Review of: "Infection with the hepatitis C virus causes viral genotype-specific differences in cholesterol metabolism and hepatic steatosis"

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Hepatitis C virus (HCV) is known for its interaction with host glucose and lipid metabolism with a genotype-specific manner[1-4]. Although HCV patients generally have lower levels of serum cholesterol and triglyceride than non-HCV comparative subjects[5], HCV genotype 3 patients are prone to have liver steatosis[6], while HCV genotype 1 patients have a higher likelihood of insulin resistance[4]. Furthermore, these HCV genotypic differences in metabolic interaction may play a role in the progression of liver fibrosis in HCV patients [7]. Nevertheless, the mechanisms involved in these genotype-specific differences in host metabolism are not fully understood. Previous studies suggested that enhanced triglyceride synthesis with reduced triglyceride secretion may be a possible mechanism to explain liver steatosis in HCV patients [8], whereas the impact of various HCV genotypes on liver cholesterol metabolism remains largely elusive. In our earlier study using an in vitro cell culture system and [9], we found that different HCV genotypes, although differ in regulating lipoprotein signaling and cholesterogenesis, all downregulated genes related to cholesterol biosynthesis and suppressed hepatocellular cholesterol content. Reduced cholesterol biosynthesis could be attributed to the action of HCV core protein in regulating the expression of HMGCR[3], and these effects could be inversed by using sofosbuvir, a direct antiviral agent. Our results echoed previous observations that cholesterol synthesis was lower in HCV-infected patients[5], and HCV eradication may increase levels of serum cholesterol and LDL in HCV patients[10].

In the study by Sheridan et al.[11], the authors examined differences in host lipid metabolism between participants chronically infected with HCV genotype 1 and HCV genotype 3 both in fasting and non-fasting states, and after sustained virological response (SVR). They found that HCV genotype 3 patients had significantly lower serum apoB, non-HDL cholesterol concentrations and more liver steatosis than HCV genotype 1 patients. Furthermore, HCV genotype 3 patients also had a significant decrease in serum lathosterol levels, without significant reductions in desmosterol. Lipidomic analysis showed lipid species associated with the reverse cholesterol transport pathway in HCV genotype 3 patients. The authors thus concluded that there exist genotype-specific lipid disturbances between HCV genotype 1 and 3. Compared to HCV genotype 1, HCV genotype 3 was characterized by low levels of LDL cholesterol, with preferential suppression of cholesterol synthesis through lathosterol, and was associated with increased liver steatosis.

Taking all these lines of evidence together, although HCV genotypes exert unique regulatory effects on gene expression

on lipoproteins and cholesterol metabolism genes, inhibition of hepatocellular cholesterogenic gene expression and total cholesterol biosynthesis is a common effect among HCV genotypes, which may explain the observations of lower serum cholesterol levels in HCV patients. Moreover, these viral genotypic variations in the interaction with host glucose and lipid metabolism may contribute to liver disease progression and the development of hepatocellular carcinoma (HCC) in HCV patients.

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