: carotid intima media thickness

RESULTS

Basic Characteristics of the Patients and Controls

A total of 40 patients including 22 males (55%) and 18 females (45%) diagnosed with IBD (age range, 22-45 years). Control group consisted of 40 healthy subjects including 22 males (55%) and 18 females (45%) with an age range between 23 and 45 years. IBD patients included 23 UC patients and 17 patients with CD. Among UC patients, 1 had ulcerative proctitis, 17 had left-sided UC and 5 had UC with pancolitis. Among CD patients, 13 had ileal CD and 4 had ileocolonic CD. 36 of patients treated with 5-aminosalicylic acid (5-ASA). 3 of patients treated with 5-ASA + azathioprine (2 UC and 1 CD), one of patients (UC patient) treated with 5-ASA + cortikosteroids. Mean age of IBD patients was 38.4±6.5 years. Mean age of control group was 38.2±6.4 years. Mean duration of disease was 52.2±48.7 months. A review for comparison of IBD and control groups with respect to age, gender, body mass index, systolic and diastolic blood pressure, serum creatinine, total cholesterol, LDL, HDL, triglycerides and sedimentation rate showed similar results and statistical analysis did not yield any significant differences (Table 1).

Pulse Wave Velocity and Carotid Intima-Media Thickness

The PWV and the CIMT values of IBD patients were higher than the normal healthy individuals ($p<0.001$) (Table 2, Figure 1,2). It has been seen that with the increasement of the PWV values, the maximal and mean CIMT values were found to be increasing ($p<0.001$, $r=0.75$ and $p<0.001$, $r=0.74$) (Figure 3).

There were no significant differences in the values of maximum CIMT (0.86 ± 0.11 vs. 0.87 ± 0.10 mm; $p=0.68$), mean CIMT (0.73 ± 0.1 vs. 0.74 ± 0.09 mm; $p=0.62$) and PWV (7.06 ± 0.83 m/sn vs. 7.19 ± 0.71 m/sn; $p=0.73$) between UC and CD patients.

DISCUSSION

In our study, values of CIMT and PWV which are non-invasive indicator of subclinic atherosclerosis have measured and an increase in values of CIMT and PWV have determined in IBD patients without atherosclerotic risk factor when compared with control group.

Inflammatory bowel disease is a group of disease that consists with exaggerated response in bowel against different types of antigens or environmental factors in genetically sensitive

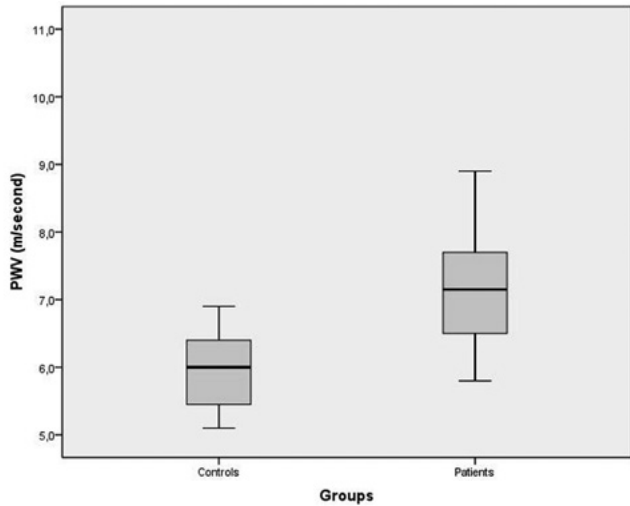


Figure 1. Comparison of groups in terms of pulse wave velocity (PWV)

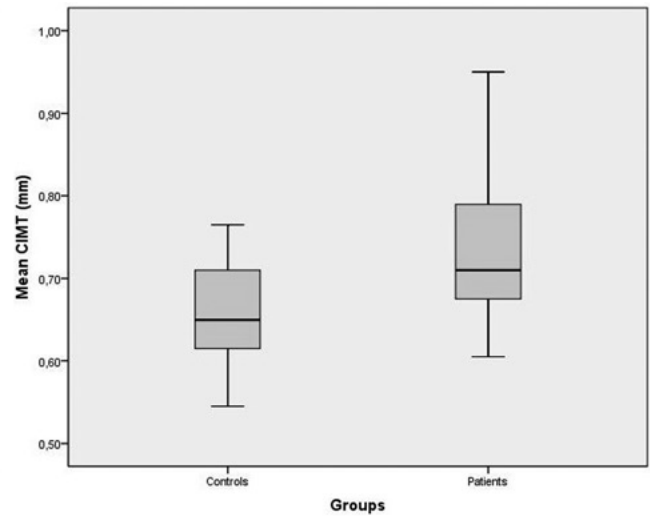
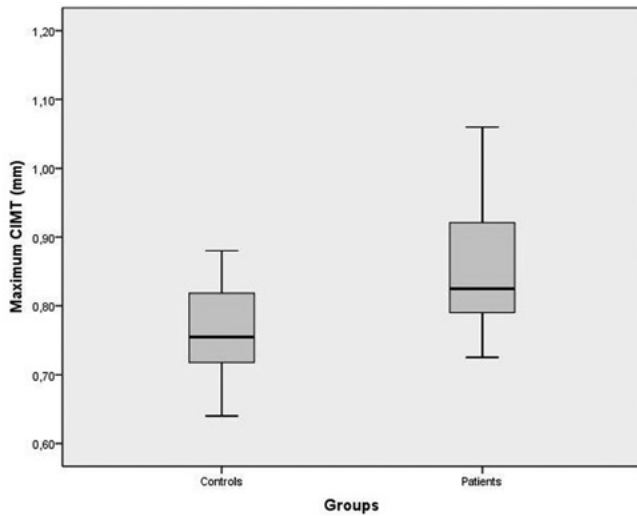


Figure 2. Comparison of groups in terms of maximum carotid intima-media thickness (Maximum CIMT) , mean carotid intima-media thickness (Mean CIMT).

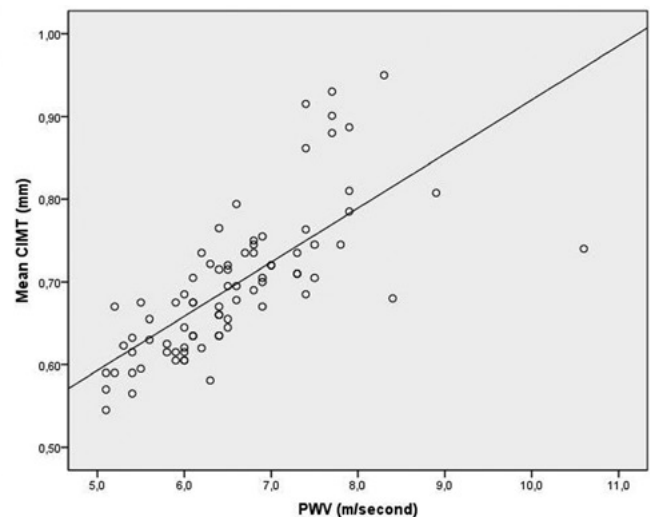
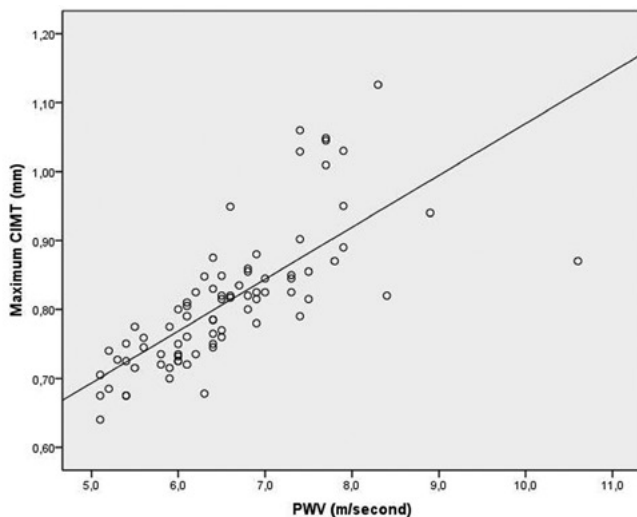


Figure 3. Corelation between maximum carotid intima-media thickness (Maximum CIMT), mean carotid intima-media thickness (Mean CIMT) and pulse wave velocity (PWV).

Increased CIMT is a marker of atherosclerosis (20). Papa et al and Dalgı et al showed that CIMT, highly predictive marker of early atherosclerosis, was significantly greater in IBD than in matched healthy controls (7,8). On the other hand, in Maharshak et al study, similar CIMT values had found between IBD and control group and emphasized that this situation did not support the relationship between IBD and early atherosclerosis (21). In our study, the relationship between IBD and subclinical atherosclerosis were investigated in IBD patients without clinically diagnosed cardiovascular disease and any coincident risk factors for atherosclerosis and the value of CIMT was found significantly higher in IBD patients than the control group. Most of the patients of Papa et al and Daglı et al studies were UC patients. In our study, the majority of patients were UC (UC: 23 patients, CD: 17 patients), the number of patients were nearly similar and all patients were in remission. We have found similar CIMT values in UC and CD patients. This situation was similar to the studies by Papa et al and Daglı et al. (7,8).

The compliance of the arterial system has a major impact on the cardiovascular system (22,23). In many studies, the arterial stiffness had been shown to be an independent predictor of cardiovascular morbidity and mortality (23-26). The direct measurement of vascular compliance is difficult. PWV analysis method enables us to determine arterial compliance noninvasively. The PWV is negatively correlated with the arterial elasticity. In many studies, the relationship between atherosclerosis and changes in PWV had been shown previously (22,23,26,27). It is known that, the increased PWV, as a reflection of arterial stiffness, is known to be an indicator of atherosclerosis (26). In Zanolı et al. (9) study, IBD patients were compared with normal healthy controls with PWV method. PWV was found significantly higher in IBD patients than controls and they have denoted that this situation was related with increased early atherosclerosis in IBD. In our study, we have found that PWV was significantly higher in IBD patients than control group and PWV was correlated with maximum CIMT and mean CIMT values.

This study shows us that, even if there were no any coincident risk factors for atherosclerosis, the IBD patients have increased PWV and CIMT values which denote the atherosclerosis development.

In conclusion, early signs of atherosclerosis are present in IBD patients. This supports the hypothesis that, IBD has an independent role in atherosclerosis progression. Because of these reasons, in these patients, screening for cardiovascular diseases is important for the prevention of cardiovascular mortality and morbidity. The patients with increased CIMT and PWV have to be identified, and because of the high risk for atherosclerosis development in these patients, treatment should be initiated in the early stage. We think that, these significant findings of our analysis can guide for the further clinical practice. However these findings must be supported clinically with prospective cohort studies.

Conflict of Interest: No conflict of interest was declared by the authors.

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