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Subrat Kumar Acharya
Room 3105, 3rd Floor, Teaching Block,
All India Institute of Medical Sciences,
New Delhi 110029,
India
E-mail address: subratacharya2004@yahoo.com
subratacharya@hotmail.com

Effect of treatment with polyunsaturated fatty acids on HCV- or diet-induced fatty liver

To the Editor:

We read with great interest an article recently published in the Journal of Hepatology [1]. In this study Miyoshi et al. demonstrate that hepatic over-expression of the hepatitis C virus (HCV) core protein is able to induce lipid metabolism dysfunction and fatty liver accumulation in HepG2 cells. In this context, HCV core protein might directly or indirectly interfere with the cellular components of hepatocytes, which ultimately contribute to the onset of steatosis. The authors discuss that one hypothesis of the direct steatogenic effect of HCV core protein could be ascribed to the ability of the viral protein to interfere with mitochondrial function resulting in the accumulation of NADH. Interestingly, Vial et al., in another recent article published in this Journal, demonstrate that the impairment of NADH oxidation to NAD, with consequent NADH accumulation, is a characteristic figure of mitochondrial dysfunction occurring in fatty liver due to high fat diet (HFD) in rats [2]. Furthermore, Miyoshi et al. [1] demonstrate that, in HepG2 cells, HCV core protein expression influences the nature of fatty acids rather than their quantity. These same effects on fatty acid composition are seen in hepatocytes from HFD rats [2]. Data from these two studies represent another relevant demonstration of numerous similarities between fatty liver by HCV, and non-alcoholic fatty liver disease. Besides fatty liver, chronic hepatitis C resembles NAFLD in numerous aspects, such as insulin resistance, and oxidative stress in the liver. Therefore, HCV infection needs to be viewed not only as a chronic liver disease but also as a metabolic disease, opening up a novel way to the molecular understanding of the pathogenesis of chronic hepatitis C, as a virus-associated fatty liver [3].

Finally, Miyoshi et al. [1] demonstrate that the treatment with exogenous polyunsaturated fatty acids (PUFAs) reverts the HCV core protein-associated changes in fatty acid metabolism. Dietary PUFAs, which are well established negative regulators of hepatic lipogenesis, are able to alleviate liver inflammation and reduce fat content in steatotic livers [4]. Recently, we demonstrate that docosahexaenoic acid (DHA) treatment in children with NAFLD reduces the levels of plasma triglycerides, and improves insulin resistance and ultrasonographic features of fatty liver [5]. DHA might downregulate hepatic triglyceride accumulation by decreasing transcriptional activity of sterol regulatory element binding protein-1 (SREBP-1), and inducing fatty acid catabolism by activating the peroxisome proliferator-activated receptors (PPARs) [6]. Since Miyoshi et al. suggest that HCV core protein may induce hepatic triglyceride accumulation by SREBP-1 activation and consequent desaturase activation, it is probable that DHA supplementation may be an efficient therapy also to prevent/treat fatty liver associated with HCV infection.

Finally, since insulin resistance is a common metabolic risk of NAFLD and chronic hepatitis C, we believe DHA might significantly reduce hepatic triglyceride content, ameliorating insulin sensitivity and other metabolic features that associate NAFLD to HCV infection. These types of treatments, for their almost complete absence of adverse effects, might be suitable for both adults and children.

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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Donatella Comparcola
Valerio Nobili
Anna Alisi*
Unit of Metabolic and Autoimmnune Liver Diseases, Bambino Gesù Children's Hospital-IRCCS, S. Onofrio 4 Square, 00165 Rome, Italy
* *Tel.: +39 0668592650; fax: +39 0668592904.*
E-mail address: anna.alisi@opbg.net (A. Alisi)

Clara Balsano
Laboratory of Molecular Virology and Oncology, A. Cesalpino Foundation, University of Rome, Rome, Italy

Reply to the Letter to the Editor 'Effect of treatment with polyunsatured fatty acids on HCV- or diet-induced fatty liver'

This is a reply to the Letter to the Editor by Comparcola et al.

We appreciate Comparcola and colleagues for their comments on our findings about the pathogenesis of lipid metabolism disturbances in hepatitis C virus (HCV) infection [1]. The pathogenesis of hepatic steatosis in hepatitis C has been enthusiastically investigated [2]. Several pathways have been described as mechanisms underlying steatogenesis in hepatitis C: the core protein of HCV inhibits the secretion of very low density lipoprotein (VLDL) from the liver by suppressing the function of microsomal triglyceride transfer protein (MTP) [3], increases the production of fatty acids by upregulating sterol regulatory element binding protein (SREBP)-1c gene expression [4], and induces hepatic insulin resistance resulting in the increased uptake of fatty acid into the liver [5]. The combination of these events would lead to a frequent development of steatosis in hepatitis C.

We thank Comparcola et al. for noting that NADH accumulation is a characteristic feature of mitochondrial dysfunction in a NAFLD model [6]. We propose that the accumulation of NADH due to dysfunction in the mitochondrial electron transfer system (ETS) may be responsible for steatogenesis in HCV infection [1]. Interestingly, tacrolimus, an immunosuppressive agent, reverses the influence of the core protein, including hepatic steatosis and insulin resistance, simultaneously with the restoration of mitochondrial ETS function, as indicated by reduction of NADH accumulation, in a mouse model [7]. This pathway may be a common one in the pathogenesis of NASH and hepatitis C, and could be a target for treatment. Hepatitis C should be recognized as a metabolic disease as well as a hepatic disease that manifests as insulin resistance and lipid metabolism disorder, resembling NASH, as previously proposed by our team [8] and Balsano et al. [9].

Of importance, exogenously administered polyunsaturated fatty acids (PUFAs) improve the accumulation and altered composition of lipids caused by HCV [1], as well as those in non-alcoholic fatty liver disease [10]. However, we would like to withhold our consent for its application in hepatitis C patients, because PUFAs did not reduce the NADH accumulation in our model system, while pyruvate did [1].

Lastly, it is crucial for hepatologists to identify hepatitis C as a metabolic disease, not only to guide patients toward improving their life style, but also to invent a measure to reverse the metabolic disorders, which are the essential aggravating factors for hepatitis C.

Conflict of interest

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Kazuhiko Koike*
Hideyuki Miyoshi
Department of Gastroenterology, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan
* *Tel.: +81 3 5800 8800; fax: +81 3 5800 8799.*
E-mail address: kkoike-tky@umin.ac.jp (K. Koike)

Hiroshi Yotsuyanagi
Department of Infectious Diseases, Graduate School of Medicine, The University of Tokyo, Japan

Kyoji Moriya
Department of Infection Control, Graduate School of Medicine, The University of Tokyo, Japan