Hepatitis C virus (HCV) is a member of the Flaviviridae family and a major cause of chronic liver disease, infecting an estimated 3% of the global population. HCV pathogenesis encompasses several interactions with the host lipid and glucose metabolism (1). This leads to the appearance of liver steatosis and, respectively, insulin resistance (IR). Although the latter two features are shared by the metabolic syndrome (MS), it has to be said that HCV infection and the MS are not associated, in other words there is no evidence that these two conditions occur in the same patient at a rate that is higher than predicted by chance (2). In addition, there no data suggesting that HCV may be associated also with other MS features, such as arterial hypertension or visceral obesity, although many studies have suggested an increased cardiovascular morbidity (arterial intima-media thickness, carotid plaques) in HCV-infected patients (3). Quite paradoxically, the serum lipid profile reported in HCV infection is characterized by decreased levels of cholesterol and occasionally triglycerides (1), conflicting with the defining criteria of MS.

Although IR and diabetes are common complications of all chronic liver diseases, a large amount of epidemiological, clinical and experimental data have shown that HCV directly alters glucose metabolism, leading to both IR and later on, in susceptible individuals, diabetes. Cross-sectional studies, comparing the prevalence of diabetes in patients with chronic hepatitis C with that of a comparator group, suggest that the former ones have diabetes more often than patients with other chronic liver diseases, even at the pre-cirrhotic stage (4). These observations have been confirmed by general population-based cross-sectional studies as well as in longitudinal studies. Importantly, HCV seems to increase the risk of developing diabetes especially in patients at risk, i.e. due to age or increased body mass index (BMI) (4).

Experimental data have demonstrated a direct interference of HCV with the hepatocyte insulin signaling. In a landmark study, liver biopsy specimens from 42 non-obese, non-diabetic HCV-infected 10 non-HCV-infected persons, matched for age and BMI, were incubated ex vivo with insulin, allowing the study of the interaction between HCV and the insulin signaling pathway (5). Mechanisms reported in subsequent works showed how HCV interferes at several steps of this signaling pathway, e.g. via an increased proteasomal degradation of insulin receptor substrate-1 (IRS-1) mediated by the activation of the suppressors of cytokine signaling-3 (SOCS-3), SOCS-1 and SOCS-7, or via the down-regulation of peroxisome proliferator-activated receptor-γ (PPAR-γ), or by triggering the endoplasmic reticulum stress or the activation of the c-Jun N-terminal kinase (reviewed in 6).

Recent, elegant evidence obtained by combination of the euglycemic hyperinsuliniemic clamp, the infusion of tracers and indirect calorimetry in HCV-infected patients without the MS has shown how HCV infection causes both hepatic and peripheral IR (7, 8), and this in spite of the fact that HCV infects only the liver. These data suggest that HCV-infected hepatocytes may secrete soluble factors that interfere with the insulin metabolic effects in distant organs, such as...
the muscles and the adipose tissue. As a result, IR occurring in patients with chronic hepatitis C recognizes a dual pathogenesis, i.e. due both to the direct and/or indirect action of the virus and to host factors.

The clinical consequences of HCV-induced IR are several: one the one hand, IR reduces the rate of virological response to interferon-alpha containing regimens (9), irrespectively of other baseline features such as HCV genotype. On the other hand, IR is an independent risk factor for accelerated fibrogenesis and for the development of hepatocellular carcinoma (1). In addition, the eradication of HCV has been shown to reduce the risk of developing diabetes or other glucose metabolism disturbances during follow-up (10). A sustained virological response has beneficial effects on glucose metabolism independently of other aggravating factors such as age and/or advanced liver fibosis (10).

These observations have important consequences on the patients’ management, especially in view of the global epidemic of the MS. The clinical management of metabolic alterations in the course of hepatitis C – irrespectively of their pathogenesis – include lifestyle changes, encouraging body weight reduction and increased physical activity. Whether pharmacological interventions may help remains to be defined. However, the goal of decreasing clinical outcomes related to IR and diabetes seem an additional, justifiable reason to achieve viral eradication in HCV-infected patients.

References