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REVIEWS IN BASIC AND CLINICAL GASTROENTEROLOGY AND HEPATOLOGY

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Extrahepatic Morbidity and Mortality of Chronic Hepatitis C

Francesco Negro,[1] Daniel Forton,[2] Antonio Craxì,[3] Mark S. Sulkowski,[4] Jordan J. Feld,[5] and Michael P. Manns[6]

[1]*Division of Gastroenterology and Hepatology and Division of Clinical Pathology, University Hospital, Geneva, Switzerland;* [2]*Department of Gastroenterology and Hepatology, St George's Hospital, London, England;* [3]*Gastroenterology and Internal Medicine, University of Palermo, Palermo, Italy;* [4]*Johns Hopkins University School of Medicine, Baltimore, Maryland;* [5]*Toronto Centre for Liver Disease, Sandra Rotman Centre for Global Health, University of Toronto, Toronto, Ontario, Canada; and* [6]*Department of Gastroenterology, Hepatology and Endocrinology, Medical School of Hannover, Hannover, Germany*

Chronic hepatitis C virus (HCV) infection is associated with several extrahepatic manifestations. Patients with HCV may develop mixed cryoglobulinemia and its sequelae, ranging from cutaneous and visceral vasculitis to glomerulonephritis and B-cell non-Hodgkin lymphoma. HCV-infected patients have increased rates of insulin resistance, diabetes, and atherosclerosis, which may lead to increased cardiovascular morbidity and mortality. Neurological manifestations of HCV infection include fatigue and cognitive impairment. The mechanisms causing the extrahepatic effects of HCV infection are likely multifactorial and may include endocrine effects, HCV replication in extrahepatic cells, or a heightened immune reaction with systemic effects. Successful eradication of HCV with interferon alfa and ribavirin was shown to improve some of these extrahepatic effects; sustained virological response is associated with resolution of complications of cryoglobulinemia, reduced levels of insulin resistance, reduced incidence of diabetes and stroke, and improved fatigue and cognitive functioning. The availability of new interferon-free, well-tolerated anti-HCV treatment regimens is broadening the spectrum of patients available for therapy, including those in whom interferon was contraindicated, and will likely result in greater improvements in the extrahepatic manifestations of HCV. If these regimens are shown to confer significant benefit in the metabolic, cardiovascular, or neuropsychiatric conditions associated with HCV infection, extrahepatic manifestations of HCV may become a major indication for treatment even in the absence of liver disease.

Keywords: Cryoglobulins; Insulin Resistance; Cardiovascular Risk; Fatigue; Health-Related Quality of Life.

Treating patients who are chronically infected with hepatitis C virus (HCV) to eradicate the infection and achieve sustained virological response (SVR; undetectable HCV RNA 12 or 24 weeks after completion of therapy) decreases the risk of cirrhosis, liver failure, and hepatocellular carcinoma (HCC).[1–3] In addition to liver-related sequelae, chronic HCV infection is associated with changes in organ systems outside the liver, including metabolic, cardiovascular, and neurological systems, and with autoimmune and immune-mediated conditions such as mixed cryoglobulinemia (MC), thyroid disease, and glomerulonephritis.[4–7] A large, prospective cohort study found that patients with chronic HCV infection, defined as having detectable HCV RNA in serum, have an elevated risk of death from both hepatic and nonhepatic diseases, including cardiovascular and renal diseases, compared with uninfected patients and those with antibodies to HCV (anti-HCV) but no detectable HCV RNA in serum.[8] These and other findings raise the question of whether successful treatment of chronic HCV infection may also improve the associated extrahepatic effects and reduce nonhepatic morbidity and mortality. One multicenter international study has already shown that achieving SVR reduces not only liver-related but also all-cause and non–liver-related mortality.[9]

The mechanisms causing the extrahepatic effects of HCV are incompletely understood. HCV drives clonal expansion of B cells[10,11] to generate immunoglobulin (Ig) M rheumatoid factor in susceptible people that results in immune complex deposition in small vessels and vasculitis, although susceptibility factors are unknown. The mechanisms of other manifestations are multifactorial, including a direct interaction between viral proteins and intracellular signaling pathways, viral replication in extrahepatic cells, or a heightened immune reaction with systemic effects. Immune activation may lead to a chronic inflammatory state that can affect a number of systems, as has been observed in human immunodeficiency virus (HIV) infection.[12] Like HIV, HCV infection is associated with decreased quality of life[13]; the most important driving factors are fatigue,

Abbreviations used in this paper: **anti-HCV, antibodies to hepatitis C virus; CI, confidence interval; CNS, central nervous system; DAA, direct-acting antiviral; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HOMA-IR, homeostasis model for assessment of insulin resistance; HR, hazard ratio; HRQOL, health-related quality of life; Ig, immunoglobulin; MC, mixed cryoglobulinemia; NHL, non-Hodgkin lymphoma; NS3, nonstructural 3; OR, odds ratio; PCT, porphyria cutanea tarda; SVR, sustained virological response.**

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depression, and cognitive impairment.[14] There is evidence that treatment to eradicate HCV infection may improve some extrahepatic manifestations of HCV independently of the severity of the underlying liver disease. The evidence is strongest for MC, which often resolves entirely with viral clearance.[15–17]

In the era of interferon-based treatment, extrahepatic manifestations of HCV were frequently regarded as contraindications to treatment because treatment could exacerbate the manifestations, or because ongoing treatment of coexisting extrahepatic syndromes could result in untoward drug-drug interactions or additional toxicities. Patients with a history of autoimmune disease or psychological instability, for example, are often ineligible for interferon-containing regimens.[18,19] Recent advances in anti-HCV therapy have led to well-tolerated, interferon-free regimens, such that more patients may be treated, leading to the potential for improvements in extrahepatic manifestations on a larger scale. Quality of life previously decreased during antiviral therapy, but interferon-free therapies may improve quality of life while patients are on treatment[20,21] and allow treatment where previously contraindicated.[22] This review will consider the impact of chronic HCV infection on sites outside the liver, focusing on immunologic, metabolic, cardiovascular, and neurological manifestations.

Metabolic Manifestations of HCV Infection

Diabetes Mellitus and Insulin Resistance

Several studies have shown that patients with chronic HCV infection have an increased risk of diabetes mellitus compared with uninfected people (Table 1).[5,6,23] White et al showed that HCV infection is associated with an increased risk of diabetes in comparison to both uninfected and hepatitis B virus (HBV)-infected controls, suggesting that HCV plays a specific role in conferring the increased risk of diabetes.[24] The elevated risk is likely due to an association between HCV and insulin resistance. Recent data suggest that HCV-induced liver inflammation may significantly increase this risk,[25,26] and the observation that increased levels of liver enzymes, rather than HCV infection, is the true risk factor for development of diabetes in the HCV-infected US population[27] should be interpreted in view of these findings.

HCV-infected patients have significantly higher levels of insulin resistance (as measured by the homeostasis model for assessment of insulin resistance [HOMA-IR]) than uninfected controls or HBV-infected patients matched for body mass index, waist circumference, age, and sex (Table 1).[28,29] However, the evidence in favor of a viral dose effect is weak; although patients with a higher viral load tend to have higher levels of insulin resistance,[29–31] the correlation between HOMA-IR score and HCV RNA level is on average very weak or absent.[32,33] Similarly, there is no consistently reported genotype specificity associated with HOMA-IR scores.[34–37]

The most compelling evidence that HCV causes insulin resistance is the observation that curing HCV with antiviral therapy results in reduced levels of insulin resistance, whereas levels remain unchanged in virological nonresponders.[38] A phase 1 study of an interferon-free short course of danoprevir, an inhibitor of the HCV nonstructural 3 (NS3) serine protease, showed a close correlation between decline in viral load and reduction of HOMA-IR scores.[39] This suggests that treatment with HCV protease inhibitors or other anti-HCV direct-acting antivirals (DAAs) may restore insulin sensitivity in patients with chronic HCV infection.

Mechanisms of HCV-Induced Insulin Resistance

HCV may directly interfere with the insulin signaling pathway. This is suggested by the finding that nonobese, nondiabetic, HCV-infected patients have hepatic insulin resistance, as determined by the hyperinsulinemic-euglycemic clamp technique. Two different studies showed that endogenous glucose production in such patients was incompletely suppressed by low-dose insulin.[34,40] In one study, the hepatic insulin resistance index increased by a factor of 3 compared with healthy controls.[34] When liver samples from HCV-infected patients and uninfected controls were challenged with insulin ex vivo, the insulin-induced activation of the protein kinase B/Akt (PKB/Akt), the key kinase responsible for most metabolic effects of insulin, was blunted in HCV-infected cells compared with controls.[41] According to experimental models, the HCV core protein seems sufficient to induce insulin resistance via several postreceptorial mechanisms.[42]

In addition to hepatic insulin resistance, however, peripheral insulin resistance is elevated in HCV infection and appears to be the most important component of HCV-associated whole body insulin resistance.[34,40] An increased peripheral insulin resistance was reported independently by the 2 previously cited groups that used a hyperinsulinemic-euglycemic clamp in nonobese, normoglycemic, HCV-infected patients.[34,40] Using high concentrations of insulin, glucose uptake and oxidative consumption were impaired, implying a deficient glucose transport and disposal, accounted for by striated muscle. Interestingly, this viral-associated insulin resistance does not appear to involve increased free fatty acid efflux from adipose tissue, which remains normally sensitive to insulin.[34,40] Thus, glucose uptake is clearly impaired in patients with HCV infection.

Finally, HCV-induced liver inflammation[25,26] may increase the risk of developing insulin resistance via the release of proinflammatory cytokines, such as tumor necrosis factor α and interleukin-6, which may in turn interfere with the insulin signaling transduction pathway in hepatocytes.[43]

In summary, HCV causes hepatic and extrahepatic insulin resistance. Although hepatic impairment of the effects of insulin may be mediated by direct interactions in infected hepatocytes, increased peripheral insulin resistance may be caused by endocrine effects of soluble mediators secreted by infected hepatocytes. These soluble mediators may also increase hepatic insulin resistance via paracrine mechanisms. They may exert their peripheral effects by reducing glucose uptake and oxidative consumption by extrahepatic tissues, specifically muscle and, probably to a lesser extent, adipose tissue.[34,40] The factors involved in the paracrine