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Increased arterial stiffness in inflammatory bowel diseases is dependent upon inflammation and reduced by immunomodulatory drugs

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ABSTRACT

Background: Inflammatory bowel diseases (IBD) are associated with an increased cardiovascular risk that is not fully explained by traditional cardiovascular risk factors but may be due to inflammation and mediated by an increased arterial stiffness. Aims: Study 1, to investigate the relationship between inflammation and arterial stiffening; Study 2, to look whether aortic stiffening is reduced by immunomodulatory therapy in IBD.

Methods: Study 1 (Cross-sectional study): pulse wave velocity (PWV) was measured in 74 IBD subjects (40 ulcerative colitis and 34 Crohn's disease) and 80 matched controls. Study 2 (Longitudinal study): the effect of therapy on PWV was measured at baseline and 3.4 ± 0.5 years later in 14 IBD subjects treated only with salicylates, 11 subjects treated with steroids and azathioprine, 7 subjects treated with anti TNF-alpha and 30 matched controls.

Results: Study 1: All parameters were comparable between subjects with ulcerative colitis and Crohn's disease. Compared to controls, subjects with ulcerative colitis and those with Crohn's disease have both higher carotid-femoral PWV (7.0 ± 1.1, 7.8 ± 1.7 and 8.0 ± 1.6 m/s, respectively; $P < 0.001$) and carotid-radial PWV (7.2 ± 0.9, 8.8 ± 1.4 and 8.8 ± 1.3 m/s, respectively; $P < 0.001$). In fully adjusted models carotid-femoral PWV was positively associated with disease duration whereas carotid-radial PWV was associated with C-reactive protein and history of relapse. Study 2: in fully adjusted model carotid-femoral PWV increased significantly at follow-up in IBD subjects treated with salicylates but not in those treated with steroids and azathioprine or anti TNF-alpha.

Conclusion: Increased arterial stiffness in IBD is dependent upon inflammation and reduced by immunomodulatory drugs.

1. Introduction

In inflammatory bowel diseases (IBD), ulcerative colitis and Crohn's disease, intestinal microvascular endothelial cells are damaged by an abnormal immune response, resulting in chronic low-grade inflammation followed by episodes of acute inflammation during the periodic reactivation of the disease (relapse). Recent studies have reported that, despite the prevalence of traditional cardiovascular risk factors is lower than in the general population [1–3], the risk of cardiovascular events is increased in IBD [4,5], suggesting that additional mechanisms, such as inflammation, could be responsible for the excess cardiovascular risk observed in IBD. In these subjects, the low cardiovascular risk associated with the low prevalence of traditional cardiovascular risk factors may be at least partly counterbalanced by the increased cardiovascular risk associated with chronic inflammation. In this regard, arterial stiffening may represent a link between inflammation and

Abbreviations: AIx_{HR}, augmentation index corrected for heart rate; IBD, inflammatory bowel disease; PWV, pulse wave velocity.

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cardiovascular risk. In a small study, we previously reported that arterial stiffness is increased in IBD subjects [6]. However, it is presently unknown whether arterial stiffness is increased in both ulcerative colitis and Crohn's disease and independently associated with current or chronic inflammation. Furthermore, there are no studies in IBD reporting the effect of immunomodulatory therapy on both aortic and muscular artery stiffness whereas in other models of chronic inflammation aortic but not muscular artery stiffness was reduced by a short-term treatment with anti TNF-alpha [7–9]. Finally, none of the existing studies have examined the long-term effects of the treatment with immunomodulatory therapy on aortic stiffening.

Consequently, in Study 1 we aimed to test whether elastic and muscular artery stiffness was increased in both ulcerative colitis and Crohn's disease and associated with chronic or acute inflammation. In Study 2 we aimed to test whether arterial stiffening can be reduced by three years of immunomodulatory drugs (steroids, azathioprine or anti TNF-alpha) in IBD subjects.

2. Materials and methods

2.1. Study population

2.1.1. Study 1

Cross-sectional study. A total of 74 IBD subjects (40 subjects with ulcerative colitis and 34 subjects with Crohn's disease) and 80 age-, gender- and body mass index-matched controls were enrolled. The diagnosis of IBD was based on established criteria of clinical, radiological, endoscopic, and histological findings. Individuals with cardiovascular disease (coronary heart disease, congestive heart failure, stroke, transient ischemic attack, or intermittent claudication), diabetes, chronic kidney disease and dyslipidaemia were excluded, as were subjects treated for hypertension and current smokers. The protocol was approved by the local ethics committee, in accordance with the Declaration of Helsinki, and all participants gave written informed consent.

2.1.2. Study 2

Observational prospective study. All subjects enrolled in Study 1 were considered eligible for inclusion in Study 2. A second non-invasive hemodynamic and clinical examination, planned in IBD subjects and controls was performed at least 2.5 years after the first examination (average 3.4 ± 0.5 years, range 2.5–4.5 years). A total of 32 IBD subjects without cardiovascular risk factors were enrolled, categorized in three groups according with the treatment for IBD (14 subjects treated only with salicylates, 11 subjects treated with steroids and azathioprine, 7 subjects treated with anti TNF-alpha, from baseline to the end of follow-up) and matched for age and baseline carotid-femoral PWV among the treatment groups and with a control group of 30 subjects without cardiovascular risk factors. Anti TNF-alpha was used in IBD subjects that have not responded at other therapies. Therapy was always prescribed before the baseline examination by a physician unfamiliar with the study to avoid selection bias.

2.2. Study design

Standard laboratory and C-reactive protein were measured in IBD subjects 1–7 days before the hemodynamic study in a centralized laboratory. All participants were studied in a quiet room with a controlled temperature of $22 \pm 1\,^{\circ}C$. In each subject, the non-invasive hemodynamic study was performed by an expert operator blinded to the clinical information, including therapy. A second operator, blinded to the hemodynamic examination, collected the clinical data using a standardized questionnaire.

2.3. Non-invasive hemodynamic data acquisition

Both in Study 1 and 2, the non-invasive investigation was performed after 15 min of recumbent rest. Brachial blood pressure measurements were taken using an oscillometric device (Dinamap ProCare 100; GE Healthcare, Milwaukee, USA). Central pressures were recorded noninvasively by applanation tonometry (SphygmoCor; AtCor Medical, Sydney, Australia) [10] after calibration with brachial cuff measurements of the diastolic and mean blood pressure in the contralateral arm [11].

Carotid-femoral and carotid-radial pulse wave velocity (PWV) were measured by a SphygmoCor device (AtCor Medical, Sydney, Australia) using the foot-to-foot velocity method, the intersecting tangent algorithm and the direct distance between the measurement sites [12]: PWV (m/s) $= 0.8 \times$ [direct distance (m)/Δt].

The augmentation index was calculated as previously described [6] and corrected for heart rate using a linear regression model (AIx_{HR}).

2.4. Clinical characteristics

Active disease was defined by the presence of rectal bleeding with an increase in stool frequency (>3/day) or abnormal mucosa at endoscopy in subjects with ulcerative colitis and Harvey-Bradshaw Index ≥ 8 [13] in subjects with Crohn's disease. Relapse was defined by detection of active disease in a subject with IBD who was previously in remission. Extensive disease was defined by ileo-colic lesions in subjects with Crohn's disease or lesions extended proximal to the splenic flexure, including pancolitis, in subjects with ulcerative colitis at endoscopy.

2.5. Statistical analysis

Statistical analyses were performed using NCSS 2007 and PASS 2005 software (Gerry Hintze, Kaysville, UT, USA). The sample size was estimated to demonstrate that IBD subjects have a higher carotid-femoral PWV than controls. The group sample sizes of 74 IBD subjects and 80 controls achieved 80% power to detect a difference of −0.6 m/s, where 0.6 m/s represents the difference of carotid-femoral PWV between IBD subjects and controls previously reported by our group in young subjects without cardiovascular risk factors [6], with a significance level (alpha) of 0.05000 using a two-sided two-sample t-test.

Continuous variables are presented as means (standard deviation); categorical variables are presented as counts and percentages. Clinical and hemodynamic parameters were compared using 1-way analysis of variance (ANOVA) for continuous variables and chi-squared tests for categorical variables. In Study 2, the 1-way repeated-measures ANOVA was used to investigate the effect of treatment on arterial stiffening, where the element of time was given as discrete time points. Sphericity was confirmed with Mauchly's test. Mixed models for repeated measures adjusted for age, gender, mean arterial pressure, heart rate and duration of follow-up were used to confirm that results of 1-way repeated-measures ANOVA. When the omnibus mixed model test was significant, Bonferroni test of within-subject contrasts was performed to test the difference between baseline and end of follow-up in both controls and IBD subjects according with the treatment. Univariate and multivariate linear regression analyses were performed to study the interrelations between PWV and clinical parameters.

2.6. Ethical considerations

This is an observational study because it was considered unethical to conduct a double-blind, randomized trial of anti-TNF