

**Title: INTERLEUKIN-6 IS ASSOCIATED WITH LIVER FIBROSIS IN HCV-INFECTED PATIENTS WITH ALCOHOL ABUSE**

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**Abstract:**

Both hepatitis C virus (HCV) and alcohol abuse cause chronic hepatic inflammation and alterations in serum inflammatory cytokines. The mechanisms by which alcohol worsens hepatitis C virus-related liver disease have not been fully clarified; however, impairment of host's immune response should be highlighted. In this context, the influence of cytokines on liver fibrosis needs to be well characterized. In this study, we investigated the association between interleukin (IL-6), IL-10, IL-17A and tumour necrosis factor (TNF- $\alpha$ ) and liver fibrosis in HCV-infected patients with current or past alcohol abuse. A total of 130 consecutive patients (73 females; mean age,  $52.6 \pm 11.6$  years) with chronic hepatitis C (CHC) were enrolled in the study. All patients completed several surveys including semi-structured interview, Mini-International Neuropsychiatry Interview (MINI-Plus 5.0) and CAGE screen (defined as two or more affirmative answers). The amount, frequency, and duration of use of alcohol were evaluated in CHC patients (alcohol abuse was defined as  $> 20$  g/day for females and  $> 40$  g/day for males). The diagnosis and staging of the underlying liver disease was based on standard clinical, biochemical, serological, radiological and histological parameters. The serum levels of IL-6, IL-10, IL-17A and TNF- $\alpha$  were determined by Cytometric Bead Array Assay. The protocol was approved by Ethical Board of UFMG. Data were analyzed with SPSS 17.0. Linear and logistic regression models were used to assess the association between cytokines and cirrhosis, adjusting for age, sex, body mass index and alcohol use. Baseline characteristics were: 102 (78.5%) with CHC and 28 (21.5%) with compensated cirrhosis; 43 (33.1%) with alcohol abuse. Higher levels of IL-6 was associated with alcohol abuse ( $\beta=0.43$ ;  $t=3.14$ ;  $p=0.003$ ) and hepatic necroinflammatory activity ( $\beta=0.41$ ;  $t=3.42$ ;  $p=0.001$ ). In multivariate analysis, cirrhosis was associated with higher levels of IL-6 (OR=15.27; IC95% 1.28-182.50;  $p=0.03$ ), but not with IL-10, IL-17A and/or TNF- $\alpha$  ( $p > 0.05$ ). Cirrhosis was also associated with alcohol abuse/dependence (OR=3.11; IC95% 1.10-9.67;  $p=0.04$ ). In the current study, alcohol abuse was associated with an imbalance in IL-6 production in CHC patients. Moreover, the highest levels of IL-6 were found in patients with hepatic necroinflammatory activity graded as moderate/severe.

**Keywords:** Hepatitis C; Alcohol; Citokines.

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