

Hepatitis C and steatohepatitis: Is there any relationship?

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Nonalcoholic fatty liver disease (NAFLD) represents the hepatic manifestation of the metabolic syndrome in the great majority of cases. The diagnosis requires a careful exclusion of alcoholic liver disease by clinical evaluation. NAFLD and hepatitis C are two common (the prevalence in general population approximately 20 and 1-2% respectively) liver diseases and coexistence of the two is to be expected. However, hepatic steatosis is a common histological finding occurring in more than 50% of patients with chronic hepatitis C, in contrast to chronic hepatitis B viral infection. So, the prevalence of coexistent hepatitis C and fatty liver is 2-3 times higher than would be expected, indicating that hepatitis C predisposes to NAFLD.¹⁻³ Both host and viral factors have been demonstrated to play an important role in the development of alterations in lipid and carbohydrate metabolism, liver steatosis and fibrosis in chronic HCV infection.^{4,5}

The association of HCV and steatosis seems to be genotype-specific. The virus has a direct cytopathic, steatogenic effect, particularly (two thirds) evident in patients with HCV genotype 3 (viral steatosis). In this case, HCV may directly interfere with fat trafficking through the liver and induce steatosis without a state of insulin resistance. Both HCV core and NS-5 proteins are associated with lipid droplets apolipoprotein A and microsomal triglyceride transfer protein impairing triglyceride export from hepatocytes in the form of very low-density lipoprotein (VLDL), leading to steatosis.⁶ Moreover, patients with genotype 3 infection tend to have lower circulating lipid levels, indicating impaired secretion of hepatic VLDL. Viral steatosis and serum lipid levels

improve with successful treatment of hepatitis C.^{7,8}

Insulin resistance is now recognized as the main cause of NAFLD. Insulin is an important regulator of lipid balance and inflammation and promotes lipogenesis while inhibiting lipolysis. In addition, certain cytokines known as adipokines are produced in areas of inflammation and promote lipogenesis or lipolysis. In those patients infected with HCV infection genotype 1, steatosis is associated with features of metabolic syndrome, in particular Body Mass Index (BMI) associated with insulin resistance and an increased supply of fatty acids to the liver.⁹ In addition, mice expressing the HCV core protein develop NAFLD. HCV infection may directly cause insulin resistance by impairing the insulin receptor substrate – 1 (IRS-1) mechanism of insulin signal transduction, due to Tumor Necrosis Factor- α (TEN- α) secretion.^{10,11}

The association between HCV and diabetes mellitus type 2, has been reported by groups all over the world. HCV infection can mediate diabetes mellitus in genetically susceptible individuals. HCV is diabetogenic through an extra hepatic effect, which might be either direct, through the core protein, or immune mediated. Alternatively and more commonly, the virus can cause glucose intolerance and diabetes by the induction of prolonged insulin resistance and associated hepatic steatosis. So, type 2 diabetes mellitus is another extra hepatic manifestation of HCV infection.^{12,13}

An association between HCV infection and carotid artery plaque formation and carotid intima-media thickening has been reported¹⁴. The role of steatosis in the development of atheroma in HCV seems worthy of further study.

Steatosis in patients with hepatitis C predisposes to accelerated fibrosis progression and an increased risk of hepatocellular carcinoma.¹⁵⁻¹⁷ Fatty liver is more vulnerable to damage induced by factors (abnormalities in the mitochondria, peroxisomes, cytochrome P450 system, iron overload and various enzyme pathways) that increase

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hepatic oxidant production. So, HCV core protein may induce oxidative stress directly through an effect on mitochondrial electron transport. The antiviral inflammatory response may provide an additional source of oxidative stress leading to increased lipid peroxidation, production of pro-inflammatory cytokines and cell death. Moreover, in the presence of steatosis, increasing apoptosis was associated with activation of stellate cells and fibrosis.¹⁸ Hepatic fibrosis probably develops as a consequence of hepatic stellate activation by inflammatory cytokines. Moreover, insulin resistance can directly promote fibrogenesis possibly through the expression of TNF- α and cytochrome P450 CYP2E1 isoenzyme. Nevertheless, increased circulating insulin and glucose stimulate the release of connective tissue growth factor (TGF- β) from stellate cells and the production of extracellular matrix (fibrosis). Fibrogenic effect of the adipose tissue-derived hormone leptin is also important.

A consequence of insulin resistance is the effect on neoplastic transformation. Hyperinsulinemia and increased levels of insulin growth factors promote cell proliferation and mutagenesis. Likewise, hepatic steatosis is a risk factor for hepatocellular carcinoma in patients with chronic HCV infection, maybe due to induction of oxidative stress by the virus.

Viral steatosis, predominantly seen in genotype 3, improves or disappears with successful antiviral therapy. This benefit is sustained following sustained virological response. Metabolic steatosis characteristic of genotype 1 infection, does not improved regardless of treatment response.

Liver steatosis may induce a mechanism of resistance to combination antiviral therapy, despite weight-based dosing, independent of genotype, viral load, extensive fibrosis, BMI and serum glucose. This is accomplished possibly via the promotion of fibrosis or by altering the metabolism of antiviral drugs.¹⁹

Weight loss in patients with chronic hepatitis C may result in a reduction in hepatic steatosis and stellate cell activation irrespective of viral genotypes and despite the persistence of the virus.²⁰

In conclusion, a growing body of evidence supports the view that steatosis plays a role in the progression of chronic HCV hepatitis to cirrhosis and hepatocellular carcinoma, providing the substrate for the virus induced oxidative stress and cytokine release to trigger inflammation, fibrosis and apoptosis. Further studies are needed to illuminate the role of HCV in disturbing lipid and glucose metabolism. Weight reduction may provide an

important new adjunct treatment strategy for patients with chronic HCV infection irrespective of genotype or virological response. The potential benefit of treating fatty liver in slowing the progression of liver disease in patients with hepatitis C and improving the response to treatment requires further investigation. Treatments directed at either oxidant stress (vitamin E) or insulin resistance (metformin, thiazolidinediones-pioglitazone, rosiglitazone) are under way.

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