Chronic viral hepatitis: a prospective factor against atherosclerosis

A study with echo-color Doppler of the carotid and femoral arteries and the abdominal aorta

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SUMMARY
Objective — To evaluate if chronic viral hepatitis may be a protective factor for atherosclerosis.

Methods — Echo-doppler of the carotid and femoral arteries and the abdominal aorta was used to examine 48 patients with a histological diagnosis of chronic viral hepatitis (42 hepatitis C virus-related, 6 hepatitis B virus-related), with a low degree of activity and preserved hepatic function, and 50 controls matched for age, sex and exposure to the main risk factors of atherosclerosis.

Results — The prevalence of atherosclerosis in patients was clearly lower than in controls in all investigated sites, although the difference was statistically significant only for the carotid arteries. The percent-age of patients with carotid atherosclerosis was 27% in patients with liver disease and 56% in controls (P < 0.005). Furthermore, and again at the carotid level, the patients with liver disease had fewer atheromatous lesions (16 plaques vs. 59; P < 0.001) than controls as well as a lower degree of vessel stenosis. None of the liver disease patients presented with vessel stenosis above 30% vs. 8% of control subjects.

Conclusions — Chronic viral hepatitis may help prevent from atherosclerosis.

The etiological complexity and the remarkable epidemiological and social importance of atherosclerosis has given rise to extensive research on its pathogenesis. A number of studies have reported a lower incidence of atherosclerosis and its clinical manifestations in the presence of cirrhosis [1, 2]. However, because of altered liver function, in cirrhosis the incidence of some atherosclerosis risk factors seems to be decreased. In fact there is a reduction of cholesterol synthesis [3], lipoprotein(a) [4-6], coagulation factors [7] as well as of platelets and their function [8]. In addition, in cirrhosis there are so many modifications in hemodynamics that, on one hand portal hypertension occurs and, on the other, there is generalized vasodilatation with reduction of systemic vascular resistance [9, 10]. Finally, in cirrhosis there is glucose intolerance up to overt diabetes [11-12] with all the well-known consequences for atherosclerosis. All this does not occur in mild chronic hepatitis where liver function is still good. For this reason, we analyzed a group of patients with mild chronic viral hepatitis without portal hypertension. Due to the controversial role of alcohol in the pathogenesis of atherosclerosis, patients with alcohol-related liver diseases were excluded [13].

The aim of the present research was to evaluate by ultrasound-color Doppler of the main arterial trunks and in particular the carotid vessels, the presence and degree of atherosclerotic alterations in 48 patients with a histological diagnosis of chronic viral hepatitis. Results were compared to those of 50 patients matched for age, sex and exposure to cardiovascular risk factors.

Patients and methods

Patients

Two groups of patients, aged between 35 and 80 years, were examined for 12 months. The first group was selected from the chronic viral hepatitis out-patients of the Infectious Disease Department of the University Polyclinic in Padua. The etiology of hepatitis was hepatitis C virus (HCV)-related in 42 patients and hepatitis B virus (HBV)-related in 6 patients. All patients had had hepatitis for more than 5 years, mean 9.7 years.

In all subjects the diagnosis of chronic viral hepatitis was based on histological test in addition to the usual serologic markers. Degree of activity of chronic hepatitis was evaluated by the Knodell-Ishak Score. Upper gastrointestinal endoscopy ruled out the presence of portal hypertension. Patients with cirrhosis, with confirmed repeated alcohol consumption, with concomitant human immunodeficiency virus (HIV)
Infection and HCV and carriers of cryoglobulins were excluded from the study. Table I shows the biological and histological parameters for the assessment of liver function and the degree of hepatitis activity. Controls were matched 1:1 with patients for age, sex and risk factors for atherosclerosis.

Patients with myocardial infarction, angina pectoris, stroke, transient ischemic attack, murmur or previous carotid endarterectomy, arteriopathy obliterans of the lower limbs, and abdominal aorta aneurysms were excluded. Patients with auto-immune, immunoproliferative and thyroid diseases, and patients receiving therapy with glucocorticoids or estrogen-progest parenthesis were also excluded. Subjects from both groups underwent a medical examination and routine biochemical tests to detect and quantify the main cardiovascular risk factors as shown in Table II.

Ultrasound-color-Doppler evaluation

Search for atheromatous lesions was performed by ATL Apogee 800 plus, using an 8.5 MHz probe for the B-mode ultrasound and a 6MHz probe for the pulsed wave Doppler. Patients were examined while lying on a bed in supine position. To explore the carotid axis, the patient probe for the pulsed wave Doppler. Patients were examined while lying plus, using an 8.5 MHz probe for the B-mode ultrasound and a 6MHz proximal, medium and distal positions with respect to the bifurcation. The search and identification of atheromatous plaques in a proximal position with respect to the bifurcation; internal carotid in

Table I. – Biological parameters in liver disease patients.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal Value</th>
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<tr>
<td>ASAT</td>
<td>68 ± 63.6 U/L</td>
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<tr>
<td>ALAT</td>
<td>100 ± 109 U/L</td>
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<tr>
<td>Total bilirubin</td>
<td>14.7 ± 5.6 micromol/L</td>
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<tr>
<td>GGT</td>
<td>50 ± 57.2 U/L</td>
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<tr>
<td>Prothrombin time</td>
<td>93 ± 11 %</td>
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<tr>
<td>Total protein</td>
<td>75 ± 6.1 g/L</td>
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<tr>
<td>Albumin</td>
<td>41.8 ± 4.1 g/L</td>
</tr>
<tr>
<td>Gamma globulins</td>
<td>21 ± 5.7 %</td>
</tr>
<tr>
<td>Plaquettes</td>
<td>208 000 ± 60 000/mL</td>
</tr>
</tbody>
</table>

Results

Ninety-eight patients were examined: 48 had chronic viral hepatitis (M = 24, F = 24) and 50 (M = 27, F = 23) were controls, who showed no clinical nor electrocardiographic signs of disease. The mean age of liver disease patients was 58.1 ± 14 years, while that of the controls was 58.3 ± 11.2 years (P = ns).

Prevalence of atherosclerosis risk factors was substantially homogeneous in the two groups (figure 1).

In liver disease patients 27% of individuals had plaques at the carotid artery level vs 56% of controls (P < 0.005); in the femoral arteries 10% of liver disease patients had plaques vs. 22% of controls (P = ns); finally, in the abdominal aorta 6% of liver disease patients had atheromatous lesions vs. 22% of controls (P = ns) (figure 2).

The degree of stenosis of the two carotid arteries (figures 3 and 4) was different in the two groups. While in the liver disease patients carotid artery plaques produced only class 1 stenosis (stenosis percentage from 0% to 30%), 8% of controls (P = ns) presented class 2 plaques (stenosis percentage from 31% to 50%). The extent of atherosclerotic disease, defined as the number of plaques (minimum 1, maximum 8) present in the individual’s carotid arteries (common carotid artery, internal and external carotid artery, bifurcation of the carotid artery), was lower in liver disease patients than in controls (figure 5). Of a total of 75 plaques found in the two groups, 16, i.e. 21.35% of the total, were found in liver disease patients versus 59% in controls (P < 0.001).

Discussion

The results of this study suggest that chronic viral hepatitis may play a protective role in the complex process leading to the onset of atherosclerotic plaques. This hypothesis is not new in the scientific literature, although it originates from studies carried out...
with different methods than those of the present work. Some Japanese researchers maintain that chronic liver disease can delay the development of atherosclerosis, using hypertension as the risk factor shared by the two populations and apolipoprotein B and A1 ratio as the atherogenic index in a case-control study [14]. Another study, via the arm-leg blood pressure ratios, has found that cirrhotic patients with diabetes mellitus have fewer atherosclerotic complications compared to a population of non-cirrhotic diabetic individuals matched for other cardiovascular risk factors [2].

Our research study therefore supports along this line of reasoning. However, by using ultrasound-color Doppler, this study provides a more precise evaluation of the degree of atherosclerosis, that is accurately quantifiable [15] and supplies morphologic information with a certain prognostic value for acute cardiovascular events [16]. In our liver disease patients, carotid atherosclerosis prevalence was 27%, while it was 56% (P < 0.005) in controls, a value consistent with that in the scientific literature in populations homogeneous with ours for age and cardiovascular risk factors [17-19]. This outcome is important for the aim of this study, as the carotid arteries can be easily and non-invasively measured for the presence of atherosclerosis and its progression in all arterial districts [20] and in the coronary arteries in particular [21]. The extent of carotid atherosclerosis, moreover, significantly correlates with major coronary risk factors [22] and has a predictive value for acute cardiovascular events [23]. In the femoral arteries and the abdominal aorta, the control group presented a higher prevalence of atherosclerotic alterations than liver disease patients, although this was not statistically significant. Moreover, the chronic liver disease patients had fewer atheromatous plaques (P < 0.001) in the carotid district and a lower degree of stenosis than that of controls (P = ns).

In the light of these results it would seem that the hypothesis that chronic viral hepatitis may be a protective factor for
atherosclerosis should be considered. Possible pathogenetic mechanisms explaining this clinical-epidemiological evidence could be the increase in chronic viral hepatitis of the HGF (hepatocyte growth factor) or ‘scatter factor’ [24-26], a cytokine which protects the vascular endothelium [27-30], and the direct influence, in HCV-related liver diseases, of HCV on lipid metabolism [31-33]. Moreover, in liver disease patients, better health education and supervision due to frequent and intense contact with medical workers and structures, could result in a lifestyle that limits cardiovascular risk factors such as smoking, hyper-caloric and hyper-lipidic food intake, lack of exercise and excess alcohol consumption, as well as a more timely diagnosis and more efficacious control of diseases such as hypertension, diabetes or hypercholesterolemia [34].

Therefore, our data show that chronic viral hepatitis patients have a lower prevalence of atherosclerosis of the carotid, femoral and abdominal arteries than control subjects matched by age, sex, and exposure to common cardiovascular risk factors. Furthermore, in the carotid district, liver disease patients showed fewer atheromatous plaques (P < 0.001) and a smaller degree of vessel stenosis, thus confirming the hypothesis that chronic viral hepatitis may be a protective factor for atherosclerosis. Further research is certainly needed to study this interesting relationship. The next aim of our study is a prolonged follow-up to evaluate the progression rate of the disease in the two populations.

REFERENCES