Inflammatory Bowel Disease Is Not Associated With Increased Intimal Media Thickening

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OBJECTIVES: Several studies have suggested that chronic inflammatory diseases might be associated with an acceleration of the atherosclerotic process. There is little information on the effect of chronic inflammation in patients with inflammatory bowel disease (IBD) on the presence of increased intimal media thickening (IMT), a surrogate marker for atherosclerotic diseases. In this work our aim was to determine whether IBD is a risk factor for increased IMT.

METHODS: IMT was measured by ultrasound of the carotid arteries; a computer software program was used to analyze 80–100 independent IMT samples from each carotid artery segment in 61 patients with IBD (45 with Crohn’s disease and 16 with ulcerative colitis) and in 61 controls matched for age (±2 yr), sex, body mass index (BMI, ±2 kg/m²), and smoking status.

RESULTS: Inflammatory markers (erythrocyte sedimentation rate, fibrinogen, high-sensitive C-reactive protein) were significantly (P < 0.001) elevated in IBD patients compared with controls. Even though there was a disease duration of 8.7 ± 8.5 yr, the mean IMT of IBD patients was similar to that of the control group (0.66 ± 0.09 vs 0.64 ± 0.07 mm; P > 0.05).

CONCLUSIONS: Despite chronic inflammation, IBD patients had IMT values similar to those of the controls. Thus, unlike other inflammatory diseases, IBD appears not to be a risk factor for accelerated atherosclerosis.

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INTRODUCTION

Atherosclerosis is a leading cause of morbidity and mortality in the western community (1, 2). Several chronic inflammatory diseases are associated with an accelerated atherosclerotic process (3). In fact, it has been shown that inflammatory mediators contribute to the pathogenesis of atherosclerosis: the inflammatory marker C-reactive protein (CRP) is considered a risk factor for atherosclerosis (4) and participates in the evolution and progression of atherosclerosis. Thus, it is plausible that longstanding chronic inflammatory disease may serve as a risk factor for accelerated atherosclerosis (5). An association of atherosclerosis with chronic inflammatory diseases has already been reported for patients with rheumatoid arthritis (6–8) and systemic lupus erythematosus (SLE) (9). Chronic active inflammation significantly contributed to carotid atherosclerosis in rheumatoid arthritis, a finding that may partially explain the high frequency of cardiovascular morbidity and mortality observed in affected individuals (10–12). Inflammatory bowel diseases (IBD) are characterized by chronic intestinal inflammation. IBD is usually diagnosed in young adulthood (13, 14) and accompanies the patients throughout their lives. Thus, the potential impact of chronic inflammation on atherosclerosis in this young population is especially important.

Intimal media thickening (IMT) is a surrogate marker of atherosclerosis (15, 16). IMT reflects early changes in the arterial wall, such as inflammatory intimal reactions and early atherosclerosis, and may appear years before atherosclerotic plaque has formed (17). Measuring the IMT of carotid arteries by ultrasonography is a useful method for detecting early atherosclerosis in epidemiological and clinical research (15) and correlates with cardiovascular risk factors (16).

One study linked IBD with increased carotid IMT (18). This observation is an intriguing one since, unlike patients with rheumatoid arthritis and SLE, IBD patients are not a risk group for atherosclerosis per se, and epidemiological studies do not indicate increased cardiovascular events among them (19–21).
If IBD is, indeed, a risk factor for accelerated atherosclerosis, this may have important clinical implications. We tested the effect of longstanding inflammation in IBD patients on carotid atherosclerosis by measuring the IMT of the carotid arteries in a group of 61 IBD patients and compared it with the IMT of 61 well-matched controls.

METHODS

Patients and Control Subjects
Sixty-one consecutive patients with confirmed IBD were recruited from the IBD Service of the Department of Gastroenterology and Liver Diseases and the Department of Internal Medicine at the Tel Aviv Sourasky Medical Center (Tel Aviv, Israel). These patients were matched to apparently healthy medical personnel on the basis of age (± 2 yr), sex, body mass index (BMI, ± 2 kg/m²), and smoking status. All study participants signed an informed consent form, and the study was approved by the local ethics committee. Excluded were individuals younger than 18 yr old or older than 60, pregnant women, or individuals with any malignancy, known cardiovascular diseases, infectious or inflammatory diseases other than IBD, as well as patients with ulcerative colitis who had undergone total colectomy.

After consenting to participate, each subject underwent an interview that included the determination of IBD activity, blood pressure measurement, laboratory tests, and carotid ultrasonography. The Crohn’s disease activity index (CDAI) (22, 23) and the Mayo (24) scores were used to assess the disease activity for patients with Crohn’s disease and ulcerative colitis, respectively. Information on disease duration and number of hospitalizations was included as well.

Laboratory Tests
Venous blood was drawn from patients and controls following a 12-h fast. Total cholesterol, low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c), triglycerides, glucose, folic acid, and vitamin B12 levels were determined. The erythrocyte sedimentation rate (ESR) was measured by the method of Westergren (25) and quantitative fibrinogen by the method of Clauss (26) and a Sysmex 6000 (Sysmex Corporation, Hyaga, Japan) analyzer. The high-sensitivity CRP (hs-CRP) level was determined using a Boering BN II Nephelometer (DADE Boering, Marburg, Germany) (27).

Atherosclerotic Risk Factors
Information was collected on age, height, weight, smoking habits, family history of cardiovascular disease, physical activity, diabetes, and current use of medications. We used the following definitions for the various risk factors:

- Hypertension: systolic blood pressure > 140 mmHg or a diastolic blood pressure > 90 mmHg or the use of antihypertensive agents.
- Hypercholesterolemia: total cholesterol level > 200 mg/dL or the use of lipid-lowering agents.
- Smoking status: nonsmokers (never smoked or stopped smoking > 5 yr ago) (28), light smokers (< 5 cigarettes daily or stopped smoking during the last 5 yr), smokers (> 5 cigarettes daily).
- Overweight: BMI of ≥ 27 kg/m².
- Diabetes: fasting glucose levels > 126 mg/dL or the use of antidiabetic medications.
- Sedentary lifestyle: < 60 min of aerobic physical activity per week.

The patients were classified into four categories of disease activity, with respective Mayo and CDAI scores for each (29, 30): remission (0–2 and 0–150), mild (3–5 and 151–220), moderate (6–10 and 221–450), and severe (11–12 and 451–600).

Intimal Media Wall Thickness
Carotid artery atherosclerosis was determined by ultrasonographic measurement of the IMT of the common carotid artery (CCA) 1.5–3 cm proximal to the carotid artery bifurcation on both the left and right sides. IMT was measured at the distal wall of the carotid artery on a 10-mm segment and 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 (31). A computer software package (M’ATH software) was used for sampling and calculating the average of 80–100 independent IMT samples of the examined segment. Ultrasonographic scanning was performed by a single sonography technician (T.N.) who was unaware of the clinical findings and who scanned the left and right CCAs using carotid duplex equipment (128XP /10, Acuson, Mountain View, CA) with a 7-MHz linear array transducer. The final IMT value represents an average of the IMT results from the left and right sides.

Statistical Analysis
All data were summarized and displayed as the mean ± SD for the continuous variables (age, BMI, inflammation markers, etc.) and as the number of patients plus the percentage in each group for categorical variables (smoking and other cardiovascular risk factors, medications, etc.). The cross-tabs and descriptive procedures were used to produce frequencies of categorical variables and the mean ± SD of the continuous variables.

Sample size was calculated assuming 0.055 mm difference in IMT between patients and controls with standard deviation of 0.11 mm, to achieve statistical significance (β = 0.2, α = 0.05). We based these values on a study of rheumatoid arthritis patients and controls (7) and on a large cohort that evaluated IMT in normal populations (32) since there were no studies on IMT of IBD patients.

Since the hs-CRP has a nonnormal distribution, we used a logarithmic transformation that converts it to a normal distribution for all statistical procedures, such as regressions; all the results expressed as hs-CRP are a back-transformed geometrical mean and standard deviation. The one-sample Kolmogorov–Smirnov test was used to verify that the
logarithmic transformation is normally distributed. The paired sample t-test was used to evaluate the difference between the groups for all continuous variables, while the $\chi^2$ Phi and Cramer’s V statistics were used for assessing the difference between the groups for all categorical variables. Assessment of the crude relation between the IMT and specific variables was performed using the Pearson partial correlation for continuous variables, and the Spearman correlation procedure was used for categorical variables.

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. The results are reported as partial correlations between the included variables and the IMT.

A one-way analysis of variance (ANOVA) was used to compare the IMTs of the different disease severity groups and the controls.

The level of significance used for all of the above analyses was 2-tailed $P < 0.05$.

The SPSS statistical package was used to perform all statistical evaluations (SSPS Inc., Chicago, IL).

**RESULTS**

Carotid IMT was analyzed in 61 IBD patients (45 Crohn’s disease and 16 ulcerative colitis) and compared with the carotid IMT values in 61 matched healthy controls. The characteristics of the study participants are presented in Table 1. The only parameter that was significantly different between the patients and the controls was physical activity, which was decreased in IBD patients ($P = 0.002$). The duration of IBD was $8.74 \pm 8.5$ (mean $\pm$ SD) yr, and the patients had $3.2 \pm 5.3$ hospitalizations each. Within the group of patients, ulcerative colitis patients were older than Crohn’s disease patients ($42 \pm 13$ vs $34 \pm 9.5$ yr, $P = 0.01$); otherwise there was no significant difference between the two groups. The average Mayo score for the ulcerative colitis patients was $3.5 \pm 3.5$ and the average CDAI for the Crohn’s disease patients was $165 \pm 121$. At the time of study entry, most patients were treated by medications—among which were anti-inflammatory and immunosuppressive medications (Table 2).

Importantly, there was no significant difference in the IMT measurements between the patients and the controls ($0.66 \pm 0.09$ and $0.64 \pm 0.07$ mm, respectively, $P = 0.16$), although IBD patients had significantly elevated levels of inflammatory markers (ESR, CRP, and fibrinogen) (Table 3). The respective mean blood levels of additional inflammatory markers and acute phase proteins among the patients: there was a ceruloplasmin level of $33.6 \pm 12$ versus $28.4 \pm 9$ ng/dL ($P = 0.006$), a total globulin level of $31.4 \pm 3$ versus $29.9 \pm 3.1$ g/L ($P = 0.001$), an albumin level of $43 \pm 3.7$ versus $44.7 \pm 2.4$ g/L ($P = 0.04$), a hemoglobin level of $12.97 \pm 1.5$ versus $14 \pm 1.3$ g/dL ($P < 0.001$), a white blood cell level of $7.8 \pm 3.3$ versus $6.4 \pm 1.4 \times 10^3$/mm$^3$ ($P = 0.005$), and a platelet level of $313 \pm 78$ versus $252 \pm 57 \times 10^3$/mm$^3$ ($P < 0.001$) in patients versus controls, respectively.

A linear regression analysis was performed in order to analyze which factors influenced IMT (Table 4). Included in this regression were age, gender, hypertension, BMI, smoking status, inflammatory marker levels (hs-CRP, fibrinogen, ESR), and total cholesterol, LDL-c, HDL-c, and triglyceride levels.

Of all the above-mentioned variables, older age ($P < 0.001$), the presence of hypertension ($P = 0.002$) and male gender ($P = 0.03$) were significantly associated with an increased IMT.

Since homocysteine levels have been reported to be elevated in IBD patients (33) and given that homocysteine can induce inflammation in the arterial wall and is probably associated with an increased risk of coronary heart disease (34), we evaluated folic acid and vitamin B12 levels, which are

<table>
<thead>
<tr>
<th>Medications</th>
<th>Number of Patients (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-ASA</td>
<td>38 (62)</td>
</tr>
<tr>
<td>Antibiotics (metronidazole/ciprofloxacin)</td>
<td>4 (6.6)</td>
</tr>
<tr>
<td>Steroids</td>
<td>14 (23)</td>
</tr>
<tr>
<td>Azathioprine/6MP</td>
<td>17 (28)</td>
</tr>
<tr>
<td>No treatment</td>
<td>9 (15)</td>
</tr>
</tbody>
</table>

*Some patients received more than one medication.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients (N = 61)</th>
<th>Controls (N = 61)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age years</td>
<td>$36 \pm 11$</td>
<td>$36 \pm 11$</td>
<td>NS</td>
</tr>
<tr>
<td>Women, no. (%)</td>
<td>$33 (54)$</td>
<td>$33 (54)$</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Cardiovascular risk factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus, no. (%)</td>
<td>$1 (1.6)$</td>
<td>$1 (1.6)$</td>
<td>NS</td>
</tr>
<tr>
<td>Hypercholesterolemia, no. (%)</td>
<td>$22 (36)$</td>
<td>$17 (28)$</td>
<td>NS</td>
</tr>
<tr>
<td>Low HDL (&lt;40 mg/dL)</td>
<td>$8 (13)$</td>
<td>$5 (8)$</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking, no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonsmoker</td>
<td>$42 (69)$</td>
<td>$44 (72)$</td>
<td>NS</td>
</tr>
<tr>
<td>Light smoker</td>
<td>$10 (16)$</td>
<td>$11 (18)$</td>
<td>NS</td>
</tr>
<tr>
<td>Smoker</td>
<td>$9 (15)$</td>
<td>$6 (10)$</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension, no. (%)</td>
<td>$5 (8)$</td>
<td>$9 (15)$</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>$118 \pm 14$</td>
<td>$118 \pm 13$</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>$74 \pm 9$</td>
<td>$75 \pm 9$</td>
<td>NS</td>
</tr>
<tr>
<td>Age (men $\geq$45, women $\geq$55)</td>
<td>$10 (16)$</td>
<td>$9 (15)$</td>
<td>NS</td>
</tr>
<tr>
<td>Family history of IHD, no. (%)</td>
<td>$4 (11.8)$</td>
<td>$6 (10.9)$</td>
<td>NS</td>
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<tr>
<td><strong>Overweight (BMI $\geq$27)</strong></td>
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<td></td>
</tr>
<tr>
<td>BMI, kg/m$^2$</td>
<td>$23.1 \pm 3.8$</td>
<td>$23.1 \pm 3.5$</td>
<td>NS</td>
</tr>
<tr>
<td>Sedentary lifestyle, no. (%)</td>
<td>$46 (75)$</td>
<td>$29 (48)$</td>
<td>0.002</td>
</tr>
<tr>
<td>Disease duration</td>
<td>$8.74 \pm 8.5$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of hospitalizations among patients</td>
<td>$3.2 \pm 5.3$</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

IBD = inflammatory bowel disease; HDL = high-density lipoprotein; IHD = ischemic heart disease; LDL = low-density lipoprotein; NS = not significant.
evaluated IMT in IBD patients. Papa et al. (18) reported an increased IMT in 52 IBD patients compared with 20 healthy controls. The differences between this single previous work and ours may be the result of confounding risk factors, such as family history of ischemic heart disease or the lack of physical activity, that were controlled for in our study, but not previously. Moreover, the larger IBD and control cohort in the current study may have added impact to data interpretation. However, the low-grade disease activity of our patients compared with the higher disease activity and much elevated inflammatory indices demonstrated in the work of Papa et al. could serve as a confounder as well. Despite this fact it should be noted that IBD is characterized by attacks of inflammation, and the status of disease activity at the time of inclusion in to the research does not necessarily mirror disease activity during the entire course of disease. The average ± SD number of hospitalizations due to disease flare-ups in our patients was 3.18 ± 5.3; 16 patients had passed surgical interventions due to disease complications. Accordingly, most of these patients, during the course of their disease, suffered from prolonged durations of high disease activity.

Noteworthy, we used strict matching of 61 IBD patients and 61 control subjects for major cardiovascular risk factors (Table 1). This was important for isolation of disease-associated variables that may affect IMT and for eliminating confounding factors. The remarkable finding was that while inflammatory indices were significantly elevated among IBD patients, the IMT in both the patient and control groups was not significantly different. Interestingly, these inflammatory indices were higher despite an average mild disease activity both for Crohn’s disease as well as for ulcerative colitis.

To further support our results, we examined whether traditional risk factors affected IMT in the combined cohort. As expected, we found that older age, hypertension, and male sex were the most significant predictors of increased IMT (Table 4). The other traditional cardiovascular risk factors were associated with increased IMT as well, but did not reach statistical significance, probably due to the sample size. Disease variables, such as disease duration, number of hospitalizations, and inflammatory indices did not affect IMT values. It could be argued that the duration of the disease was too short to have an effect on IMT, but others have demonstrated IMT differences in children who suffered from obesity or allergic rhinitis, despite few years of exposure to inflammation (45, 46). Furthermore, an article comparing premenopausal women suffering from rheumatoid arthritis with healthy controls demonstrated IMT differences between the two groups. Disease duration among rheumatoid arthritis patients was 9.5,
similar to the disease duration in our article (47). The average disease duration in our patients was 8.7 yr, but the range of disease duration was 0.5–38 yr. Thirty percent of patients suffered from IBD for 11 yr or more.

The existence of nonmajor risk factors (48, 49) among the control subjects compared with the IBD patients could possibly serve to explain the lack of difference in IMT. As shown in Table 1, obesity did not differ between the two groups while physical inactivity was significantly more common among IBD patients. This additive cardiovascular risk factor in IBD patients emphasizes the paradox of nonaccelerated atherosclerosis among these patients.

In light of the growing recognition of inflammation as a risk factor for atherosclerosis (48, 49), we hypothesize that IBD patients may be protected from atherosclerosis by a factor yet to be detected. HDL cholesterol level above 60 mg/dL (50) could serve as a protective factor against atherosclerosis but it did not differ between the groups (data not shown).

There could be a diminished exposure to one of the emerging risk factors (48, 49) for cardiovascular diseases, such as lipoprotein (a), oxidative stress, or an atherogenic diet, among IBD patients, but those risk factors have not been thoroughly evaluated in these patients. On the other hand, longstanding inflammatory medications that are administered to patients with IBD may protect these patients against atherosclerosis. Although we did not find any correlation between IMT and current use of medications, such an anti-inflammatory approach might attenuate, at least in part, the inflammatory machinery in the vessel wall. Clarification of this possibility awaits studies on larger cohorts of patients. It is most probable that interactions between environmental and genetic factors and the immune system serve to modify cardiovascular risk factors in patients with IBD.

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What Is New Here

- IMT is not increased in IBD patients compared with matched controls.
- In IBD patients there is no correlation between disease duration or disease severity and IMT.
- Our findings may suggest that, in contrast to other inflammatory diseases, in IBD the inflammatory process does not increase the risk for atherosclerosis and its complications.

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CONFLICT OF INTEREST

The authors have declared no potential conflicts of interest.