Hepatitis C Virus, Diabetes and Steatosis: Clinical Evidence in Favor of a Linkage and Role of Genotypes

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Abstract
Infection with hepatitis C virus (HCV) primarily causes chronic liver disease with characteristic histopathologic features, including hepatic steatosis. Moreover, chronic hepatitis C is also closely related to insulin resistance (IR) and an increased risk of type 2 diabetes mellitus (DM). This review summarizes the available clinical evidence for a linkage of chronic HCV infection and developing IR or DM that comprises (i) retro- and prospective clinical studies, (ii) the excess risk of chronic hepatitis C patients to develop DM compared to hepatitis B patients, (iii) a preferential relationship of IR with HCV type-1, -2 or -4 infections, (iv) a correlation between IR, viral load and responsiveness to antiviral treatment and (v) a decreased incidence of DM in chronic hepatitis C after sustained virological response. This review further refers to the clinical evidence of a preferential relationship between hepatic steatosis and HCV type-3 infection, and that two distinct genotype-specific pathogenic mechanisms underlie steatosis in hepatitis C. In HCV type-3 infections, steatosis is related to viral load but not to metabolic factors, and, thus, is termed ‘viral steatosis’. In HCV type-1, -2 or -4 infections, steatosis appears to be secondary to IR and regarded as ‘metabolic steatosis’. In conclusion, multiple lines of clinical evidence support a linkage of HCV infection and both hepatic carbohydrate and lipid metabolism. The extent to which targeting the host’s metabolism by drugs or by lifestyle change translates into an improvement of health or in a better response to interferon-α will provide further valuable insights into virus-host interactions, and is topic which is currently addressed in clinical studies.

Introduction
An estimated 3% of the world’s population or 210 million people are currently affected by hepatitis C virus (HCV) infection [1]. Infection with HCV primarily causes a chronic, mostly mild, inflammatory liver disease which does, however, hold a significant risk of developing into fibrosis and proceeding to liver cirrhosis. Further characteristic histologic alterations may include hepatic steatosis. It is now widely recognized that chronic hepatitis C, moreover, is closely related to insulin resistance (IR) and to an increased risk of developing type 2 diabetes mellitus (DM). In view of the central role of the liver for maintaining overall energy homeostasis and for the con-
version of carbohydrates into fat, it is not astonishing that infection with a hepatotropic virus might affect those pivotal liver functions, too [2]. As such, hepatitis C might be regarded not only as a viral disease of the liver, but also as a systemic disease that can exacerbate a number of other metabolic conditions.

**Clinical Evidence for a Linkage of Hepatitis C and IR**

The risk of chronic hepatitis C patients of developing IR or DM was addressed recently by a comprehensive meta-analysis [3]. Fourteen eligible retrospective studies which compared the risk of developing diabetes in chronic hepatitis C patients and noninfected controls yielded a pooled OR of 2, indicating a twofold excess DM risk with HCV infection. Multivariate estimates (n = 7), which were adjusted for various confounding parameters such as ethnicity, smoking, viremia, etc. yielded a comparable overall risk of 1.7. In addition to these retrospective studies, which cannot establish a temporal relationship because of their cross-sectional nature, three long-term longitudinal studies with prospectively collected data were also available. Here, the incidence of developing DM was examined in hepatitis C patients as well as in noninfected controls over several years of follow-up. Results from these prospective studies revealed, irrespective of whether adjusted or unadjusted data were considered, that anti-HCV-positive individuals had a higher cumulative incidence of diabetes than anti-HCV-negative individuals, or, in other terms, that HCV conveys an approximately 1.7-fold excess DM risk. These prospective data indicate a temporal relationship between HCV infection and subsequent occurrence.

Evidence that the presence of HCV itself precedes development of diabetes rather than the liver injury it generates comes from the comparison of diabetes risk in hepatitis C and an HCV-unrelated cause of liver injury, hepatitis B. The meta-analysis of nine eligible studies yielded pooled unadjusted (n = 9) and adjusted (n = 3) ORs of 1.7 and 1.8, respectively. These data thus show that HCV conveys a significant excess diabetes risk beyond the risk that is conveyed by relative liver pathology and, thus, argue for a direct role of the virus in promoting carbohydrate dysregulation.

The relationship between HCV infection and glucose metabolism deregulation is even more pronounced when viral genotypes are considered. A study by Moucari et al. [4] of 600 hepatitis patients reported, by multiple logistic regression, HCV types 1 and 4 to be independent predictors of IR in nondiabetic patients among age, metabolic syndrome, significant fibrosis and severe steatosis. Among a subgroup of 145 patients without significant fibrosis or metabolic disorders, i.e. BMI <25, patients with IR were almost exclusively infected with type 1 or 4 (n = 22), and IR was found to be positively correlated to serum viral load [4]. A similar dose-response relationship between HCV titer and the degree of IR after adjustment for age, gender and BMI could also be demonstrated in type 1 and type 2 patients from Taiwan [5]. These data further substantiate the presumption of IR being a direct viral feature predominately due to infection with HCV types 1, 2 or 4.

In line with the finding of a dose-response relationship between HCV titer and IR, and in line with the assumption that HCV predisposes to the development of glucose metabolism alterations, is the finding that successful intervention with virus replication, i.e. sustained virological response (SVR) to an antiviral therapy, was demonstrated to improve IR (HOMA-IR) and beta-cell function (HOMA-%B) in a cohort of 89 type-1- and type-2-infected patients in contrast to a less successful therapy outcome, i.e. therapy relapse or treatment non-response [6].

Moreover, two recent studies, one from Europe and one from Japan, addressed the incidence of diabetes after the termination of an antiviral therapy in hepatitis C, both of which came to comparable results [7, 8]. In the larger one, more than 2,800 Japanese patients were prospectively followed over a period of up to 15 years [7]. The cumulative development rate of DM was determined to be 3.6% at 5 years, 8.2% at 10 years and 17% at 15 years. SVR was found to cause a two thirds reduction of development of DM in patients treated with interferon (IFN). Although the absence of cirrhosis and prediabetes, as well as younger age, are also associated with a reduction of development of DM, SVR could reduce the onset of DM even in patients who are older than 50 years and in patients with liver cirrhosis and prediabetes [7].

Taken together, the available clinical evidence for a linkage of chronic HCV infection and IR/DM development comprises the findings that carbohydrate dysregulation: is more prevalent in hepatitis C than in noninfected controls, has a higher incidence in hepatitis C than in noninfected controls, is more prevalent in hepatitis C than in hepatitis B, is preferentially associated with HCV genotype-1, -2 and -4 infections, correlates to serum viral load, improves after successful antiviral therapy, and is less incident after successful eradication of the virus.
This evidence, however, does not rule out that patients with DM might be more susceptible to HCV infection than nondiabetics. A study from Egypt on patients suffering from chronic renal failure in hemodialysis showed that patients with noninsulin-requiring or insulin-requiring DM had a ten-fold increased risk of HCV infection with a higher annual seroconversion rate (11 vs. 7%) than nondiabetic patients [9]. A higher susceptibility of type 2 diabetes patients to HCV infection might be due to impaired immune defense mechanisms in diabetic patients.

**Clinical Evidence for a Linkage of Hepatitis C and Steatosis**

Prevalence of hepatic steatosis in patients with chronic hepatitis C ranges from 40 to 80% [10]. After adjustment for steatogenic factors, prevalence of steatosis in chronic HCV infection is still 50% and thus significantly higher when compared to the general population (non-alcoholic fatty liver disease), chronic hepatitis B virus infection or autoimmune liver disease, amounting to 21%, 18% and 16–21%, respectively [11–14]. As for IR, the prevalence of steatosis in chronic HCV infection varies with viral genotype, i.e. hepatic steatosis was shown to be more frequent among patients with HCV type-3 infections [10, 15]. The largest study on this issue is that from Leandro et al. [11], who performed a meta-analysis on individual data from more than 3,000 patients from different geographic origins. This study clearly showed that HCV type-3 infection is the strongest factor that is independently associated with liver steatosis in lean, but also in overweight as well as obese patients. Moreover, the lipid phenotype observed in patients with HCV infection is different, e.g. from patients with non-alcoholic fatty liver disease who typically have increased serum levels of triglycerides, cholesterol and apolipoprotein B. In contrast, hepatitis C features total hypocholesterolemia and low density lipoprotein cholesterol serum levels when compared to healthy donors. In HCV type-3-infection, serum lipid levels are even lower than in HCV non-type-3 infections [16]. Thus, HCV type-3-related steatosis, in particular, is accompanied by hypolipoproteinemia.

HCV-related hypolipoproteinemia is suggested to have implications for viral spread. Circulating HCV has been shown very early by Thomssen et al. [17, 18] to be precipitable by antibodies directed against β-lipoproteins and immunoglobulins, leading to the hypothesis that circulating HCV might be associated with β-lipoproteins and immunoglobulins in low-density lipop--virai particles. Since the low-density lipoprotein receptor might mediate HCV entry into hepatocytes, low very-low-density lipoprotein/low-density lipoprotein plasma levels might promote viral dissemination by a less competitive inhibition of virus uptake [19, 20].

Analogous to HCV type-1, -2 and -4 infections where IR severity is associated with viral load, in HCV type-3 infection, steatosis was found to be correlated to viral load [21]. Also analogous to HCV type-1, -2 and -4 infections where IR improves with IFN-α responsiveness, in HCV type-3 infection, steatosis has been shown to be reversible after eradication of HCV by successful anti-viral therapy [21, 22]. It was unaltered, in contrast, in HCV type-3-infected patients in whom a SVR was not achieved and in those with HCV type-1 infection, irrespective of treatment outcome.

At the same time, sustained clearance of HCV type 3 was associated with a normalization of baseline low serum cholesterol [22]. By contrast, cholesterol values remained unchanged in HCV type-3 nonresponders and in HCV type-1 patients, regardless of treatment response.

Whereas steatosis in HCV type-1, -2 or -4 infection is directly related to metabolic factors such as obesity or IR (but not to viral load), steatosis in HCV type-3 infection does not relate to metabolic factors but to viral load. These two obviously distinct genotype-specific pathogenic mechanisms which underlie steatosis in chronic hepatitis C have thus been termed ‘metabolic’ and ‘viral’ steatosis (fig. 1).

In conclusion, multiple lines of clinical evidence support a linkage of HCV infection and both hepatic carbohydrate and lipid metabolism. The better understanding of the pathophysiological linkage allows a more holistic and a genotype-based management of patients. Whether metabolic deregulation reacts upon hepatitis C disease parameters as fibrosis progression or sensitivity to exogenous IFN-α might be attempted by therapeutic interventions targeting those systemic conditions.

**Current Interventional Approaches**

A pilot study which addressed the intervention through a change in lifestyle showed that even mild weight loss improves liver histology in chronic hepatitis C as early as 3 months after the start of a weight reduction program, despite the persistence of the virus [23]. Obes-
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Fig. 1. Linkage between hepatitis C, diabetes and steatosis. In chronic hepatitis C, IR/DM has been shown to be independently related to HCV type 1, -2 or -4 infection. IR/DM is associated with viral load and improves in patients who respond to an antiviral treatment. Steatosis is regarded secondary to IR/DM, thus termed ‘metabolic’. It is related to metabolic factors as BMI, not to viral load, and steatosis does not resolve after viral clearance. In HCV type-3 infection, however, steatosis is the predominant feature which is related to viral load, but not to metabolic parameters. After successful antiviral treatment, steatosis resolves as hypolipoproteinemia normalizes, a condition also unique for the so-called ‘viral’ steatosis.

The extent to which these approaches translate into an improvement of hepatitis C disease or better sensitivity to IFN-α might provide further valuable insights into further clinical evidence for the linkage of HCV infection and carbohydrate and lipid metabolism.

Disclosure Statement

The author declares that no financial or other conflict of interest exists in relation to the content of the article.
