Original Article

Preclinical atherosclerosis in patients with inflammatory bowel diseases: a case-control study

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Background: An independent role of chronic inflammation in the atherosclerotic process in patients with inflammatory bowel diseases (IBD) has been suggested, but data are still contentious. We assessed pre-clinical atherosclerosis in the IBD patients without traditional risk factors.

Methods: In this case-control study we assessed the early atherosclerotic alterations by carotid artery intima-media thickness (CIMT) measurement in IBD patients and matched controls. The normal CIMT values were ≤0.9 mm; moderate thickness when >0.9 and ≤1.2 mm, and pre-clinical atherosclerosis when >1.2 mm. We selected a homogeneous group of IBD patients, all in ongoing biologic therapy, without any traditional risk factor for atherosclerosis as well as controls.

Results: The study enrolled 23 consecutive patients (16 with ulcerative colitis and 7 with Crohn's disease) and 20 controls matched for age and sex. The mean of CIMT values was not statistically different between patients and controls (0.68±0.21 *vs*. 0.82±0.2 mm; P=0.4). The prevalence of moderate CIMT thickness was significantly lower in cases than in controls (8.7% *vs*. 42.8%; P=0.01; OR: 0.15, 95% CI: 0.03–0.85).

Conclusions: This case-control study found that the atherosclerotic process is not more apparent in IBD patients without traditional risk factors.

Keywords: Inflammatory bowel diseases (IBD); atherosclerosis; carotid artery intima-media thickness (CIMT); biologic therapy

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Introduction

Atherosclerosis is the main condition predisposing to the onset of cardiovascular (CV) events (1). There are some well-recognized risk factors for atherosclerosis development, including hypertension, hypercholesterolemia, diabetes mellitus, current smoking, and obesity (2). Besides these traditional risk factors, a role for chronic inflammation itself has been suggested in the last decade, particularly in patients with rheumatic and inflammatory bowel diseases (IBD) (3,4). This a clinically relevant issue, since immune-mediated mechanisms could early cause atherosclerosis in these patients, even in absence of other CV risk factors (5). However, data are still contentious, particularly for IBD patients. Indeed, a meta-analysis of 11 studies showed no role for chronic inflammation in increasing the CV risk in these patients (6), whilst another by including data of nine studies found an increased risk (7). Therefore, further studies are needed to clarify such a field.

Preclinical arterial wall atherosclerotic damage has been shown to be a reliable surrogate to estimate the CV risk. In detail, carotid artery intima-media thickness (CIMT)

may be accurately measured by ultrasound (8), and it is now widely used as an early marker for atherosclerosis (9,10). Indeed, IMT values are predictive of CV events and stroke in individuals without a clinically evident disease (9). We therefore designed this case-control study to assess the CIMT values in patients with IBD without traditional CV risk factors.

Methods

Patients

This was a case-control study involving consecutive patients with an established IBD diagnosis, present for more than 2 years prior to the study, without extra-intestinal manifestations, who were receiving a biologic therapy in our center. Age and sex matched controls were consecutively selected among hospital personnel in the same period. Those patients and controls with a presence of any traditional CV risk factor, including hypertension, hypercholesterolemia, diabetes mellitus, current smoking, and obesity (BMI >30), were excluded.

Carotid artery ultrasound

Doppler ultrasonography was performed, in a quiet semi-dark room, with subjects lying supine with their necks slightly hyper-extended, and rotated away from the imaging transducer. Both carotid arteries were scanned. The right common carotid artery proximal to the bulb was imaged in multiple longitudinal planes for the best resolution of the CIMT of the far wall. CIMT was defined as the distance between the leading edge of the lumen intimal interface and the leading edge of the media adventitia interface of the far wall, measured in end diastole, 1 cm proximal to the bifurcation (8). All examinations were performed by the same experienced investigator (intraobserver variability: r =0.979). CIMT was measured, and values were grouped in the following three classes: normal (CIMT ≤0.9 mm), moderate thickness (CIMT: >0.9 and ≤1.2 mm), and pre-clinical atherosclerosis (CIMT >1.2 mm) (11). The investigator was blinded to the subjects (case or control).

Statistical analysis

Data between groups were compared using the Student's *t*-test and Fisher's exact test, as appropriate. The ORs with their 95% confidence intervals were also calculated, when appropriate. By considering a mean difference of 0.5 mm in the CIMT value between IBD patients (1.1 mm) and controls (0.6 mm) as suggested elsewhere (12), the enrolment of 22 cases for each group allows to detect a significant difference with power of 80% and alfa-error of 5%.

Results

The study enrolled 23 consecutive patients and 20 controls matched for age (mean age: 49.4±10.9 *vs.* 51±12.4) and sex (male/female: 17/6 *vs.* 10/10) distribution, meeting the inclusion criteria. IBD group included 16 patients with Ulcerative Colitis and 7 with Crohn's disease, all in ongoing treatment with biologics, including Infliximab (N=15) and Adalimumab (N=8). The mean of disease duration was 11.7±1.3 years, and the median of biologic therapy was 5 (range, 2–8) years.

The mean of CIMT values was not statistically different between patients and controls (0.68±0.21 *vs.* 0.82±0.2 mm; P=0.4). When performing the analysis of distribution, the prevalence of moderate CIMT thickness was significantly lower in cases than in controls (8.7% *vs.* 42.8%; P=0.01; OR: 0.15, 95% CI: 0.03–0.85). No cases of pre-clinical atherosclerosis (CIMT values >1.2 mm) were observed in both IBD cases and controls (*Table 1*).

The mean of CIMT values did not significantly differ between patients with Crohn's and those with Ulcerative Colitis, although the values tended to be lower in the latter group (0.83±0.22 *vs.* 0.64±0.19 mm; P=0.07).

Discussion

Atherosclerosis is involved in the onset of both ischemic heart events and strokes, with relevant—and potentially life-threatening—consequences (1,2). Besides the well-established risk factors, a chronic systemic inflammation has been proposed as an essential CV risk factor (13). Indeed, the inflammatory status could contribute to atherosclerosis development through endothelial dysfunction caused by different pro-inflammatory cytokines [tumor necrosis factor (TNF), IL-1, IL-6, etc.] (10). In addition, an important role has been attributed to the high levels of C-reactive protein (CRP), which is involved in the overexpression of adhesion molecules and rupture of the atherosclerotic plaque (14).

There are some data suggesting an independent role of chronic inflammation in the atherosclerotic process in patients with rheumatic diseases, but others failed to confirm the association (15,16). Likewise, the

Table 1 Distribution of IMT value classes in patients and controls

IMT value (mm)	Patients (N=23)	Controls (N=21)	P value
≤0.9	21	12	–
>0.9 and ≤1.2	2	9	0.009
>1.2	–	–	–

heterogeneity depends on the fact that classical risk factors for atherosclerosis were not taken into account in several studies (14). Similarly, the existence of an accelerated atherosclerosis in IBD patients, purely due to the chronic inflammation, remains controversial based on data of two meta-analysis (6,7). A more recent meta-analysis, including 16 studies, found that IBD patients had a significantly higher CIMT mean values (standardized mean difference: 0.534 mm; 95% CI: 0.230–0.838; P=0.001) as compared to controls (12). However, a very high heterogeneity (I^2=87.6%) was present among the studies, which undermines the weight of the results. Moreover, the difference remained statistically significant only for ulcerative colitis, but not for Crohn's disease patients (12).

To accurately assess whether chronic inflammation itself could play a role in pre-clinical atherosclerosis development, in this study we enrolled only IBD patients without any well-known risk factor for atherosclerosis. Moreover, we considered only patients with a more aggressive disease receiving a biologic therapy. To assess pre-clinical atherosclerosis, we used the CIMT measurement, which is a non-invasive and highly accurate method (11). In detail, it has been shown that a 0.1 mm increment of CIMT corresponds to 10–15% and 13–18% increased risk for acute myocardial infarction and stroke, respectively (17).

Our data failed to find an increase in the CIMT values in such a homogeneous group of IBD patients without CV risk factors. Therefore, the atherosclerotic process in IBD without CV risk factors did not appear to be earlier or more accelerate than other subjects. Moreover, a recent study found that both CRP and erythrocyte sedimentation rate (ESR) did not correlate with either CMIT values or endothelial function of brachial artery in IBD patients (18). Of note, we found that CIMT mean tended to be even lower in patients than in controls (0.68 *vs.* 0.82 mm), particularly in those with Ulcerative Colitis (0.64 mm). Our data are in keeping with the results of a cross-sectional study performed on a database including 148,229 IBD patients where an even lower risk for heart diseases was observed. In detail, both Ulcerative Colitis (OR: 0.56; 95% CI: 0.49–0.63) and Crohn's Disease (OR: 0.62; 95% CI: 0.56–0.68) patients resulted to be protect towards heart diseases when data were adjusted for the CV risk factors (19). The reason for which IBD patients should have a reduced risk for atherosclerosis remains unclear. A potential role for reduced visceral obesity in IBD patients has been suggested, since leptin—which is produced in the adipose tissue—exerts a pro-inflammatory action (20).

In conclusion, this case-control study found that the atherosclerotic process is not earlier in IBD patients without traditional risk factors.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: In this study, no experimental drugs or procedures were performed and patients voluntarily participated, so the ethical approval was reputed not mandatory.

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