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Lipids and HCV

Do high lipids help clearance of hepatitis C?

Stephen Ryder

High triglyceride levels may be a factor in the high rate of spontaneous clearance of HCV

A large volume of evidence suggests that lipids and lipid receptors are important in hepatitis C infection.

Hepatic steatosis is common, with at least 65% of liver biopsy specimens demonstrating steatosis. In genotype 3 infection, a specific mechanism of steatosis induction exists, via core antigen expression. The incidence of diabetes is higher in hepatitis C virus (HCV) infection and increases with increasing severity of liver disease. The mechanism of this is via insulin resistance, but it is uncertain whether hepatic steatosis is a result of the insulin resistance or plays a pivotal role in its induction.

HCV is associated with lipid in the serum and almost certainly uses lipid receptors to enter hepatocytes. The low-density fractions of serum contain HCV RNA particles and lipoviral particles (LVP) associated with triglyceride (TG)-rich lipoproteins. Such particles rich in TG have been shown to contain viral capsid and RNA.¹ TG is contained within chylomicrons or within very low-density lipoprotein (VLDL). Chylomicrons are synthesised in the intestine and transported via lymph into the circulation where they are broken down by the action of lipoprotein lipase in many cell types. The chylomicron remnant is then taken up by the liver via the low-density lipoprotein (LDL) receptor (LDLR) or the LDL receptor-related protein.

Chylomicrons contain apolipoprotein B48 at the time of synthesis and later acquire apolipoprotein E (ApoE).

VLDL is synthesised in both liver and intestine, and, whatever the origin, is degraded by lipoprotein lipase-producing remnants. In man, these are primarily hydrolysed to form LDL. Some VLDL remnants may be taken up directly by the liver.

Upregulation of the LDLR increases the entry of HCV-LVP into hepatocytes, and binding of HCV-LVP can be blocked by anti-apolipoprotein B (anti-ApoB) and anti-ApoE.^{2–3} Endocytosis of HCV can be mediated by LDLR,⁴ which normally transports two different classes of cholesterol-containing lipoprotein particles into cells: LDL, which contains a single copy of ApoB-100, and VLDL, which contains multiple copies of ApoE.

An alternative lipid-based entry site for HCV in liver has been established using retrovirus/HCV pseudovirus particles.⁵ These experiments suggest that attachment to hepatocytes is via a scavenger receptor protein, SR-B1, with cell entry via a coreceptor CD-81. SR-B1 is a component in the reverse cholesterol transport pathway, and recognises a number of lipoproteins, including high-density lipoprotein, LDL, VLDL and oxidised LDL.

ApoE, a ligand for both LDLR and SR-B1, has three major isoforms, Apo-E2,

Apo-E3 and Apo-E4. These differ from one another by single amino acid substitution with marked differences in function. Apo-E3 has normal function, whereas Apo-E2 binds poorly to LDLR and Apo-E4 down regulates LDLR.⁶

A study of *APOE* gene polymorphisms in HCV infection suggested decreased severity of liver disease in patients with the E4 allele,⁷ and ApoE2 and ApoE4 alleles have both been associated with an increased likelihood of viral clearance.⁸ Both these alleles could help enhance viral clearance as the E2 allele binds poorly to LDLR and E4 down regulates it. Such defective binding could result in poor uptake of HCV-LVP into hepatocytes, with a resultant decrease in replication of the virus, favouring clearance of the virus before chronic infection can be established.

Changes in serum lipid profiles in chronic HCV infection are well described, serum cholesterol is significantly lower than in people not infected with HCV,⁹ markedly more so in HCV genotype 3 infection.¹⁰ This seems to be a definite effect of the virus as it reverses after successful treatment. The low cholesterol levels are associated with a decrease in ApoB levels in comparison with healthy controls, and ApoB levels negatively correlate with hepatic steatosis and viral load.¹¹

In this issue of *Gut*, Marzouk *et al*¹² (see page 1105) show that in a rural Egyptian population with a high incidence of hepatitis C infection, the chance of clearing HCV infection was significantly greater in patients who had high TG levels. Unlike cholesterol levels that were lower in patients with chronic HCV infection but the same in uninfected controls and in patients who had spontaneously cleared HCV, TG levels were substantially lower in patients with chronic HCV infection than in uninfected individuals (102 vs 121 mg/dl), but those

with resolved infection had substantially higher levels than either (140 mg/dl). The authors speculate that this may be a factor in the high rate of spontaneous clearance of HCV in anti-D cohorts where pregnancy would be likely to cause a significant rise in TG levels. Is this finding robust, and what potential mechanisms could underlie it? The study is by definition a retrospective one, there are as yet no data on prospective cohorts of patients with acute HCV, and the levels of TG in blood are affected by many other factors, not least age, diet and weight. The authors control for this using a linear regression model; this is the best that can be attained but at least remains open to substantial bias. The interaction of HCV with the lipid profile of the host has other complexities; HCV genotype 3 has a more profound effect than others on induction of steatosis and the changes in serum lipid levels. This may be either positive or negative in terms of establishing a mechanism as cohorts of mixed genotype may mask real associations, whereas the mechanisms of virus interaction with lipid metabolism in HCV genotype 3 may be different.

The effect of TG levels is plausible, HCV is associated with TG in blood and transport of virus into hepatocytes could be affected by TG levels; laboratory data do show competitive inhibition of HCV entry with VLDL.⁴ It is also plausible

that the high TG levels in spontaneous clearers of HCV may be mediated by polymorphisms in the lipid metabolic pathway, which could lead to increased levels of TG in blood. Individuals deficient in ApoE have high levels of VLDL and an increased risk of atherosclerosis. ApoE2 homozygotic individuals, however, make up about 1% of the population and do not seem to have hyperlipoproteinaemia, which suggests that if the high TG is a secondary factor to an underlying polymorphism affecting the potential entry sites for HCV infection it must be a more complex situation than a single genetic factor.

Marzouk *et al*'s¹² data highlight the complex interactions of HCV with lipid metabolism. It is clear that lipids are important in the interaction of HCV with its host. Before we can say that high TG levels are important factors in our ability to clear this infection, we will require more data from other cohorts and a better understanding of the potential sites of interaction of HCV with lipids and their receptors on hepatocytes.

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BSG Treasurer 2008–2013

Professor Chuka Nwokolo's term of office as Treasurer ends in March 2008 and we are now actively seeking his replacement for this five-year appointment. This is quite a time-consuming position but detailed knowledge of Society finances' and Charity Commission law are not necessarily essential. The incumbent is automatically a member of Council and would work closely with the Society's accountants and bookkeeper and Chris Romaya in the office. If you are interested in finding out more about this interesting position, Professor Nwokolo would be more than happy to talk to you about it. Please contact him on 07768 251540.

Applications should be sent to the BSG Secretariat, 3 St Andrews Place, London NW1 4LB. Closing date 31 August 2007. Interviews will take place towards the end of the year and the new appointee will work alongside Professor Nwokolo from the beginning of 2008.