Review

Hepatitis C and hepatic steatosis


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Summary

Hepatic steatosis is commonly seen in patients with chronic hepatitis C infection, and the two together have a greater association than by chance alone. Hepatitis C virus is closely associated with lipid metabolism throughout its lifecycle. Hepatic steatosis is more common in genotype 3 infection, due to direct viral effects including through microsomal triglyceride transfer protein, peroxisome proliferator activating receptor, and sterol regulatory element binding protein. In non-genotype 3 infection, hepatic steatosis is considered largely to be due to alterations in host metabolism, particularly through insulin resistance. The clinical relevance of this association has yet to be fully explored. Hepatic steatosis is associated with increased hepatic fibrosis and a reduced level of sustained virological response to pegylated interferon and ribavirin. Small studies trialing adjuvant anti-diabetic therapies or HMG-CoA reductase inhibitors with pegylated-interferon and ribavirin have shown an improved sustained virological response and reduced viral titer. Furthermore, simple lifestyle alterations showed positive effects on parameters of disease activity. These insights raise the possibility of novel treatment options.

Introduction

The World Health Organization estimates that hepatitis C virus (HCV) infection has a global prevalence of 3%, or 200 million people, but there is wide geographical variability. In northern Europe, chronic infection rates are estimated to be between 0.1 and 1%; in central Europe, between 0.2 and 1.2% and in southern Europe, these are higher still at 2.5–3.5%. Egypt is worst affected with a prevalence of 22% or higher, owing to the high transmission of HCV in the parenteral antischistosomal therapy campaign in the 1980s.

Fatty liver, or hepatic steatosis, is a common finding in the general population and is a frequent cause for elevated serum aminotransferase levels. This condition is considered to be the hepatic manifestation of the metabolic syndrome, where insulin resistance is the underlying factor with diabetes mellitus, obesity and hypertriglyceridaemia prominent clinical sequela. Steatosis may occur with other assaults on the liver, particularly in alcohol abuse and also in chronic HCV infection.

Non-alcoholic fatty liver disease (NAFLD) is defined as the presence of hepatic steatosis in the absence of excessive alcohol consumption. It encompasses a spectrum of disease, ranging from simple steatosis to steatohepatitis (NASH), with or without the development of fibrosis and cirrhosis. Estimates of hepatic steatosis prevalence vary. Clark and colleagues analysed the National Health and Nutrition Examination Survey (NHANES III) to determine the prevalence of hepatic steatosis in the US population (National Centre for Statistics...
1988–1994), 23% of the 12,241 adults in the study had evidence of hepatic steatosis.\(^5\)

HCV infection and hepatic steatosis are both independently common in the general population. Data estimating the prevalence of HCV infection\(^6\) and hepatic steatosis\(^5\) show that the frequency of chance concurrence would be 20% of HCV-infected patients. Since the prevalence of hepatic steatosis in HCV-infected patients is nearer to 50%,\(^7\) the association is greater than one would expect to see from chance alone, suggesting an association between the two.\(^7\) Furthermore, hepatic steatosis is only seen in \(\approx\)18% of patients with hepatitis B infection.\(^8\)

The pathogenic association between HCV infection and hepatic steatosis is multifactorial. While hepatic steatosis in patients with HCV may be associated with features of the metabolic syndrome, so-called ‘metabolic steatosis’, associating with non-genotype 3 infection,\(^9\) it may be present in the absence of these findings, often associated with genotype 3 infection: ‘viral steatosis’ (Figure 1).

This review will first discuss the pathogenic mechanisms of HCV infection and hepatic steatosis, particularly the direct effects of viral proteins on hepatic lipid metabolism and the effect of the virus on insulin resistance; second, the clinical relevance of hepatic steatosis in HCV-infected patients and potential novel therapeutic strategies in HCV management and third, will speculate on the potential evolutionary advantage that the HCV-induced changes in lipid metabolism may confer.

Relevant studies were identified from: Medline, Pubmed, Cochran and ISI Web of Knowledge. Original articles and reviews in English were collated using the following search terms: liver, hepatitis C, HCV, hepatic steatosis, NAFLD, fibrosis, insulin resistance, geranylgeranylation.

**Pathogenesis**

HCV is an enveloped, positive stranded RNA virus of \(\approx\)9.6 kilobases, encoding a single polyprotein, which is cleaved by host and viral enzymes, forming structural and non-structural protein components.

The core protein is found at the amino terminal end of the protein and is involved with viral packaging. It is implicated in host cell damage, including inflammation,\(^10\) oxidative stress\(^11\–13\) and hepatic steatosis development.\(^14\)

**Viral steatosis**

The intimate association between HCV and steatosis is illustrated by evidence from a number of studies demonstrating mechanisms by which the virus utilizes aspects of lipid metabolism for its own benefits. The virus ‘hijacks’ the lipid producing machinery within the hepatocyte in order to reproduce and circulate around the body, so it may come as no surprise that there is more than a chance association between hepatic steatosis and chronic HCV infection.

Within the hepatocyte itself, the intracellular lipid droplet has been associated with HCV replication by co-localisation of viral proteins. Miyanari and colleagues showed that HCV capsid protein (core) recruits the viral replication complex to the lipid droplet-associated membrane and that non-structural proteins are located in the immediate vicinity. Mutations of these viral proteins, causing failure to associate with the lipid droplet membrane, led to impaired viral replication.\(^15\)

**Specific mechanisms** have been proposed in the pathogenesis of ‘viral’ steatosis including: decreased

![Figure 1. HCV may cause hepatic steatosis by a direct effect of the virus on the host, associated clinically with genotype 3 infection. HCV can also cause hepatic steatosis through insulin resistance, ‘metabolic HCV-induced steatosis’, associated with non-genotype 3 infection.](image-url)
microsomal triglyceride transfer protein (MTP); decreased peroxisome proliferator activating receptors (PPAR); and increased sterol regulatory element binding proteins (SREBP). In murine models, HCV core protein decreased the activity of MTP. MTP is located within the endoplasmic reticulum lumen enabling the stabilisation of apolipoprotein B by lipida
diation. Lipidated apolipoprotein B binds triglyceri
des, forming very low density lipoprotein (VLDL) particles for export from hepatocytes. Decreased activity of MTP results in the accumulation of intracellular lipid. Using a HCV subgenomic replicon system, Domitrovich and colleagues demonstrated that HCV non-structural proteins in the absence of core proteins are also capable of decreasing MTP activity. The association between MTP and apoli
poprotein B is further supported by two studies showing a decreased serum apolipoprotein B in patients with hepatic steatosis and HCV infection. In human liver biopsies, MTP mRNA levels were inversely correlated with the degree of hepatic steatosis, independent of HCV genotype. Genotype 3 infection had a significantly lower MTP activity compared with the other genotypes. Several other studies have shown that HCV infection is associated with decreased serum triglyceride, suggesting that viral proteins decrease the activity of MTP, resulting in decreased export of VLDL from hepatocytes and intracellular accumulation of lipids.

PPARs are nuclear receptors belonging to the steroid superfamily. The subtypes (α, δ and γ) differ in terms of their activating ligands principally consisting of fatty acids and lipid-derived substrates. PPARs is highly expressed in hepatocytes, cardiomyocytes, kidney cortex and skeletal muscle, whereas PPARγ is more widely spread. They regulate lipid metabolism through fatty acid import into mitochondria and activation of oxidative enzymes. A quantitative comparison of PPARγ expression in 86 human liver biopsies in patients with untreated HCV infection and non-infected controls was performed. There was a significantly decreased concentration of PPARγ and its target gene in those liver biopsies with HCV infection, compared with controls. Another study examining both liver biopsy and Huh7 cell lines showed that PPARγ mRNA was further reduced in livers of patients with genotype 3, compared with genotype 1. These data suggest that HCV infection is associated with decreased PPARγ in a genotype dependent manner. It is likely that reduction in PPARγ activity causes fatty acid uptake, and reduced mitochondrial oxidation, resulting in hepatic steatosis.

SREBPs are a family of transcription factors associated with endoplasmic reticulum membrane. They regulate production of enzymes involved in lipogenesis. There are at least three SREBP iso

forms, SREBP-1a, SREBP-1c and SREBP2. SREBP-1c is expressed predominantly in human liver. In its inactive form it is bound with SREBP cleavage activating protein (SCAP). Low levels of intracellular sterol result in a two-step cleavage process, initially of SCAP from SREBP, then further cleavage of the -NH₂ terminal active domain (nuclear SREBP). nSREBP translocates to the nucleus where it binds SREBP response element (SRE), acting as a positive transcription factor for genes involved in cholester
genesis and lipogenesis (Figure 2). SREBP-mRNA is increased in cells transfected with HCV core protein, resulting in increased fatty acid synthesis within hepatocytes. 'Viral steatosis' has been particularly associated with genotype 3 infection. MTP inhibition is greater in genotype 3 HCV infected patients and PPARγ inhibition was also more specifically associated with genotype 3 infection. However, in that study, the authors could find no evidence that HCV mediated SREBP inhibition was genotype dependent. In genotype 3 infection the histological grade of hepatic steatosis has been directly related to the intrahepatic titre of HCV RNA, unlike the situation with

Figure 2. SREBP activate the transcription of genes, which code for enzymes involved in lipogenesis and cellular uptake of lipoproteins. (A) SREBP is bound to SREBP cleavage-activating protein (SCAP) in its inactive form. (B) Low cholesterol, and HCV proteins within the cell are detected by SCAP, resulting in proteolytic cleavage of the complex and activation of SREBP. (C) SREBP translocates to the nucleus, binds the SREBP response element (SRE) to act as a transcription factor.
genotype 1 infection. In addition, a study using two histological analysis techniques assessed pre- and post-treatment liver biopsies in both genotype 1 and genotype 3 infected patients. The genotype 1 cohort showed no change in hepatic steatosis pre- and post-treatment, regardless of a sustained virological response (SVR). However, those in the genotype 3 cohort who underwent SVR also showed a significant decrease in hepatic steatosis. This was not seen in those genotype 3 patients who did not achieve a SVR. This provides evidence that a viral cytopathic effect of genotype 3 causes hepatic steatosis. Poynard and colleagues examined a cohort of 1428 patients enrolled in a randomized trial; they showed that in genotype 3 infected patients, hepatic steatosis was associated with high serum viral titre and lower serum cholesterol. They also showed a decrease in hepatic steatosis in genotype 3 infected patients among those who had a SVR.

**HCV-induced insulin resistance**

A prospective study of men and women aged between 44 and 65 years showed that patients with HCV infection and a high risk of type 2 diabetes (based on age and body mass index), were 11 times more likely than those without HCV infection to develop overt diabetes. However, among those at low risk there was no significant difference. This suggests that the presence of HCV infection either modifies or acts synergistically with pre-existing risk factors to culminate in either the development or earlier onset of type 2 diabetes. Hui and colleagues compared fasting serum insulin, C peptide and homeostatic model assessment (HOMA-IR) as a surrogate for insulin resistance between HCV infected patients and healthy volunteers. They showed that patients with HCV infection had significantly higher levels of fasting serum insulin, C peptide, and HOMA-IR compared with matched controls. This effect was genotype related, with genotype 3 infected patients having significantly lower HOMA-IR than other genotypes. Since genotype 3 infection has been widely shown to be associated with hepatic steatosis, this indirectly supports a direct viral effect as described above, rather than induction of a pro-steatotic metabolic state.

An elegant study by Shintani and colleagues showed, using a murine model, that plasma glucose levels were higher at all time points in HCV core transgenic mice than in control mice following a glucose tolerance test. The transgenic mice also exhibited marked insulin resistance as well as significantly higher basal serum insulin levels. Transgenic mice fed on high fat diets developed diabetes while control mice did not. Furthermore, the group revealed that transgenic mice had a higher serum tumour necrosis factor-alpha (TNFα) than control mice and that administration of an anti-TNFα antibody restored insulin sensitivity. The association between TNFα and insulin resistance has been illustrated in numerous other animal models. TNFα induces serine phosphorylation of IRS-1, hypophosphorylation of IRS-2 and down-regulation of glucose transporter GLUT4 via ceramide, resulting in insulin resistance. Furthermore, TNFα also modulates adipocytes, affecting cytokine, adiponectin and leptin production, further worsening insulin resistance.

**Insulin resistance and hepatic steatosis**

Whereas genotype 3 infection has been closely associated with the direct mechanism of hepatic steatogenesis, other genotypes have been associated with causing hepatic steatosis through clinical risk factors for NAFLD, specifically—inulin resistance. This was illustrated by Fartoux and colleagues who showed that HOMA-IR was higher in patients with genotype 1 infection compared with those with genotype 3 infection.

Liver tissue is rich in insulin receptors. The liver controls hepatic glucose production, replenishment of glycogen stores, increased triglyceride biosynthesis and decreased VLDL and apolipoprotein B production and secretion. In a state of insulin resistance, hepatic steatosis has been shown to be mainly due to an increased influx of fatty acids to the liver, owing to increased peripheral lipolysis and hepatic lipogenesis. Reduced fatty acid oxidation and decreased export of fat further contribute to hepatic steatosis. Furthermore, hyperinsulinaemia causes direct activation of the SREBP-1c, causing lipogenesis.

**Oxidative stress**

A key step in the development of both hepatic steatosis and hepatic injury is oxidative stress. Oxidative stress may be defined as an imbalance of reactive oxygen species (ROS) and antioxidants, such that the pro-oxidant activity exerted on different molecules are potentially able to alter their structure and function.

Both viral proteins and inflammation may lead to ROS production. HCV core protein increases ROS and lipid peroxidation products through inhibition of electron transport and alterations in permeability of mitochondria. Reducing viral replication has been shown to reduce the quantity of ROS, and increase mitochondrial electron transport activity. Ethanol metabolism and cytochrome P4502E1 also cause mitochondrial injury, and may act
synergistically with HCV to produce ROS. \textsuperscript{58} Aside from the direct virological effect of HCV on the mitochondria, HCV induced immune activation may also cause oxidative stress by cytokine release and the activation of macrophages. \textsuperscript{57} Moreover, proinflammatory cytokines such as TNF$\alpha$ further promote insulin resistance, as described above.

ROS have numerous effects in the liver: induction of cytokine formation by hepatocytes and Kupffer cells leads to increased TNF$\alpha$ production and insulin resistance, while development of insulin resistance may result in hepatic steatosis. ROS may cause genetic mutations and chromosomal alterations contributing to carcinogenesis. \textsuperscript{60,61} They use lipids, particularly polyunsaturated fatty acids (PUFA) owing to their multiple electron-dense bonds, as a substrate for peroxidation resulting in the production of hydroperoxides and endoperoxides, including covalently-bonded malondialdehyde (MDA) and 4-hydroxy-2,3-nonenal (HNE) adducts. These have been detected in human liver biopsy samples using immunohistochemistry in chronic hepatitis C and correlated with fibrosis score and histological activity. \textsuperscript{62}

**Clinical relevance**

**Hepatic steatosis and the progression of fibrosis**

A large number of studies have shown a positive correlation between hepatic steatosis and the progression of hepatic fibrosis in HCV infection. \textsuperscript{7,36,38,51,63–71} However, there has been less convincing evidence supporting a specific genotype as responsible, with some studies finding the correlation to only exist in genotype 1, \textsuperscript{71} and others being associated specifically with genotype 3. \textsuperscript{68–70} Most of these studies are cross-sectional, showing weakly positive results and offering no temporal evidence for the association. Longitudinal studies, such as those by Castera and colleagues offer stronger evidence for a causal relationship: paired liver biopsies in 96 untreated patients with HCV infection showed that worsening of steatosis was associated with hepatic fibrosis progression. Multivariate analysis showed that the only factor independently associated with fibrosis progression was worsening of steatosis. \textsuperscript{69} These data were later corroborated by another group. \textsuperscript{67} A multinational, multicentre meta-analysis further concluded that steatosis was independently associated with fibrosis in patients with HCV infection. \textsuperscript{63} Aside from clinical data supporting the association between hepatic fibrosis and steatosis, there is good pathogenic evidence concerning insulin resistance and oxidative stress.

Insulin resistance not only contributes to the development of steatosis, but also independently to the progression to fibrosis. In liver biopsy samples, both from patients with NAFLD and Zucker rats (model of type 2 diabetes and obesity), connective tissue growth factor (CTGF) was upregulated. CTGF plays a vital role in hepatic stellate cell fibrogenesis \textsuperscript{72–74} and has been illustrated in several other human fibrotic disorders, such as scleroderma, atherosclerosis and conditions associated with glomerulosclerosis in the kidney. \textsuperscript{75} Analysis of CTGF as a serum marker of fibrosis showed both a high sensitivity and specificity. \textsuperscript{76} In a study of 153 HCV infected patients enrolled in the Swiss Hepatitis C Cohort Study, CTGF was higher in patients with steatosis and fibrosis than in those without these features. However, there was no association between CTGF concentration and either insulinaemia or glycaemia. \textsuperscript{77}

Kitase and colleagues quantified lipid peroxidation products [4-hydroxy-2-hexenal (HHE)-protein adducts] as a marker for oxidative stress in liver biopsy samples from patients with HCV infection and correlated these data with hepatic steatosis. They showed that areas stained for HHE-protein adducts were significantly larger in those patients with steatosis, compared with those without. Multivariate analysis revealed that the HHE positive areas were associated with the presence of hepatic steatosis. In those patients without hepatic steatosis there were still detectable peroxidation products. However, they were at a much lower concentration. This suggests that oxidative stress is not only a feature of hepatic steatosis, but also of the viral infection itself. \textsuperscript{61} Furthermore, increasing lipid peroxidation products correlate with worsening hepatic fibrosis in 43 patients with chronic HCV infection. \textsuperscript{62} A hepatic proton magnetic resonance spectroscopy (MRS) study assessed lipid profiles in liver biopsy samples \textit{in vitro} from 47 patients with HCV and in the liver \textit{in vivo} using whole body MRS in 59 patients. Results from both cohorts showed that polyunsaturation decreased with increasing fibrosis stage. \textsuperscript{78} Taken together, these studies indicate a contribution of ROS to changes in lipid composition with disease severity. ROS are also involved both in the initiation and perpetuation of hepatic fibrogenesis, where exposure to ROS results in activation of hepatic stellate cells from predominantly vitamin A storage cells to the myofibroblastic phenotype. Indeed, culture medium taken from hepatocytes undergoing oxidative stress led to increased proliferation and collagen production in hepatic stellate cells. \textsuperscript{79}

\textit{Hepatitis C and hepatic steatosis}
**Hepatic steatosis and response to antiviral treatment**

Hepatic steatosis in patients with HCV infection is negatively correlated with SVR to antiviral therapy and insulin resistance has been implicated as a causative factor in a number of studies. In vitro studies have shown that fluvastatin used as monotherapy had a ‘modest, variable, but short-lived’ effect on serum HCV RNA titre. However, the efficacy may be greater when given alongside interferon therapy, as found in in vitro studies. A retrospective case–control analysis showed that patients on pegylated interferon, ribavirin and a statin had a SVR of 82% compared with those on pegylated interferon and ribavirin alone (53%).

Fish oils are rich in polyunsaturated fatty acids, which reduce HCV viral replication, and low in saturated and monounsaturated fatty acids, which promote HCV replication. Despite good laboratory data there is a lack of large-scale clinical evidence. A small cohort of patients with chronic hepatitis C was given eicosapentaenoic acid (EPA) with vitamins C and E or vitamins C and E alone, alongside interferon and ribavirin therapy. There was a significant reduction in serum ALT in those taking EPA supplements compared with controls, unfortunately there are no data on serum HCV RNA viral titres.

Thiazolidinediones, a group of drugs frequently used to treat type 2 diabetes, act on PPARγ to reduce insulin resistance. A randomized double blind cohort of 20 patients with type 2 diabetes was given either metformin or rosiglitazone. Patients in the rosiglitazone cohort were shown to have raised serum adiponectin and decreased hepatic steatosis, compared with those on metformin. These data suggest that reduction in insulin resistance causes decreased hepatic fat. This was further illustrated in at least two other studies using other thiazolidinediones. A large, multicentre, randomized, double-blinded placebo-controlled trial investigated oral metformin therapy alongside pegylated-interferon and ribavirin vs placebo alongside pegylated-interferon and ribavirin in patients with genotype 1 HCV infection. They showed that compared with the control group, patients receiving metformin had decreased insulin resistance and increased SVR rate. A retrospective analysis showed that administration of thiazolidinediones or metformin prior to interferon alpha and ribavirin therapy reduced insulin sensitivity and significantly lowered baseline viral load. Despite these promising results, there has been some conflicting evidence. Another randomized double-blinded controlled study which included patients of different genotypes showed no significant differences in viral response in patient receiving metformin or those taking placebo. Further large, genotype-specific trials are needed to further investigate the

**Novel therapeutic approaches**

Currently, the average SVR rate to pegylated interferon and ribavirin is 50%, so there is need for novel therapeutics in the management of HCV. Clearer understanding of viral replication and pathogenesis of hepatic steatosis in HCV has brought new ideas in the management of HCV infection. Modulation of hepatic lipid may affect both viral replication and the sequelae of metabolic steatosis. Approaches include the targeting of ‘viral’ steatosis through treatment with fish oils or statins and HCV-associated metabolic steatosis, through the use of glitazones.

A simple measure, weight loss over a period of 3 months in patients with chronic hepatitis C reduced steatosis, serum alanine transferase, fasting insulin and fibrosis. It is possible that decreased metabolic steatosis resulted in reduced oxidative stress, reducing further steatosis and hepatocellular damage. In lean patients with genotype 3 infection, whose steatosis is thought to be principally ‘viral-induced’, weight loss caused a significant reduction in hepatic steatosis. Although, hepatic steatosis has been shown to correlate negatively with SVR rate, further work is needed to ascertain if there is a correlation between weight loss in patients with HCV infection and their SVR rate.

HMG-CoA reductase inhibitors, have been shown to inhibit geranylgeranylation of host proteins, and to reduce viral replication. Different statins have been tested in vitro for efficacy. Ikeda and colleagues used an RNA replication system to analyse five different statins, finding that fluvastatin in combination with interferon showed the greatest inhibitory effect on HCV replication. Human trials of fluvastatin have also been encouraging. Bader and colleagues initiated fluvastatin therapy in a cohort of 31 patients with chronic hepatitis C infection. They showed that fluvastatin used as monotherapy had a ‘modest, variable, but short-lived’ effect on serum HCV RNA titre. However, the efficacy may be greater when given alongside interferon therapy, as found in in vitro studies. A retrospective case–control analysis showed that patients on pegylated interferon, ribavirin and a statin had a SVR of 82% compared with those on pegylated interferon and ribavirin alone (53%).

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potential therapeutic benefits of metformin alongside antiviral therapy.

**Hepatitis C and lipids in evolution**

The requirement to employ host cellular replication machinery is common to all viruses, yet it is intriguing to speculate that the close association between the HCV and host lipid metabolism confers an evolutionary advantage. A number of strands of evidence presented in this review support this hypothesis. The cholesterol biosynthesis pathway is required, and, in particular, the geranylgeranylation of host proteins, for viral replication at the membranous web. By usurping the VLDL synthesis pathway, a low density lipo-viral particle is produced. The VLDL machinery is not required for viral replication, but for viral export from hepatocytes. The circulating HCV RNA virion itself is contained within the lipo-viral particle, which is effectively a modified VLDL particle. Consequently, the virus is shielded and is not directly exposed to serum, perhaps conferring a mechanism for immune evasion. These lipo-viral particles efficiently bind and enter hepatocytes through low density lipoprotein (LDL) receptors, causing hepatocyte-selective infection and thus this, at least partly, explains the hepatic tropism of the virus. In a state of insulin resistance associated with chronic inflammation, *de novo* lipogenesis and fatty acid influx into hepatocytes is enhanced, providing the substrate for triglyceride synthesis and intrahepatic lipid droplet formation, required for viral replication. Finally, the alpha interferons have been shown to lower the plasma level of total cholesterol, VLDL-cholesterol, LDL-cholesterol, high density lipoprotein (HDL)-cholesterol, and apolipoprotein A-1. Simultaneously, the activity of postheparin plasma hepatic lipase and lipoprotein lipase decreased by 20–50%. These observations may be of importance in the interpretation of lipoprotein changes seen in acute and chronic hepatitis C infection, particularly the low total cholesterol seen in chronic HCV infection. As the complex mechanisms of virus–lipid interactions are unravelled, so the understanding of the viral mechanisms for chronicity within the host will be enhanced.

**Conclusions**

Numerous pathways contribute to the development hepatic steatosis in patients with HCV infection, either through direct effects of HCV proteins or through metabolic mechanisms, which may also...
be associated with HCV infection. These are summarised in Figure 3. It should be noted that there is no clear dichotomy between hepatic steatosis caused by HCV and that which is metabolically derived, rather that there is considerable overlap in many patients.

Coexistence of hepatic steatosis and HCV infection is associated with an expedited progression towards fibrosis, and a poorer sustained virological response to interferon-alpha and ribavirin, having adjusted for genotype. The addition of an adjuvant therapy, such as fish oils and statins (targeting virally-induced mechanisms), or glitazones and weight loss (targeting metabolic syndrome mechanisms) to standard HCV therapy, in a genotype selective manner, may offer an inexpensive, clinically effective, and tolerable method of improving virological response rate and reducing morbidity and mortality. Further clinical trials are required in this area.

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Insulin resistance is a major determinant of sustained virological response in genotype 1 chronic hepatitis C patients receiving peginterferon alpha-2b plus ribavirin. 

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