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EDITORIALS

The Relationship Between Hepatitis C Virus Infection and Diabetes: Time for a Divorce?

See Article on Page 1139

Obesity and type 2 diabetes (T2DM) are major public health problems characterized by insulin resistance (IR) and a state of "lipotoxicity,"[1] making them share metabolic complications, such as atherogenic dyslipidemia, nonalcoholic fatty liver disease (NAFLD), subclinical inflammation, and cardiovascular disease (CVD). The public health burden of hepatitis C virus (HCV) infection is estimated to affect 200 million patients worldwide, also causing considerable premature morbidity and mortality.[2] Interestingly, HCV infection is also associated with IR, steatosis, subclinical inflammation, and perhaps even CVD.[2,3] Several mechanisms have been described for HCV infection to cause or exacerbate IR, including an impairment in hepatic insulin signaling, particularly at the level of the insulin receptor substrate 1 and 2 and phosphoinositide-3-kinase/protein kinase B pathways.[4] In addition, core proteins of HCV genotype 1[5] or 2[6] may induce suppressor of cytokine (SOC)-3, whereas core proteins form HCV genotype 3 may induce SOC-7.[7] Activation of proinflammatory pathways involving c-Jun N-terminal kinase or mammalian target of rapamycin have been reported on, as well as alterations of the proteasome activator 28γ–dependent pathway.[2,4] Other mechanisms are related to increased viral replication in hepatocytes with induction of chronic subclinical inflammation or impairment in peroxisome proliferator-activated receptor (PPAR)-α and PPAR-γ expression and function. Hepatic steatosis in HCV genotype 3 infection is believed to be more viral related, whereas HCV genotype 1, 2, or 4 infections are viewed more as metabolically related and strongly associated with IR. Given the common soil of obesity, IR, and steatosis among patients with HCV infection, it has not been entirely unexpected that T2DM has been often associated with this viral disease. Countless studies have tried to understand this relationship and dissect one condition from the other, although, within this tangled web of metabolic factors, it has proven to be extremely challenging.

Most work has come from investigators, usually from tertiary care referral centers, that have reported a significant association between HCV infection and diabetes, with an odds ratio (OR) of ~1.7.[3,8] However, this clinic-based approach may cause an inevitable ascertainment bias as patients from hepatology clinics may not be fully representative of less-advanced disease in the general population. This is important because advanced liver disease *per se* is a well-established risk factor for the development of T2DM by a number of mechanisms.[9] Another shortcoming of many studies has been that the diagnosis of diabetes was performed only by questionnaires, or the investigators lacked a strict definition of diabetes. But, perhaps, the greatest limitation across the field has been not to control adequately for plasma alanine aminotransaminase (ALT) levels. By not doing so, studies most likely inadvertently included patients with nonalcoholic steatohepatitis (NASH) or advanced liver disease within the analysis, conditions strongly associated with prediabetes and T2DM.[10] Therefore, with the above-mentioned limitations, the association between HCV infection and prediabetes or T2DM would have been almost unavoidable.

In this issue of HEPATOLOGY, Ruhl et al.[11] revisit the association between HCV infection and diabetes in 15,128 adults. This study has several strengths that, combined, provide a fresh look at the topic and support to consider an "amicable divorce" to this relationship. First, the researchers used a well-established population-based cohort: the 1999-2010 National Health and Nutrition Examination Survey (NHANES)

Abbreviations: ALT, alanine aminotransferase; CVD, cardiovascular disease; GGT, gamma-glutamyl transpeptidase; HCV, hepatitis C virus; HIR, hepatic insulin resistance; HOMA-IR, homeostatic model assessment of IR; IR, insulin resistance; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NHANES, National Health and Nutrition Examination Survey; OR, odds ratio; Peg-IFN, pegylated interferon; PPAR, peroxisome proliferator-activated receptor; RBV, ribavirin; SOC, suppressor of cytokine; T2DM, type 2 diabetes.

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database. In addition, prediabetes and diabetes were defined using standard American Diabetes Association criteria and confirmed by laboratory testing. Insulin resistance was measured by the traditional homeostatic model assessment of IR (HOMA-IR), an adequate surrogate marker for large-scale, population-based studies. Finally, data were not only well-adjusted for major confounders, but, most important, ORs for diabetes among cases and controls were carefully examined according to the presence of normal or increased plasma ALT (and gamma-glutamyl transpeptidase [GGT]) concentration, a key aspect often overlooked in earlier analysis. Prevalence of anti-HCV+ (as an indicator of ever having been actively infected), HCV-RNA+ (as an indicator of active infection), prediabetes, and diabetes were 1.7%, 1.1%, 32.8%, and 10.5%, respectively. In multivariate analysis including all relevant variables, the researchers clearly demonstrate that prevalence of prediabetes or diabetes was not associated with HCV infection status, but rather with increased plasma ALT and GGT concentration, regardless of HCV infection status. Moreover, IR was not associated with HCV infection or diabetes, also something at odds with previous reports. These findings led the researchers to conclude that, in the U.S. population, HCV is not associated with diabetes and speculate that previous reports linking them were rather a product of the effect of elevated plasma ALT (possibly of NAFLD?), and not viral infection.

The findings are important for two main reasons: On one hand, it confirms quite conclusively the lack of a clear association between HCV infection and diabetes, something already suggested in previous reports from the NHANES database,[12,13] as well as other studies.[14,15] Moreover, there was no link with IR (see Fig. 3 of the article), a finding also consistent with some earlier work.[13,14,16] More important, by carefully controlling for ALT and GGT and finding a direct link to diabetes, but not with HCV infection, it begs the question of how did HCV infection really get tangled with diabetes and calls for a paradigm shift within the field. Is T2DM really a consequence of HCV infection, or an innocent bystander begging to break away? There will never be a simple answer, but future studies will have to take into account, and control more carefully for, the link between advanced liver disease and cirrhosis (a major factor for hyperglycemia and diabetes) when assessing HCV infection in clinic-based studies. This is because most earlier studies that have linked HCV infection with diabetes have usually found a stronger association in the presence of more-severe liver disease and/or fibrosis.[3,8,17]. Thus, liver disease severity is clearly one confounding factor. In the study by Ruhl et al.,[11] this did not play a role (see their response to this issue under letters of correspondence).

In addition, previous studies, by failing to correct for ALT levels, also may have incorporated not only sicker patients, but also many with more severe IR and with steatohepatitis (NASH), which is common in patients with prediabetes and T2DM. Thus, IR-associated steatosis and NASH probably also played a significant role. Of note, NAFLD is present in ~80% of overweight or obese patients with prediabetes or T2DM.[1,18] As a result, an unintended selection bias could have easily occurred because overweight or obese HCV infection patients overlapped with patients with metabolic syndrome and hepatic steatosis with an elevated plasma ALT concentration. Elevated ALT and liver disease have been long associated, in many epidemiological studies, with IR, prediabetes, or new-onset T2DM.[17,19] and several large, longitudinal studies recognize hepatic steatosis as a risk factor for development of T2DM.[20,21]

Finally, the little effect of active HCV infection on HOMA-IR within groups of normal or elevated ALT (as well as GGT; see Fig. 3A,B of the article), when compared to HCV− patients, suggest that the multiple potential mechanisms for HCV-induced hepatic insulin resistance (HIR) appear to have no clinical relevance, at least in community-based populations with HCV infection. Insulin resistance in patients with an active infection (HCV-RNA+) was no worse than in the rest, either when compared to HCV+ or HCV− patients. Of note, patients, on average, already were quite insulin resistant. Insulin-sensitive patients typically have a HOMA-IR index of $\leq$2.0, whereas HOMA-IR was ~3.0 in patients with normal glucose metabolism and ~4.5 in the group with prediabetes. One would speculate that, in the setting of preexisting IR from obesity, prediabetes, or T2DM, many of the putative mechanisms for HCV-induced HIR cannot further impair the already deeply disturbed insulin-signaling pathways of these patients, and that it plays a modest, if any, role in the pathogenesis of HCV infection. Alternatively, many of the metabolic effects described in HCV infection models *in vitro* and *in vivo* may not strictly apply to HCV-infected patients or be relevant to its natural history in humans. As proof of concept, amelioration of IR by coadministration of pioglitazone with pegylated interferon (Peg-IFN) and ribavirin (RBV) in patients with HCV infection does not improve virological response rates, compared with Peg-IFN/RBV alone.[23]

The study does have some limitations. Overall, the proportion of patients with HCV infection was small and somewhat lower than in hepatology clinic-based studies. As such, this may be a shortcoming, but also more reflective of rates expected from a community-based study. The rate of diabetes could have been higher for a middle-aged population if the gold-standard oral glucose tolerance test would have been used for the diagnosis of diabetes. In addition, the HOMA-IR is a rather crude measure of IR with a weak correlation with the gold-standard euglycemic insulin clamp, and does not take into account the significant reduction in insulin clearance of patients with NAFLD.[22] Finally, the combination of a low disease prevalence and the significant variability (standard deviation) in prevalence of diabetes (see Fig. 2A) in this cohort leaves room for having missed a potential association, at least for some HCV+ subgroups (HCV genotypes were not tested or reported). However, even taken together, they are unlikely to significantly modify the lack of an association between HCV infection and diabetes.

In summary, the study by Ruhl et al.[11] is provocative and calls one to reconsider the dogma on the role of IR in the pathogenesis of HCV infection and its association with T2DM. The researchers have provided compelling evidence that possibly other (metabolic) factors, rather than HCV+, play a role in the association between elevated ALT and T2DM in this setting. The findings need to be replicated in larger, longitudinal studies and across other ethnic groups and populations. Future work will need to assess the role of IR and hepatic steatosis more in depth to understand the association between HCV infection and diabetes. Until then, it appears that this relationship may be going separate ways and "talk of divorce" is in the air.

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