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ORIGINAL ARTICLE

Detection of high biliary and fecal viral loads in patients with chronic hepatitis C virus infection

Hugo Monrroy[a], Jenniffer Angulo[b], Karla Pino[b], Pilar Labbé[a], Juan Francisco Miquel[a], Marcelo López-Lastra[b], Alejandro Soza[a,*]

[a] *Department of Gastroenterology, Pontificia Universidad Católica de Chile, Chile*
[b] *Laboratorio de Virología Molecular, Instituto Milenio de Inmunología e Inmunoterapia, Departamento de Enfermedades Infecciosas e Inmunología Pediátrica, Escuela de Medicina, Pontificia Universidad Católica de Chile, Chile*

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KEYWORDS
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Abstract
Background: The life cycle of the hepatitis C virus (HCV) is closely associated with lipid metabolism. Recently, NPC1L1 (a cholesterol transporter) has been reported to function as an HCV receptor. This receptor is expressed in the hepatocyte canalicular membrane and in the intestine; serving as a key transporter for the cholesterol enterohepatic cycle.
Objectives: We hypothesized that HCV might have a similar cycle, so we aimed to study the presence of HCV in bile and stools of infected patients.
Materials and methods: Blood, feces, and duodenal bile samples were collected from patients infected with HCV. The biliary viral load was normalized to the bile salt concentration of each sample and the presence of HCV core protein was also evaluated. A total of 12 patients were recruited. HCV RNA was detected in the bile from ten patients.
Results: The mean viral load was 2.5 log10 IU/60 mg bile salt. In the stool samples, HCV RNA was detected in ten patients (mean concentration 2.7 log10 IU/g of feces).
Conclusions: HCV RNA is readily detectable and is present at relatively high concentrations in the bile and stool samples of infected patients. This may be relevant as a source of infection in men who have sex with men. Biliary HCV secretion may perhaps play a role in the persistence of viral infection via an enterohepatic cycle of the virus or intrahepatic spread.

* Corresponding author.
E-mail address: asoza@med.puc.cl (A. Soza).

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PALABRAS CLAVE
Colesterol;
Intestino;
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Bilis;
Heces;
Virus de la hepatitis C

Detección de concentraciones víricas elevadas en la bilis y en las heces de pacientes con infección crónica por el virus de la hepatitis C

Resumen
Introducción: El ciclo de vida del virus de la hepatitis C (VHC) está estrechamente ligado al metabolismo lipídico. Recientemente, se ha descrito que el NPC1L1 (un transportador del colesterol) actúa como un receptor del VHC. Este receptor se expresa en la membrana canalicular de los hepatocitos y en el intestino, y actúa como uno de los principales transportadores durante la circulación enterohepática del colesterol.
Objetivos: Planteamos la hipótesis de que el VHC podría tener un ciclo similar, por lo que nuestro objetivo fue estudiar la presencia del VHC en la bilis y en las heces de pacientes infectados.
Materiales y métodos: Se obtuvieron muestras de sangre, heces y bilis duodenal de pacientes infectados por el VHC. La concentración vírica en la bilis se normalizó respecto a la concentración de sales biliares de cada muestra y también se evaluó la presencia de la proteína central del VHC. Se reclutaron un total de 12 pacientes. Se detectó el ARN del VHC en la bilis de 10 pacientes.
Resultados: La media de la concentración vírica fue 2,5 log10 UI/60 mg de sales biliares. En las muestras de heces, se detectó el ARN del VHC en 10 pacientes (media de la concentración 2,7 log10 UI/g de heces).
Conclusiones: El ARN del VHC es fácilmente detectable y está presente en concentraciones relativamente elevadas en las muestras de bilis y heces de pacientes infectados. Esto puede tener importancia como foco de infección en varones que mantienen relaciones sexuales con otros varones. Es posible que la secreción biliar del VHC pueda desempeñar un papel en la persistencia de la virosis a través de la circulación enterohepática del virus o la propagación intrahepática.

Introduction

Chronic hepatitis C affects more than 170 million individuals who are at risk of developing cirrhosis and hepatocellular carcinoma.[1] The impact of this disease is evident, and the mortality due to hepatitis C virus (HCV) infection has superseded the mortality from HIV infections in the United States.[2] New, oral direct-acting antivirals (DAAs) are showing remarkable results. Nevertheless, DAAs have some shortcomings, such as high cost, risk of developing resistance-associated variants and drug-drug interactions.[3–5] A better understanding of the viral cycle may facilitate the development of alternative treatment strategies or strategies that complement DAAs.

HCV circulates in human serum associated with several lipoproteins forming lipo-viral particles (LVPs).[6–8] LVP formation occurs during lipoprotein synthesis in hepatocytes, which is a process that may shield the virus from neutralizing antibodies.[9] LVPs are characterized by their low density, presence of apolipoprotein B (apoB) and enrichment of triglycerides.[10] HCV is not evenly distributed in the different plasmatic lipid fractions and is especially abundant in the very-low-density fractions, which comprise triglyceride-rich lipoproteins (TRL).[11]

TRL particles have a density less than 1.006 g/mL and have a core made of triglycerides and cholesterol esters surrounded by a phospholipid monolayer of free cholesterol, apoB and other lipoproteins.[12] There are two types of TRLs: very-low-density lipoproteins (VLDLs) and chylomicrons. VLDLs are assembled with one apoB100 molecule per particle and are secreted by hepatocytes, whereas chylomicrons contain one molecule of apoB48, which is a truncated form of apoB and is enterocyte specific.[13] In humans, apoB100 is synthesized primarily by the liver, whereas apoB48 is synthesized only in the intestines. Intriguingly, apoB100 and apoB48 are equally represented in LVPs purified from HCV-infected patients.[14] This observation led to the suggestion that the intestine could be a reservoir of HCV and that enterocytes could contribute to an estimated 18% of the plasmatic viral load.[14] An intestinal contribution to the overall HCV load in infected patients could be explained either by viral extrahepatic replication in the enterocyte or by the intestinal absorption of HCV.

Based on evidence suggesting that enterocytes can be a reservoir for HCV,[14,15] it is plausible that HCV has an enterohepatic cycle similar to that of cholesterol: secretion into the bile, reabsorption in the enterocyte and secretion bound to chylomicrons. This possibility would imply that some HCV particles could escape reabsorption by enterocyte, shedding to the feces of infected patients. However, detection of HCV particles in bile and stools of infected patients remains controversial. Thus, we designed a study to evaluate the presence of HCV in the bile and feces of Chilean patients chronically infected with the virus. We also assessed whether the viral load correlated with different compartments and plasmatic cholesterol and triglyceride levels.

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