Vascular endothelial growth factor (VEGF) is a specific mitogen for endothelial cells. In contrast to other cytokines, VEGF stimulates endothelial cell proliferation, acting as a circulating hormone rather than a paracrine factor [1]. At the liver level, VEGF is significantly expressed by sinusoidal endothelial cells and hepatocytes [2,3], whereas modest and inconstant expression has been reported for Kupffer cells [2,3]. Serum VEGF levels change simultaneously with aspartate aminotransferase (AST) and alanine aminotransferase (ALT) concentrations in patients with acute hepatitis, supporting the claim that acute hepatocellular damage leads to marked VEGF release into the bloodstream [4]. By contrast, serum VEGF concentrations are decreased in chronic liver diseases, such as chronic hepatitis and liver cirrhosis, which suggests that VEGF levels might correlate with disease severity [4]. In spite of this, the possible relationship between serum VEGF concentrations and the degree of liver dysfunction has not previously been evaluated in chronic liver diseases.

To investigate this, serum VEGF concentrations were evaluated by a sensitive chemiluminescence enzyme immunoassay [4,5] in 77 patients with chronic hepatitis and 74 patients with liver cirrhosis. The histological grading and staging system proposed by Ishak et al. [6] was used to assess the severity of chronic hepatitis. After blood biochemical (including viral markers) and histological examinations patients affected by chronic hepatitis were divided as follows: group A (grading score ranging from 1 to 6) consisted of 36 patients (16 male, 20 female, mean age 47.1 ± 6.8 years; hepatitis B surface antigen positive (HbsAg+) = 5, anti-hepatitis C virus positive (anti-HCV+) = 29, both HbsAg+ and anti-HCV+ = 2); group B (grading score ranging from 7 to 12) consisted of 27 patients (11 male, 16 female, mean age 45.4 ± 6.4 years; HbsAg+ = 1, anti-HCV+ = 24, both HbsAg+ and anti-HCV+ = 2); group C (grading score ranging from 13 to 18) consisted of 14 patients (7 male, 7 female, mean age 53.8 ± 8.6 years; HbsAg+ = 4, anti-HCV+ = 10, five patients showed initial histological features of cirrhosis). The 74 patients with liver cirrhosis (44 male, 30 female, mean age 52.8 ± 7.2 years; HbsAg+ = 12, anti-HCV+ = 62) were divided according to the Child–Pugh classification into three classes: A (n = 19), B (n = 36) and C (n = 19). A group of healthy volunteers (12 male, 9 female, mean age 50.0 ± 4.0 years) served as controls.

Compared with controls, serum VEGF concentrations were lower in patients with chronic hepatitis. The lowest level of serum VEGF was found in the patients in group C, whereas the highest level of serum VEGF was found in the patients in group A (Figure 1A). In group A and group B the serum VEGF levels and grading scores were inversely correlated (r = −0.318, P = 0.005 and r = −0.436, P = 0.023 respectively); in group C this correlation was not statistically significant (r = −0.507, P = 0.064). The mean staging score for fibrosis was lower in group A (0.63 ± 0.59) than in group B (1.52 ± 0.58, P < 0.0001 versus group A) and group C (3.57 ± 1.28, P < 0.0001 versus group A and group B), and inversely correlated with serum VEGF levels in group A (r = −0.340, P = 0.042) and group C (r = −0.597, P = 0.024).

In cirrhotic patients, serum VEGF levels decreased according to progression of the disease, according to the Child–Pugh classification (Figure 1B). The VEGF levels in pooled serum from cirrhotic patients were lower than the levels in the pooled serum from patients with hepatitis (P < 0.05).

In spite of the points raised above, serum VEGF

Key words: chronic hepatitis, cirrhosis, vascular endothelial growth factor.

Abbreviations: ALT, alanine aminotransferase; anti-HCV+, anti-hepatitis C virus positive; AST, aspartate aminotransferase; HbsAg+, hepatitis B surface antigen positive; VEGF, vascular endothelial growth factor.

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Figure 1  Serum VEGF levels

(A) Serum VEGF levels (mean ± S.D.) in patients with viral chronic hepatitis who were divided into groups A, B and C according to their histological features (grading scores ranging from 1 to 6, 7 to 12 and 13 to 18 respectively). No symbol, versus controls; *, group B versus group A; †, group C versus group A and group B. (B) Serum VEGF concentrations (means ± S.D.) in patients with liver cirrhosis divided according to the Child–Pugh classification. No symbol, significantly different from controls; *, class B versus class A; †, class C versus class A; ‡, class C versus class B.

In the pooled serum of cirrhotic patients was a direct significant correlation between albumin and VEGF concentrations found ($r = 0.398$, $P < 0.001$).

In conclusion, the present study expands upon previous data [4] showing that serum VEGF levels decrease in cirrhotic patients according to the Child–Pugh classification and, in patients with chronic hepatitis, with the severity of histological findings. However, in agreement with previous findings [4], VEGF levels did not correlate with blood biochemical indexes of hepatocyte injury and/or function. Therefore hepatic VEGF release and/or production is abnormal in chronic liver diseases and decreases with advancing liver dysfunction. Mechanisms regulating VEGF release from damaged hepatocytes and the role of sinusoidal endothelial cells in VEGF production during chronic liver diseases require further investigation. Our data suggest that measurement of serum VEGF concentrations may be useful, in conjunction with other markers of liver function, in the prognosis of chronic liver disease.

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