

Hepatology Highlights

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Diabetes worsening of hepatitis C cirrhosis: are alterations in monocytic tissue factor (CD 142) is the cause?

Abu El Makarem, *et al.* Etiology of cirrhosis influences the incidence of diabetes mellitus (DM). Non-alcoholic fatty liver disease, alcohol liver disease, hemochromatosis and hepatitis C virus are frequently associated with DM.¹ Patients with chronic hepatitis C have higher prevalence of insulin resistance and type 2 diabetes mellitus (T2DM).² Some studies have evaluated the effect of T2DM on the outcome of cirrhosis, and it was found that diabetic patients present greater mortality rate.³ Nowadays, it is unclear the physiopathological pathways of damage of T2DM over liver function. Abu El Makarem, *et al.* provide the first study about the significance of monocytic tissue factor (MTF) expression in T2DM and hepatitis C cirrhotic patients. They compared the expression MTF in four groups; cirrhotics with T2DM (n = 139), cirrhotics without T2DM (n = 130), diabetics without liver disease (n = 100) and a healthy group (n = 100). MTF expression was significantly higher in T2DM

groups, but T2DM with cirrhotics presented the highest expression of MTF and it increased in relation of stage of the Child-Pugh score. A secondary finding was that the use of exogenous insulin is associated with significantly higher MTF expression when compared with sulphonylurea and insulin sensitizers. Authors propose that endothelial dysfunction in patients with T2DM and cirrhosis increased flow of inflammatory cytokines, and activation of TF on monocytes, which can intensify immunological and inflammatory environment. Participation of inflammatory cells has been explored in patients with non-alcoholic steatohepatitis; in this setting, inflammatory monocytes appears significantly expanded in relation to controls.⁴ In patients with different stages of cirrhosis, it was found increased accumulation of monocyte in the liver tissue and has been proposed that monocytes cause intrahepatic perpetuation of inflammation and direct activation of stellate cells.⁵ Role of monocytes in the progression of liver disease must be extensively researched, especially when in presence of a condition of impaired glucose metabolism.

Statin use is not associated with liver related mortality

Younoszai, *et al.* Cardiovascular disease (CVD) events are the first cause of death globally.⁶ Statin treatment had showed major benefits in primary prevention of CVD. A recent systematic review and meta-analysis of eighteen randomized control trials and 56,934 participants showed that statins reduce

all-cause mortality, fatal and non-fatal CVD, fatal and non-fatal coronary heart events and fatal and non-fatal stroke; and also reduce rates of revascularization, total cholesterol and LDL cholesterol. This meta-analysis did not find evidence of any serious harm caused by statin treatment.⁷ It is clear the benefit of statin treatment in cardiovascular disease; nevertheless, use of statins has been limited by the false perception of wide association with hepatotoxi-

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city, because elevated liver enzymes have been used as surrogate marker for hepatotoxicity. However, it should be considered that target population for statins treatment are in risk of metabolic syndrome or NAFLD with pre-treatment abnormal liver enzyme levels. The aim of Younoszai, *et al.* study was to assess the association of statins with all-cause, cardiovascular and liver related deaths in a population based database. Data were obtained from Third National Health and Nutrition Examination Survey (NHANES III) and the NHANES III linked mortality file. It was enrolled 65 statin users and 8,901 no statin users. Patients in treatment with statins had significantly higher prevalence of obesity and hypertension, and all-cause mortality was significantly greater, but cardiovascular-mortality was not different between both groups and liver related mortality was significantly increased in no statin group. Despite the limited number of statin users in this cohort, this study supports the lack of evidence of hepatotoxicity and increased mortality among statin users. The effect of statins on liver enzymes was also evaluated, and it was showed no association of

statins treatment with elevations of liver enzymes. A meta-analysis compared the effect of statins *vs.* placebo on the liver enzymes and found that all statins, except fluvastatin, have not a significant difference *vs.* placebo in liver test abnormalities.⁸ At present there is no evidence supporting the monitoring of liver function tests in patients on treatment with statins.⁹ Patients with chronic liver disease can safely take statins, and is recommended that in case of NASH considered statin therapy because of high cardiovascular risk.¹⁰ Younoszai, *et al.* suggested that statins are not associated with liver related mortality or elevation of liver enzymes. Finally, do not forget, that although in rare cases, statins can cause hepatotoxicity represented as metabolic idiosyncratic form; that is, with a low incidence at normal doses and with long and variable latency period, unpredictability behavior, dose independency, absence of clinical features of hypersensitivity and delayed response to re-challenge.¹¹ Clinicians must assess suspected cases and take into account other variables like co-medication, preexisting liver diseases and viral infection.

Incidence of hepatocellular carcinoma in hepatitis C cirrhotic patients with and without HIV infection: a cohort study, 1999-2011

Di Benedetto, *et al.* Hepatocellular carcinoma (HCC) is the fifth most common cancer in worldwide and the third most lethal one, causing 600,000 deaths every year. Near 80% of cases of HCC are associated with chronic hepatitis B virus or hepatitis C virus (HCV) infections.¹² Many retrospective cohorts and cross-sectional studies had examined the effect of HIV infection on the development of HCC,¹³ because HCV is frequently seen in HIV-positive patients and it seems that progression to end-stage liver disease occurs faster in these setting.¹⁴ Since the introduction of HAART the life expectancy of HIV-infected patient has really improved, so cirrhosis and HCC may be increasing rate in HIV/HCV co-infected patients. In this regard, a systematic review did not associate HIV/HCV co-infected patients on antiretroviral therapy with incremented risk for HCC, but this analysis only included a small number of cases of HCC.¹⁵ Di Benedetto, *et al.* show results of a prospective cohort study that included 79

HIV/HCV co-infected patients and 69 HCV mono-infected patients, with median follow-up time of 45 and 37 months respectively; in order to determine the incidence of HCC in HCV infected cirrhotic patients with and without HIV infection in the HAART era. The first interesting finding was the presence of greater alcohol consumption, higher median HCV RNA, lower median age and lower rate of HCV treatment in HIV/HCV co-infected group. During the follow-up time, only twelve patients develop HCC, five in HIV/HCV co-infected group and seven in HCV mono-infected group. The Kaplan-Meier test for cumulative risk of HCC showed no statistically significant difference between the groups. Due to the design quality of previous studies, it has been unclear the impact of HIV infection in patients with HCV in relation to the development of HCC, however, this prospective study showed that co-infection is not associated with increased incidence of HCC, and should be considered the association of other factors like alcohol consumption. Finally, for a hard conclusion in this area, it is required studies with longer follow-up to evaluate the real incidence of HCC in HIV/HCV co-infected patients.

REFERENCES

1. Tolman KG, Fonseca V, Dalpiaz A, Tan MH. Spectrum of liver disease in type 2 diabetes and management of patients with diabetes and liver disease. *Diab Care* 2007; 30: 734-43.
2. Kobashi-Margáin RA, Gutiérrez-Grobe Y, Ponciano-Rodríguez G, Uribe M, Méndez-Sánchez N. Prevalence of type 2 diabetes mellitus and chronic liver disease: a retrospective study of the association of two increasingly common diseases in Mexico. *Ann Hepatol* 2010; 9: 282-8.
3. Bianchi G, Marchesini G, Zoli M, Bugianesi E, Fabbri A, Pisi E. Prognostic significance of diabetes in patients with cirrhosis. *Hepatology* 1994; 20(1 Pt. 1): 119-25.
4. Henning JR, Graffeo CS, Rehman A, Fallon NC, Zambirinis CP, Ochi A, Barilla R, et al. Dendritic cells limit fibroinflammatory injury in nonalcoholic steatohepatitis in mice. *Hepatology* 2013; 58: 589-602.
5. Zimmermann, et al. Functional Contribution of Elevated Circulating and Hepatic Non-Classical CD14+CD16+ Monocytes to Inflammation and Human Liver Fibrosis. *PLoS ONE* 2010; 5: e11049.
6. Global status report on noncommunicable diseases 2010. Geneva, World Health Organization; 2011.
7. Taylor F, Huffman MD, Macedo AF, Moore TH, Burke M, Davey Smith G, Ward K, et al. Statins for the primary prevention of cardiovascular disease. *Cochrane Database Syst Rev* 2013; 1: CD004816.
8. De Denu S, Spinler SA, Miller K, et al. Statins and liver toxicity: a meta-analysis. *Pharmacotherapy* 2004; 24: 584-91.
9. Demyen M, Alkhaloufi K, Pysopoulos NT. Lipid-lowering agents and hepatotoxicity. *Clin Liver Dis* 2013; 17: 699-714.
10. Cohen D, Anania F, Chalasani N. An assessment of statin safety by hepatologists. *Am J Cardiol* 2006; 97: C77-C81.
11. Teschke R. Hepatotoxicity associated with statins. *Ann Hepatol* 2012; 11: 418-20.
12. Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. *Hepatology* 2011; 53: 1020-2.
13. El-Serag HB. Epidemiology of viral hepatitis and hepatocellular carcinoma. *Gastroenterology* 2012; 142: 1264-1273, e1261.
14. García-Samaniego J, Rodríguez M, Berenguer J, Rodríguez-Rosado R, Carbó J, Asensi V, Soriano V. Hepatocellular carcinoma in HIV-infected patients with chronic hepatitis C. *Am J Gastroenterol* 2001; 96: 179-83.
15. Kramer JR, Giordano TP, El-Serag HB. Effect of human immunodeficiency virus and antiretrovirals on outcomes of hepatitis C: a systematic review from an epidemiologic perspective. *Clin Gastroenterol Hepatol* 2007; 5: 1321-8.