INCREASED CAROTID INTIMA-MEDIA THICKNESS IN INFLAMMATORY BOWEL DISEASE PATIENTS

EPAISSISSEMENT DE L'INTIMA-MEDIA CAROTIDIENNE CHEZ LES PATIENTS ATTEINTS DE MALADIE INFLAMMATOIRE CHRONIQUE DE L'INTESTIN

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Abstract

Background: Patients with inflammatory bowel disease (IBD) might have accelerated atherosclerosis.
Patients and Methods: The study consisted of IBD cases (n = 60) and healthy persons (n =60). The IBD group was selected so as not to have vascular disease. IMT was measured proximal to the carotid bifurcation over both right and left common carotid arteries in all patients and controls. The clinical characteristics and the laboratory parameters relevant to disease activity were recorded for all IBD patients.
Results: IMT of the common carotid artery was significantly higher in IBD patients. Multiple regression analysis revealed a significant association of IMT of the common carotid artery with systolic blood pressure, HDL-cholesterol and CRP.
Conclusions: IBD patients have an increased risk of early atherosclerosis. Systolic blood pressure, CRP and HDL-cholesterol were independently associated with the increased arterial wall thickness.

Keywords : Inflammatory bowel disease; Early atherosclerosis; Intima media thickness; Carotid ultrasonography.

Résumé

Introduction: Les données de la littérature sont discordantes quant à la responsabilité des maladies inflammatoires chroniques de l'intestin (MICI) dans le risque d'athérosclérose.
Patients et Méthodes: étude prospective incluant deux groupes : groupe MICI (n=60) et groupe contrôle (n=60) en excluant tous les cas ayant des facteurs de risque cardio-vasculaires établis. L'épaisseur de l'intima média(IMT) a été mesurée, pour chaque malade et témoin, des deux côtés, à un cm de la bifurcation carotidienne. Les caractéristiques cliniques et les paramètres biologiques ont été recueillis.
Résultats: L'IMT était significativement élevée en cas de MICI. L'analyse multi-variée a révélé une association significative entre l'IMT de l'artère carotide commune et la pression artérielle systolique, le HDL-cholestérol et la CRP.
Conclusion: Les MICI constituent un facteur de risque précoce d'athérosclérose. La pression artérielle systolique, le HDL-cholestérol et la CRP sont indépendamment associés à l'épaisseur de la paroi artérielle.

Mots clés : Maladie inflammatoire chronique de l'intestin; Athérosclérose; Epaisseur de l'intima média; Echo-doppler carotidienne.

ملخص

المقدمة: تتضارب البيانات الأدبية للموسوعة العلمية الطبية بالنسبة لمسؤولية مرض التهاب الأمعاء مع خطر حصول تصلب الشرايين.المرضى والطرق: دراسة مستقبلية تنطوي على مجموعتين مجموعة مرضى تتكون من 60 مريضا ومجموعة ضابطة تتكون من 60 شخصا بعد استبعاد جميع الحالات و خاصة منها عوامل الخطر القلبية الوعائية التي تم تحديدها. وقد تم قياس سمك الجدران الداخلية للأوعية الدموية لكل مريض. وقد تم جمع المظاهر السريرية والمعلومات البيولوجية لكل منهم.
النتائج: كان سمك الغلاف الأوسط و الباطني بشكل أكبر و ملحوظ في حالات مرض التهاب الأمعاء. وكشف تحليل الانحدار المتعدد جود علاقة وثيقة بين هذا السمك بمستوى الشريان السباتي المشترك وضغط الدم الانقباضي، والكولسترول المرتفع الكثافة والبروتيين المنشط ج.الخلاصة: مرض التهاب الأمعاء هو عامل خطر و في وقت مبكر لاحتمال ظهور تصلب الشرايين. وترتبط مستويات ضغط الدم الانقباضي و الكولسترول المرتفع الكثافة والبروتيين المنشط ج بشكل مستقل مع سمك جدران الشرايين.

الكلمات المفاتيح : مرض التهاب الأمعاء المزمن ; التهاب القولون التقرحي ; مرض كرون ; تصلب الشرايين ; سمك جدار الأوعية ; صدى دوبلر للشريان السباتي.

INTRODUCTION

Inflammatory bowel disease (IBD) represents a chronic inflammatory disorder of the intestine, classified by histopathological and clinical features into two major entities: Crohn's disease (CD) and ulcerative colitis (UC)[1]. Their etiology is still unknown, but gut tissue injury seems to be the result of an abnormal immune response and involves multiple non-immune cellular systems, including intestinal microvascular endothelial cells [2-4]. Thrombosis of mesenteric vessels was also involved in the pathogenesis of IBD. In fact, leukocytes can adhere to activated endothelium and transmigrate to the sub endothelial space. Subsequently, immune cell activation leads to atherosclerosis plaque progression and eventually plaque rupture, resulting in atherothrombotic disease. Conversely, systemic inflammation itself has been suggested to promote the atherosclerotic process [5-6]. Indeed, in several chronic inflammatory disorders, such as systemic lupus erythematosus and rheumatoid arthritis, systemic inflammation has been linked to enhanced atherogenesis, illustrated by an increased incidence of cardiovascular disease [7]. Several mechanisms by which a systemic inflammatory state can accelerate atherosclerotic process have been suggested. Cytokine-mediated damaging of the endothelium, immune cell activation and activation of the coagulation cascade have all been implicated [3].IBD is usually diagnosed in young adulthood and accompanies the patients throughout their lives. Thus, the potential impact of chronic inflammation on atherosclerosis in this young population is especially important. The aim of our study was to evaluate the risk of atherosclerosis in IBD patients as assessed by measurement of the intima–media thickness (IMT) of the wall of the common carotid artery (CCA) by high-resolution ultrasonography.

PATIENTS AND METHODS

Patients and Control Subjects

Sixty consecutive patients with confirmed IBD were recruited from the Department of Gastroenterology and Liver Diseases at Hedi Chaker University Hospital (SFAX, TUNISIA).
These patients were matched to 60 healthy persons, without a history of neoplastic, metabolic or inflammatory disease, on the basis of age, sex, body mass index (BMI), smoking status and physical activity. To avoid the confounding effect of atherosclerosis risk factors, we used the following exclusion criteria: individuals older than 45 years; hypertension as defined by blood pressure >140/ 90 mm/Hg or the use of antihypertensive medications; hyperlipidemia as defined by levels of total cholesterol >5.6 mmol/l or triglycerides >2 mmol/l, or the use of lipid-lowering medication; diabetes mellitus defined by fasting glucose levels >126 mg/dl or the use of antidiabetic medications; past personal history of cardiovascular or cerebrovascular events , past familial history of cardiovascular events. We excluded subjects younger than 18 years old, those suffering from infectious or inflammatory diseases other than IBD, as well as patients with ulcerative colitis who had undergone total colectomy. The diagnosis of IBD was based on established criteria of clinical, radiological, endoscopic and histological findings. After consenting to participate, each subject underwent an interview that included the duration and extension of disease, number of hospitalizations, clinical behavior, previous intestinal resections and current administration of drugs, blood pressure measurement, laboratory tests, and carotid ultrasonography. The Crohn's disease activity index and the Truelove and Witt's scores were used to assess the disease activity for patients with Crohn's disease and ulcerative colitis, respectively.

Laboratory measurements

All venous blood samples were drawn from patients and controls following a 12-h fast. C reactive protein (CRP) was measured using a commercial high-sensitivity CRP kit for human CRP (his CRP). The minimum detectable CRP concentration of the assay was 2 mg/l. ESR was measured by an ultracentrifugation method. Plasma concentrations of total cholesterol and triglycerides were measured by enzymatic colorimetric methods (CHOD_PAP) and (GPO_PAP) respectively. HDL and LDL cholesterol and blood glucose were measured enzymatically.

Intimal Media Wall Thickness

Carotid artery atherosclerosis was determined by ultrasonographic measurement of the IMT of the CCA 1 cm proximal to the carotid artery bifurcation on both the left and right sides[8]. IMT was defined as the distance from the leading edge of the lumen intimal interface to the leading edge of the media-adventitia interface of the far wall.

Ultrasonographic scanning was performed in simple blind by a single experienced ultrasonographer who was unaware of the clinical findings and who scanned the left and right CCA using a 10-MHz linear array transducer (Esaote My Lab 50 ultrasonograph). The final IMT value represents an average of the IMT results from the left and right sides. The participants were studied in the morning under standardized conditions, in a quiet room at comfortable temperature. All fasted for 12 hours and were asked to refrain from alcohol or caffeine intake 24 hours before the exam. Patients were examined in the supine position with the neck rotated 45 ° in the direction opposite the site being.

Statistical Analysis

All data were summarized and displayed as the mean ± SD for the continuous variables (age, BMI, inflammation markers, etc.) and as percentage in each group for categorical variables (smoking and other cardiovascular risk factors, medications, etc.). Comparison of risk factors among the different groups of study was performed with Chi² test. The comparison between quantitative and qualitative variables was performed by the Student test. The level of significance for above analyzes was 0.05. To assess which variables have significant influence on IMT, we used a stepwise linear regression procedure in which all variables that had a significant bivariate relation (defined by a *p* value <0.05) with IMT as well as known variables that influence atherosclerosis were evaluated for inclusion in the model. We adjusted significance level so that threshold was 0.1 and 0.2. The SPSS statistical package was used to perform all statistical evaluations (SSPS 18).

RESULTS

Carotid IMT was analyzed in 60 IBD patients (27 CD and 33 UC) and compared with carotid IMT values in 60 matched healthy controls.The characteristics of IBD patients are presented in Table I. There were no significant between-group differences in age, sex, body-mass index, smoking and physical activity (Table II). The duration of IBD was 65.76 ± 58,85 months (minimum 2 months, maximum 240 months). There was no significant difference between the two groups of IBD patients. At the time of study entry, most patients were treated by medications among which were anti inflammatory, corticosteroids and immunosuppressive medications (Table III). Chirurgical treatment was performed for 15% of patients. No focal atherosclerotic plaques (localized lesions >2 mm in thickness) in common carotid arteries were found in patients or controls. Mean carotid IMT value was significantly higher in IBD patients 0.74 ± 0.23 mm than in controls 0.49 ± 0.08mm ($p < 0.01$). Also considering CD and UC patients separately, carotid IMT value was increased compared to healthy subjects (figure 1). Independently of IBD activity, IMT was higher in this group of patients in comparison with controls (figure 2). IBD patients had significantly elevated levels of inflammatory markers (ESR, CRP) (Table IV). Mean HDL cholesterol value was significantly lower in IBD patients 0.72 mmol/l than in controls 1.02 mmol/l ($p < 0.01$). The linear regression analysis confirmed the association of systolic blood pressure, CRP and HDL cholesterol with IMT (Table V). Importantly, IMT did not correlate with either disease duration (Figure 3) or IBD treatment (table VI). Patients who were treated with infliximab showed an increased mean of IMT when compared with controls 0.66 mm versus 0.49 mm respectively, $p<0.01$.

Table I: Clinical characteristics of patients with Inflammatory Bowel Disease

Type of IBD	UC	CD
Age (years)	32.81	32.55
Sex (F/M)	20/13	11/16
Weight (kg)	58.94	63.7
Height (m)	1.64	1.64
BMI (kg/m²)	22.08	23.06
Smoking (%)	30.3	44.4
Disease duration (months)	61.18	71.37
Number of hospitalisations	2	3
Familial history of IBD	3	10

Table II: Epidemiological data of inflammatory bowel disease patients and controls

Characteristics	Controls n=60	IBD n=60	p
Age (years)	31.83	32.7	NS
Gender (M/F)	(29 /31)	(29 /31)	NS
BMI (kg/m²)	22.3	22.52	NS
Smoking n (%)	25 (41.6%)	24(40%)	NS
Physical activity n (%)	8 (13.33%)	8 (13.33%)	NS

Table III: Different medical treatment for Inflammatory Bowel Disease

Medical treatment	Number of patients (%)
Salicylates :	
Salazopyrin	42 (70%)
Aminosalicylates	26 (43.33%)
	16 (26.66%)
Corticosteroïds	35 (58.33%)
Immunosuppressive :	
Azathioprine	24 (40%)
Methotrexate	22 (36.66%)
	2 (3.33%)
Infliximab	9 (15%)

Table IV: Comparison of inflammatory markers between the 2 groups of study

Variable	IBD n=60	Controls n=60	p
ESR	36.06	12.66	<0.01
CRP	27.71	7.86	<0.01

Table V: Correlation between IMT and systolic blood pressure, CRP, HDL cholesterol

Variable	ß	p
Systolic blood pressure	0.67	<0.01
HDL cholesterol	0.32	0.05
CRP	-0.07	0.15

Table VI: Correlation between IMT and IBD treatment modalities

Variables	ß	p
Corticosteroïds	0.6	0.34
Salicylates	-0.1	0.51
Immunosuppressive	-0.04	0.15
Infliximab	0.04	0.79
Surgery	0.28	0.08

IMT: dependant variable

Figure 1: Comparison of the IMT among controls, patients with Crohn's disease and ulcerative colitis

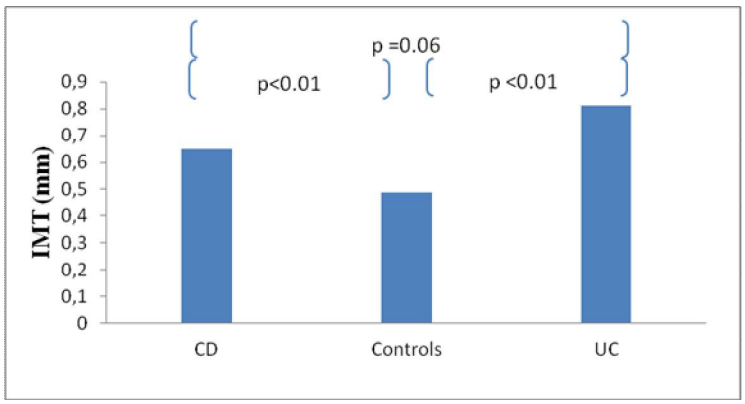


Figure 2: Comparison of the IMT according to disease activity

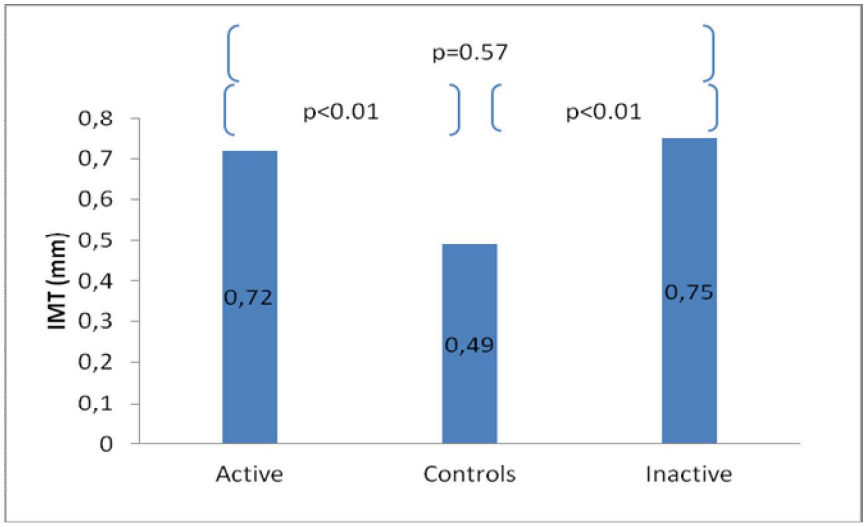
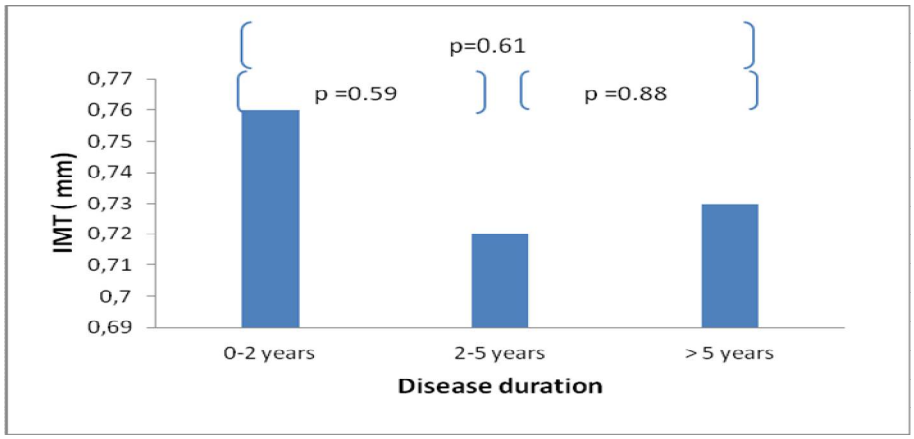


Figure 3: Variation of IMT according to disease duration



DISCUSSION

Our study revealed an increased risk of atherosclerosis in IBD patients as shown by the higher value of IMT in this group compared to healthy matched controls. Few studies have assessed this risk in IBD patients and the results were contradictory. Our results were consistent with those of three recent studies. Papa et al [1], showed that IMT was significantly higher in a group of 52 patients with IBD 0.63 ± 0.15mm versus 0.53 ± 0.08mm in a group of 20 healthy controls, p = 0.008. Similarly, Dagli et al[2] showed that IMT was higher in 40 patients with IBD compared to 40 healthy controls matched for age, sex and BMI (0.74 mm and 0.70 mm respectively; p = 0.01). Leuven et al [3], compared a group of 60 CD to healthy controls. Similar results were observed and the IMT was 0.71 mm in the first group and 0.59 mm in the second one; p <0.001. However, two other studies haven't revealed an increased risk of atherosclerosis in IBD patients. Thus, Marshak et al[4], found a comparable value of IMT between a first group of 61 IBD patients and a second group including 61 healthy controls matched for age, sex, BMI, smoking and physical activity (0.66 ± 0.09 versus 0.64 ± 0.07 mm; p> 0.05). Similarly, the study of Broide et al [5], including 50 CD patients aged between 20 and 45 years and 25 control subjects, analyzed each side separately: the right IMT was 0.51 mm in IBD group and 0.54 mm in healthy controls; p = 0.15; the left one was 0.52 mm and 0.55 mm respectively; p = 0.13.

In our study, we showed that type of IBD does not influence the progression of atherosclerosis process. Also, we demonstrated that the IMT does not vary within disease activity. These results are in accordance with literature data [2, 4, 5].

Overall, our study showed an increased risk of atherosclerosis in IBD without being influenced by sex, type of IBD, disease activity and duration. Early atherosclerosis is a clinical feature common to several inflammatory and immunological disorders[1]. Atherosclerosis affects both muscular and elastic arteries; its progression is marked by alterations of arterial wall initially preserved by repairment phenomenon. Thus it remains clinically asymptomatic at the beginning and may be undetected for decades. It can lead to atherothrombotic complications which represent a major cause of morbi-mortality in IBD[4,5]. The increased risk of atherosclerosis can be explained by the pathogenesis of these diseases which seems to be the result of environmental, genetic and immunological factors where an immune response could cause inappropriate intestinal inflammation in genetically predisposed persons [9]. Dysfunction of the intestinal immune system and cross-reactivity towards epithelial cells of the host are the main mechanisms involved in the inflammatory process. Other mechanisms may promote atherosclerosis in systemic inflammation[10]; such as activation of immune cells, promoting of coagulation cascade and endothelial damage mediated by cytokines promoting a Th1 response (rather than a Th2 response) and inducing production of many inflammatory and cytotoxic molecules in macrophages and vascular cells that tend to promote the initiation and progression of atherosclerosis [11,12]. Intestinal infarctions with multifocal vascular lesions, focal fibrin arteritis deposition and / or granulomatous lesions are the most common features within the intestinal mucosa

of patients suffering from IBD [13]. An additional effect of micro vessels's dysfunction and reduction of endothelium vasodilatation capacity was observed[14]. These different lesions contribute to the decline of intestinal perfusion and maintenance of chronic inflammation [14,15]. Furthermore, IBD is associated with an hypercoagulable state especially with UC [15].

We have shown that IMT was significantly higher in the subgroup of IBD patients treated with anti-TNF alpha than in healthy controls. In contrast, Papa et al [1] found no difference in IMT value between IBD subgroup treated with anti-TNF alpha and healthy controls. It suggests that this option would have a beneficial effect. Indeed, infliximab, an anti-TNF alpha, is a monoclonal antibody introduced recently in the treatment of rheumatoid arthritis and IBD. It is able to improve not only the inflammatory processes but also the endothelial dysfunction [16]. However, the small number of controls in the study by Papa et al [1] and the small number of patients treated with infliximab for a short period in our series can not characterize the benefit of this treatment. Other large studies should be encouraged to clarify these findings.

We showed that corticosteroids have no effect on atherosclerosis in IBD patients. Indeed, IMT was lower in the subgroup of patients treated with corticosteroids than in those who haven't had this treatment but the difference wasn't statistically significant. In fact, their effect on endothelium depends on dose and duration of exposure to corticosteroids. It has been shown that corticosteroids induce an increased production of free radicals in endothelial cells [17]. These free radicals reduce the availability of nitric oxide (NO) by inducing superoxide production leading to peroxynitrite formation. This decrease in NO availability can induce endothelial dysfunction, leading to atherosclerosis and cardiovascular pathology.

In linear regression analysis, IMT wasn't correlated with any treatment in our study. Similarly, Broide et al [5], found no correlation between IMT and different treatment modalities. This lack of correlation can be explained by the reduced number of patients in each subgroup of different treatment modalities.

Also, linear regression analysis revealed that systolic blood pressure, CRP and HDL cholesterol were the only independent factors associated with an increased IMT. These results are very interesting so that they allow us to identify typical risk factors of atherosclerosis in IBD patients.

In Papa et al study [1], linear regression analysis revealed that homocysteine concentrations and age were associated with an increased IMT. However, mechanisms through which hyper homocysteine promote atherosclerosis still remain unknown. In vitro studies have suggested that homocysteine induces endothelial cell damage, disruption of arterial flow contributing to vascular inflammation [1]. It has been suggested that high blood pressure is not only a cardiovascular risk factor, but also an atherosclerosis risk factor [18]. Clinical trials have shown that it contributes significantly to atherosclerosis in a comparable manner to that attributed to high cholesterol levels [12]. In fact, atherosclerotic plaques tend to develop in high pressure areas [18]. However, the mechanisms of this synergistic effect are not yet well defined. Hypertension is characterized by a thickening of the wall arteries promoted by an increased proliferation of muscle cells and deposition of connective tissue [19]. By analyzing the relationship between atherosclerosis and blood pressure, it would be interesting to consider the mechanisms common to both diseases [18]. The endothelium role was the most studied over the past two decades and seems to be important in atherosclerosis pathogenesis and high blood pressure. The importance of endothelium role in the development of atherosclerosis has been demonstrated in animal models. Similarly, changes in the morphology and function of the endothelium are essential characteristics of hypertension [19, 20]. Thus, the relationship between atherosclerosis and increased blood pressure is well established through endothelial dysfunction. Furthermore, CRP represents a predictive marker of atherosclerosis similarly to blood pressure and total cholesterol levels [6,21]. In vitro studies have suggested several mechanisms to explain the association between CRP and atherosclerosis in IBD. In fact, CRP can bind to phosphocholine presented by oxidized phospholipids of LDL, favoring their absorption. Also, it can promote endothelial activation and the production of NO [22]. As to HDL cholesterol, it is the most potent endogenous protective marker from atherosclerosis, as shown by the reverse relationship between concentration of HDL cholesterol and the incidence of cardiovascular disease [10]. Systemic inflammation leads to quantitative and qualitative impairment of HDL cholesterol. These changes damage the anti atherogenic functions of HDL and can make them pro-atherogenic.

In summary, the present study found evidence of subclinical atherosclerosis in IBD patients, as demonstrated by greater IMT of the common carotid artery compared with healthy subjects. HDL cholesterol levels, CRP and systolic blood pressure were the most important factors associated with increased IMT in our cohort of IBD patients. Although we did not find any correlation between IMT and current use of anti- inflammatory medications, such treatment might attenuate the inflammatory machinery in the vessel wall. Clarification of this possibility awaits studies on larger cohorts of patients.

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