Metabolic syndrome in chronic hepatitis C infection: does it still matter in the era of directly acting antiviral therapy?

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Abstract: Metabolic syndrome is prevalent in patients with hepatitis C virus (HCV) infection. Given the pandemic spread of HCV infection and metabolic syndrome, the burden of their interaction is a major public health issue. The presence of metabolic syndrome accelerates the progression of liver disease in patients with HCV infection. New drug development in HCV has seen an unprecedented rise in the last year, which resulted in better efficacy, better tolerance, and a shorter treatment duration. This review describes the underlying mechanisms and clinical effects of metabolic syndrome in HCV infection, as well as their importance in the era of new directly acting antiviral therapy.

Keywords: HCV, genotype 3, metabolic syndrome, steatosis, directly acting antiviral agents

Introduction
There are approximately 170 million people in the world infected with hepatitis C virus (HCV) and 350,000 deaths each year are caused by HCV infection. The prevalence of HCV infection in the United Kingdom is estimated to be 0.54% or 218,000 people. HCV infection is associated with the development of insulin resistance, diabetes mellitus, and hepatic steatosis. Epidemiological studies have demonstrated that hepatic steatosis occurs more frequently in patients with HCV infection (55%) than in the general population (20%–30%) in the Western world. The macrovesicular steatosis present in patients with HCV infection is also distributed in the periportal areas rather than the centrilobular region which is more commonly seen in non-alcoholic fatty liver disease, indicating that HCV may be directly inducing steatosis rather than being an unrelated finding. It has been suggested that there are two main types of steatosis. The first type is thought to be a direct viral effect, which develops in the absence of “metabolic syndrome” (obesity, hyperlipidaemia, and insulin resistance), and is more prevalent in genotypes 2 and 3 HCV infections. The second type is associated with metabolic syndrome, and is prevalent in genotype 1 HCV infection. These two forms of steatosis can coexist in patients with genotype 3 infections.

Insulin resistance linked to HCV infection was first reported by Allison et al., who observed that type 2 diabetes mellitus was more prevalent in patients with HCV-associated cirrhosis compared to other causes of cirrhosis. Following that, several other cross-sectional studies have also linked HCV and insulin resistance. Insulin resistance, evaluated through the homeostasis model assessment (HOMA-IR), can be genotype specific, although the different studies are not consensual in that regard.
Some studies have shown that insulin resistance is more prevalent in genotypes 1 and 4, as compared to genotypes 2 and 3 HCV infections.\(^{17,18}\)

Treatment for hepatitis C has evolved rapidly over the last few years. In 2013, the Food and Drug Administration (FDA) approved the use of simeprevir and sofosbuvir for the treatment of hepatitis C infection, which will improve treatment outcomes significantly. This review focuses on the pathophysiology and the relevance of metabolic syndrome in hepatitis C infection in the era of these new directly acting antiviral therapies.

**Pathogenesis of metabolic syndrome in HCV infection**

**Steatosis**

The close association of HCV and steatosis is evident from in vitro studies demonstrating that HCV hijacks the lipid-producing machinery of hepatocytes for its benefit.\(^{19,20}\)

The HCV core protein has been studied at length in both cell culture and in transgenic mice. Intracellular lipid buildup seems to occur when HCV core protein is highly expressed.\(^{20}\)

The core protein localizes at the surface of lipid droplets within the cytoplasm in cells transfected with HCV.\(^{21}\)

Other studies have shown that the core protein interacts with the cell machinery involved in lipid metabolism such as apolipoproteins A1 and A2, which are involved in triglyceride accumulation and storage in the hepatocytes.\(^{20}\)

HCV core protein also upregulates sterol regulatory element binding protein 1c (SREBP-1c), a transcriptional factor that mediates several lipogenic genes in lipid metabolism,\(^{22–24}\) as well as binds to DNA-binding domain of retinoid X receptor alpha (RXRa), a nuclear receptor that regulates several genes involved in cellular lipid synthesis, thus promoting de novo lipogenesis.\(^{25}\)

Furthermore, it inhibits microsomal triglyceride transfer protein (MTP) activity. As this is a rate-limiting enzyme playing a key role in the very low density lipoproteins (VLDL) assembly, the direct and likely consequence of its inactivation is accumulation of unsecreted triglycerides, hence steatosis.\(^{26}\)

Accumulation of core protein in mitochondria can impair electron transport and thus increase the production of reactive oxygen species (ROS).\(^{27}\)

Oxidative stress leads to peroxidation of lipids and structural proteins, disturbing the cellular traffic apparatus and VLDL secretion.\(^{28}\)

Recent studies have demonstrated a diminished peroxisome proliferator-activated receptor alpha (PPAR\(\alpha\)) expression induced by HCV core protein. PPAR\(\alpha\) regulates the transcription of mitochondrial carnitine palmitoyl acyl-CoA transferase 1 alpha (CPT1A), which is a rate-limiting enzyme in mitochondrial beta-oxidation mediating the entry of fatty acids into the mitochondria.\(^{29,30}\)

**Insulin resistance**

Insulin binding to the insulin receptor results in phosphorylation of the receptor and tyrosine phosphorylation of intracellular insulin receptor substrate (IRS) proteins, mainly IRS-1 and IRS-2. This activates two major cellular signaling pathways, the phosphoinositide-3 kinase (PI3K)/Akt and the Ras/mitogen-activated protein kinase (MAPK) pathways.\(^{31}\)

HCV directly perturbs insulin signaling by modulating the insulin receptor and IRS-1 and subsequently downregulating PI3K.\(^{32}\)

Knockout of the IRS-1 and -2 genes in murine models induces insulin resistance and results in hyperinsulinemia, thus indicating the importance of IRS-1 and -2 as mediators of insulin action.\(^{33,34}\)

The effects of HCV core protein on the expression of IRS-1 and -2 were investigated in 357 patients with chronic liver disease, and HCV core protein in serum was associated with insulin resistance and decreased levels of these proteins.\(^{35}\)

It is thought that HCV core protein can also induce insulin resistance via the upregulation of suppressor of cytokine signaling-3 (SOCS-3), SOCS-7, and proteasome-activator 28-gamma (PA28\(\gamma\)), and downregulation of peroxisome proliferator-activated receptor-gamma (PPAR\(\gamma\)).\(^{35,36}\)

Activation of the mammalian target of rapamycin (mTOR) downstream of the PI3K/Akt pathway has also emerged as a critical event in rendering IRS unresponsive to insulin.\(^{37}\)

Lastly, tumor necrosis factor-\(\alpha\) (TNF-\(\alpha\)) also induces insulin resistance in HCV infection by impairing insulin signaling through serine phosphorylation of IRS-1 and -2, thus downregulating glucose transporter-2 and -4 (Glut2/Glut4) gene expression.\(^{38}\)

**Clinical consequences of metabolic disease in HCV infection**

**Hepatic fibrosis**

A close relationship between insulin resistance and liver fibrosis has been shown in many studies.\(^{39,40}\)

New onset diabetes is a poor predictor in patients with HCV infection without cirrhosis. In this group, the cumulative incidence of cirrhosis and decompensated cirrhosis was significantly higher in patients with diabetes than those without.\(^{41}\)

Regardless of the viral genotype and severity of liver damage, serum insulin concentrations and homeostasis model assessment of insulin resistance (HOMA-IR) index scores increase with the severity of hepatic fibrosis.\(^{18,42}\)

It is believed that hyperinsulinemia and hyperglycemia directly stimulate hepatic stellate cells, leading to activation of connective tissue growth factor and subsequent accumulation of extracellular matrix.\(^{43,44}\)

Most retrospective studies have shown positive correlations between the severity of steatosis and
stage of hepatic fibrosis. It is difficult to ascertain whether the two types of hepatic steatosis contribute equally to the overall disease progression in patients with HCV infection. The majority of studies have not separated the two types of steatosis when examining these questions.

Hepatocellular carcinoma
It is also well recognized that the presence of metabolic disturbance in patients infected with HCV accelerates the development of hepatocellular carcinoma. Elkrief et al followed 348 cirrhotic patients with HCV infection treated in hospital between 2006 and 2008. At baseline, 29% of the patients had diabetes. This was independently associated with the development of ascites, bacterial infections, and hepatocellular carcinoma. The underlying mechanisms linking insulin resistance and hepatocellular carcinoma remain to be elucidated. Hypotheses are based on the mitogenic role of insulin on cell proliferation and its binding on insulin-like growth factor-1 receptors, resulting in the activation of downstream cascade of intracellular responses. Patients infected with HCV also seem to have poorer quality of life, increased liver and cardiac mortality, as well as all-cause mortality.

Effect of metabolic disease on treatment outcomes

Interferon-based therapy
The presence of hepatic steatosis and insulin resistance reduces the likelihood of achieving sustained virological response (SVR) with standard pegylated interferon (peg-IFN) and ribavirin therapy in HCV patients. Steatosis is also associated with higher rates of relapse, irrespective of viral load, in patients with genotype 3 HCV infections. An increase in HOMA-IR index score is associated with reduced early virological response (EVR) and SVR rates in genotypes 1 to 3 HCV infections.

In contrast to peg-IFN/ribavirin dual therapy, metabolic factors and insulin resistance do not seem to have a significant effect on telaprevir-based treatment efficacy. In treatment-naïve patients with genotype 1 HCV infection receiving triple therapy consisting of peg-IFN, ribavirin and telaprevir, HOMA-IR values were not predictive of virological response rates, even though SVRs appeared to be associated with improved insulin sensitivity. The lack of association between baseline HOMA-IR and treatment outcomes with telaprevir-based therapy is also seen in treatment-experienced HCV patients in the REALIZE trial.

If lipid metabolism and metabolic syndrome are linked to HCV infection, lipid modification represents a novel target for therapeutic intervention in HCV infection. Studies looking at the effect of insulin sensitizers such as metformin and thiazolidinediones in improving treatment outcomes have been disappointing. Data from studies looking at peroxisome proliferator-activated receptor-gamma (PPAR-γ) agonist pioglitazone therapy with peg-IFN and ribavirin in HCV patients have failed to show increased SVR. Other studies have shown that 3-hydroxy-3-methylglutaryl CoA (HMG CoA) reductase inhibitors, when used as monotherapy, are able to inhibit de novo lipogenesis and HCV replication in vitro, but these effects were not replicated in human studies. However, when used in combination with peg-IFN and ribavirin, statin does seem to improve virological response to dual therapy. Their role for use in conjunction with directly acting antiviral therapy has not been evaluated.

Interferon-free therapy
Treatment of HCV infection is transitioning from IFN-based to IFN-free regimens composed of directly acting antiviral agents (DAAs), which result in higher rates of SVR. The association between baseline metabolic characteristics and treatment outcome during IFN-free DAA treatment has not been fully elucidated. One recent study looked at the impact of HCV infection on host metabolism and its association with treatment outcome with sofosbuvir and ribavirin in genotype 1 HCV patients. Clearance of HCV using this combination results in rapid changes in peripheral and intrahepatic metabolic pathways, irrespective of treatment outcome, implicating a direct effect of HCV replication on lipid homeostasis. Importantly, lower baseline serum low-density lipoprotein (LDL) and lower expression of fatty acid metabolism and lipid transport genes at the end of treatment were associated with relapse, suggesting the relevance of host metabolism on treatment outcome with this DAA combination in genotype 1 HCV infection. In a Phase Ib placebo-controlled study, the use of danoprevir monotherapy, a second-generation protease inhibitor, seems to restore insulin sensitivity in treatment-naïve patients and previous nonresponders with genotype 1 HCV infection. These results are not surprising, as one would expect a drop in viral load to improve insulin resistance. Its effect on insulin sensitivity and treatment outcomes when used in combination with other antiviral treatment remains to be determined in the era of IFN-free therapy.

Both the first and next generations of DAAs appear to be less effective against genotype 3 infections. Hepatic steatosis may be, at least in part, responsible for the persistently low rates of SVR associated with genotype 3. It may be that intrahepatic fat sequestration by the replicating virus reduces
access of DAAs, thereby reducing the efficacy of these drugs. Most observations on metabolic changes and dyslipidemia associated with the use of DAAs focused on genotype 1 HCV infections. Therefore, further work to examine the mechanisms underlying treatment failure with genotype 3 is urgently required.

**Summary**
The landscape of therapy for HCV infections is changing rapidly. The tremendous improvement in SVR rates in genotypes 1 and 2 has rendered genotype 3 HCV infection the major challenge with DAA, as it continues to afflict a large population of patients. Furthermore, the prohibitive costs of such therapies may limit their use in patients in developing countries where most of the HCV infections exist. For these reasons, HCV genotype 3 has emerged as a priority for future therapy development. Its unique link to insulin resistance and its highly pro-steatogenic effect in the liver suggest that understanding of the pathology and mechanism of metabolic syndrome in HCV infection is still paramount.

**Disclosure**
The author reports no conflicts of interest in this work.

**References**

