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Letters to the Editor

HCV and fat: Something is missing

To the Editor:

We read with interest the article by Dai and Colleagues [1] evaluating the association of virologic status with serum lipids in hepatitis C virus (HCV) antibody positive subjects. In their study carried out in 11,239 residents in an area endemic for both hepatitis B virus (HBV) and HCV infection, the authors observed that HCV viraemia seems to be associated with both low serum total cholesterol and triglyceride levels. Furthermore, they observed that anti-HCV subjects who were positive for HCV-RNA were more likely to be affected by diabetes as compared to HCV-RNA negative ones (odds ratio = 3.592). On the basis of their results they conclude that HCV itself might play a significant role on serum lipid profiles in these patients.

Although we agree with the authors that, as recently reviewed, the biology of HCV is strictly entangled with lipid homeostasis [2,3], we also acknowledge the fact that other aspects not taken into account by the authors may be responsible for low lipid serum levels in patients with supposed liver disease. Indeed, it has been clearly shown that a statistically significant trend towards lower serum cholesterol levels exists among patients with cirrhosis, chronic hepatitis and controls [4], that low serum cholesterol levels are independently associated with significant fibrosis in HCV patients [5,6], and that a progressive decrease in serum cholesterol has prognostic value in patients with decompensated viral cirrhosis [7]. Thus, what is missing in the study by Dai and colleagues is the clinical status of their HCV subjects, and whether patients who were HCV-RNA negative were spontaneously so, or the condition had been induced by previous anti-viral therapy. Furthermore, since in the study population HBV surface antigen positivity was independently associated with low serum lipid levels as well it is not clear why HBV-DNA status of the patients was not investigated. Thus, it is reasonable to hypothesise that the non-viraemic anti-HCV population included in the study was made up of "subjects", while HCV-RNA positive subjects were actually patients. This hypothesis is emphasised by the fact that patients *without* elevated cholesterol levels were significantly more likely to have abnormal alanine aminotransferase, a counterintuitive *phenomenon* in an era of positive association between altered liver enzymes, dyslipidemia, and liver steatosis [8]. Finally, the independent association between diabetes and HCV-RNA positivity in the study population further strengthens this hypothesis, since patients with (advanced) liver disease – not only those infected by HCV – are more likely to be affected by diabetes [9]. Therefore, the hypotheses put forward by the authors regarding the association between serum lipids and HCV-RNA status in their population, albeit conceivable and interesting, remain largely speculative and the observed association rather spurious in the absence of deeper insights into the clinical and virologic characterisation of their population.

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Hepatitis C viremia and serum lipid levels: A clue from an epidemiology study

To the Editor:

We would like to thank Dr. Giannini and Dr. Savarino for their interest in our article and we appreciate their comments. The clinical status of hepatitis C virus (HCV) infection in terms of the severity of histopathology is lacking in our study [1]. It is indeed neither appropriate nor possible to undergo liver biopsy for more than 11,000 residents in a large-scale study. Based on the cross-sectional survey in our community-based study, we found HCV-viremic patients had lower serum lipid levels than anti-HCV-negative or anti-HCV-positive (but non-viremic) individuals which provided strong evidence of the association between HCV viremia and lower serum lipid levels. Furthermore, with the advantage of a large scale study, our report demonstrated the impact of HCV viremia among anti-HCV positive individuals. We also observed hepatitis B virus surface antigen positivity was independently associated with low serum lipid levels by multivariate analysis. The residents enrolled were aged 40–65 years and around 10% of them, according to previous studies, may be positive for hepatitis B e antigen which has been recognized to be strongly associated with an increased risk of active cirrhosis [2,3]. In addition, we have also observed a reciprocal viral interaction between hepatitis B virus (HBV) and HCV after interferon-alpha/ribavirin therapy [4]. Hence, HBV infection might play a less important role among anti-HCV-positive subjects, particularly among the HCV viremic patients in our study. Nevertheless, the lack of HBV DNA is an important limitation in our study to validate the association between serum lipid levels and the severity as well as viral load of chronic HBV infection.

Recently, the association between cholesterol metabolic pathway and the life cycle in terms of HCV production, secretion and entry by human hepatocytes has been reported [5,6]. HCV replicates on membrane vesicles involved in the assembly and secretion of very low-density lipoproteins and the low density lipoprotein receptor involved in HCV entry were observed [7,8]. Incidentally the development of drugs that target the cholesterol or lipoprotein metabolism and might be useful in treating HCV infection by inhibition of HCV RNA replication or production of HCV particles from infected cells is still ongoing, although their safety profiles and benefits require more sufficient evidence [5,9,10]. Accordingly, we believe our epidemiologic study, also taking the viral genotype into consideration, implicates an evident association between HCV RNA status and serum lipids. We deem it necessary at the same time to investigate the mechanisms of interaction between HCV and lipids.

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