European Journal of Internal Medicine 37 (2017) 83–89

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Original Article

Increased expression of markers of early atherosclerosis in patients with inflammatory bowel disease☆

Maria Cappello [a,*,1], Anna Licata [a,1], Vincenza Calvaruso [a], Ivana Bravatà [a], Alessandra Aiello [a], Daniele Torres [b], Vittoriano Della Corte [b], Antonino Tuttolomondo [b], Maria Perticone [c], Giuseppe Licata [b], Antonio Craxì [a], Calogero Cammà [a]

[a] Gastroenterology and Hepatology Section, DIBIMIS, University of Palermo School of Medicine, Palermo, Italy
[b] Internal Medicine and Cardioangiology, DIBIMIS, University of Palermo School of Medicine, Palermo, Italy
[c] Department of Experimental and Clinical Medicine, University of Magna Græcia of Catanzaro, Italy

ARTICLE INFO

Article history:
Received 24 August 2016
Received in revised form 1 October 2016
Accepted 6 October 2016
Available online 21 October 2016

Keywords:
Arterial stiffness
IBD
Carotid intima-media thickness
Early atherosclerosis

ABSTRACT

Background & Aims: Recent studies documented an increased cardiovascular risk in patients with inflammatory bowel disease (IBD). Our study aimed at investigating the prevalence of intima-media thickness (IMT) of the carotid arteries and the arterial stiffness indices as markers of early atherosclerosis in young IBD patients.
Methods: We recruited 68 consecutive IBD patients, and 38 matched healthy controls less than 45 years old (median age 31.6 ± 8.1 years). Clinical and demographic features, cardiovascular risk factors, history of cardiovascular events, concomitant therapies were registered on a dedicate database. Carotid IMT was evaluated by using high resolution B-mode ultrasonography. Arterial stiffness was assessed by measurement of carotid-femoral Pulse Wave Velocity (PWV) and Augmentation Index (AIx).
Results: Total cholesterol ($P < 0.013$) and LDL-cholesterol ($P < 0.019$) levels were significantly lower in IBD patients compared to controls. Carotid IMT was higher in IBD than in controls ($P < 0.047$), but there was no statistically significant difference among Crohn's Disease (CD) and Ulcerative Colitis (UC) patients. Moreover, PWV and AIx were significantly higher in patients as compared to controls ($P < 0.006$ and $P < 0.004$ respectively). No medication seemed to affect vascular measurements, though stiffness parameters were significantly higher in patients treated with 5-ASA (11.9 (9.7) vs 18.2 (10.2), $P < 0.021$), suggesting a lack of efficacy of 5-ASA in protecting IBD patients from early atherogenesis.
Conclusions: Young IBD patients show an increase in subclinical markers of atherosclerosis. Future studies need to address whether these markers result in an increased risk of cardiovascular events in these patient.

1. Introduction

Inflammatory bowel diseases (IBD), Crohn's Disease (CD) and Ulcerative Colitis (UC), are chronic inflammatory disorders of the gastrointestinal tract. Pathogenesis may be the result of interaction between environmental factors and intestinal bacteria in genetically predisposed individuals, which may give rise to an aberrant immune response leading to bowel damage [1].

Several studies have investigated the association between IBD, cardiovascular and thromboembolic disease [2–3]. Recently, researchers have focused on cardiovascular risk and on the possibility of early onset and rapid progression of the atherosclerotic process, with conflicting results [4–9].

Atherosclerosis is a pathological condition mainly characterized by loss of elasticity of arterial walls. Atherogenesis is a chronic inflammatory process of the arterial wall, finally leading to endothelial dysfunction [10,11], which involves the alteration of the control of the vascular tone, leukocytes trafficking and platelets adhesion. The risk of early onset of atherosclerosis is well known in individuals suffering from other chronic inflammatory disorders such as rheumatoid arthritis and systemic lupus erythematosus [12–14], thus it should not be surprising that, in the last decade, an increasing body of data, both epidemiological and clinical, have supported this association also in IBD.

Epidemiological studies on incidence of cardiovascular events in patients with IBD have led to discrepant results [15–19]. A retrospective

Abbreviations: IBD, Inflammatory bowel disease; CD, Crohn's Disease; UC, Ulcerative Colitis; IMT, Intima media thickness; PWV, Pulse wave velocity; AIx, Augmentation index; DBP, Diastolic blood pressure; SBP, Systolic blood pressure; FMD, Flow mediated dilation; ESR, Erythrocyte-sedimentation rate; CRP, C-reactive protein.

☆ Source of support: none.

* Corresponding author at: Gastroenterology & HepatologySection, Dipartimento Biomedico di Medicina Interna e Specialistica, Piazza Delle Cliniche 2, 90127 Palermo, Italy.
E-mail address: marica.cappello61@gmail.com (M. Cappello).

[1] Those authors equally contributed to this paper.

http://dx.doi.org/10.1016/j.ejim.2016.10.004
0953-6205/

study from North America [16] showed that the incidence of coronary artery disease in patients with IBD was higher as compared to a control group, in spite of a low incidence of traditional risk factors (smoking, diabetes, hypertension and hypercholesterolemia). Two Danish nation-wide cohort studies demonstrated an increased risk of ischemic heart disease and also showed that the risk was lower in those treated with 5-ASA [17,20]. Finally, a systematic review has confirmed the key role of chronic inflammation in causing progression of the atherosclerotic process and thus, coronary risk in IBD [19].

From a clinical point of view, the assessment of early atherosclerosis has been made by investigating surrogate markers such as the carotid artery intima-media thickness (IMT), flow-mediated vasodilatation of the brachial artery (FMD) and arterial stiffness by pulse wave velocity (PWV) [21–30]. The study by Aloi et coll, reported signs of endothelial dysfunction and early atherosclerosis even in children with IBD [27]. Zanoli et al. reported results from two studies [29,30] carried on IBD adult patients evaluated by measuring arterial stiffness, the first being a cross-sectional study, the second evaluating the effect of long-term therapy. Both studies showed that there was an increase in both carotid-radial and carotid-femoral PWV in IBD patients as compared with controls and that arterial stiffness of these patients was related to the degree of inflammation and reduced by immunomodulatory drugs. More recently, Ozturk et al. [31] added further evidence to the association of early atherosclerosis markers and IBD by investigating arterial stiffness, FMD and IMT, showing a significant relationship between disease duration and hemodynamic parameters.

In the current cross-sectional study, we aimed to demonstrate in a homogeneous prospective Mediterranean cohort of young IBD patients (aged less than 45 years) early signs of atherosclerosis through the assessment of IMT of the carotid arteries and of arterial stiffness studied by PWV and Augmentation Index (AIx). Furthermore, we tried to evaluate whether 5-aminosalicilyc acids (5-ASA), steroids, immunosuppressant drugs and biologics could affect hemodynamic parameters.

2. Materials and methods

2.1. Patient's selection

One hundred-six subjects aged between 17 and 45 years have been enrolled from September 2012 until December 2013; sixty-eight were patients consecutively diagnosed as suffering from IBD and attending our IBD outpatient clinic and 38 were healthy individuals enrolled as age and sex-matched controls. Written informed consent for participation in the study was obtained from both patients and controls.

Clinical and demographic data were recorded in a dedicated database. Clinical data included: age, gender, family history of IBD, co-morbidities, (e.g. diabetes and/or hypertension), traditional risk factors for the onset of atherosclerosis (Blood Pressure, Body Mass Index, smoking, Total-Cholesterol, Triglycerides, LDL-Cholesterol, HDL-Cholesterol), disease features (IBD type, extent, extra-intestinal manifestations, previous surgery), disease activity assessed by Mayo Score [32] for UC and the Harvey Bradshaw Index for CD [33], C-reactive protein (CRP) values, concomitant drug therapies. A blood sample was drawn for the evaluation of lipid profile and other laboratory parameters.

On recruitment, traditional risk factors were evaluated for both cases and controls on the basis of the criteria shown below. Smoking habit was explored and recorded in the database. Hypercholesterolemia was defined as the presence of total cholesterol blood levels ≥ 200 mg/dL. Hypertension was defined as present, if subjects has been previously diagnosed according to the World Health Organization/International Society of Hypertension guidelines and were routinely receiving antihypertensive therapy. Patients were defined as type 2 diabetics if they had diabetes treated by diet, or if they were taking oral hypoglycemic drugs or insulin. Individuals with already known cardiovascular disease (coronary heart disease, stroke, transient ischemia attack) were excluded.

Standard laboratory parameters, including CRP and erythrocyte-sedimentation rate (ESR), were measured in the blood at time of hemodynamic measurements. All participants were evaluated in a quiet room, where non-invasive assessment of hemodynamic parameters was performed by an expert physician blinded to clinical information, including therapy. Another physician, blinded to hemodynamic measurements, collected and recorded all clinical data of enrolled patients and controls.

2.2. Carotid artery evaluation

Carotid atherosclerosis was assessed by an expert physician (D.T.) using high-resolution B-mode ultrasonography equipped with a multi-frequency linear probe. Carotid arteries were investigated in longitudinal projections of both the left and right side, at the level of the common carotid artery, of the bulb and of the internal carotid. Carotid IMT was measured as the difference between a first interface (lumen-intima) and a second interface (media-adventitia), along the wall of the common carotid artery, in a free section of plate, for 10 mm upstream and 10 mm downstream of their bifurcations. For each subject, three measurements were made on both sides, projection in front, side and rear, and were made an average of the measurements. A carotid plaque was defined the finding of a focal thickening of >1.3 mm at the level of the common carotid arteries and their bifurcations. The operator assessed the intra-observer variability repeating in two different times the carotid IMT measurements in ten IBD patients and five controls randomly chosen. The concordance coefficient between the intra-observer evaluations was 0.97. The inter-observer evaluation was not calculated because all measurements were performed by the same operator.

2.3. Pulse wave velocity assessment

Examinations were carried out by an expert physician (V.D.C.), after 15 min of rest, carefully following the directions given for a correct standardization of the conditions of the subjects examined. Approximately every 2 min, blood pressure was checked at the level of the brachial artery (DinamapProCare 100; GE Healthcare).

The values of the central pressures were recorded in a non-invasive manner through the applanation tonometry (SphygmoCor; AtCor Medical, Sydney, Australia). Carotid-femoral PWV was measured in the supine position using the automatic device (SphygmoCor version 7.1) that measured the time delay between the rapid upstroke of the carotid and femoral artery pulse waves. The distance between the two arterial points was measured on the surface of the body using a tape measure. PWV was calculated as the distance travelled by the arterial pulse wave (meters) divided by the time delay between the two arterial points (seconds), thus expressed as meters per second (m/s). The "distance between the two arterial points" was measured using the total distance between the carotid and femoral sites of measurement [34,35].

PWV assessment has been repeated in two different times in ten IBD patients and five controls randomly chosen. The concordance coefficient between the intra-observer evaluations was 0.96. The inter-observer evaluation was not calculated because all measurements were performed by V.D.C.

2.4. Pulse wave analysis

Applanation tonometry was used to record radial arterial pressure waveform continuously, and mean values of ≥2 screens of pulse waves of good quality were used for analysis. On the basis of the collected data, an averaged radial pressure waveform was generated and a corresponding aortic pressure waveform and blood pressure calculated by the validated transfer function. The aortic pressure waveform was used to calculate the Aortic AIx (difference in height between