

Hepatitis C, insulin resistance and fatty liver: Bad things come in threes

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Man may be the captain of his fate, but he is
also the victim of his blood sugar
– Wilfrid G Oakley,
Trans Med Soc London 1962;78:16

It is clear that hepatitis C virus (HCV), insulin resistance (IR) and fatty liver disease, when severe and progressive, can each by itself lead to significant morbidity and mortality. What then when such an ‘unholy trinity’ afflicts a single, unfortunate individual? The inter-relationships among HCV, IR and fatty liver disease has been an area of significant scientific interest recently. Based on the past two decades of research, three observations seem to be well accepted: HCV-infected patients have a higher prevalence of IR and liver steatosis than patients with other liver diseases and the general population, suggesting that HCV may be a direct cause of IR in these patients; HCV patients with evidence of IR, steatosis or diabetes have more advanced fibrosis compared with patients lacking these factors; and HCV patients with IR or steatosis have a lower response rate to antiviral therapy compared with other HCV-infected patients (1).

Beyond that, many questions related to the HCV and IR story remain unanswered. What is the exact mechanism of IR in HCV-infected patients? Why do some patients develop IR while others do not? What is the best preventive and therapeutic strategy in this situation? Is this phenomenon affected by the HCV genotype?

In the current issue of the *Canadian Journal of Gastroenterology*, Ziada et al (2) (pages 325-329) try to address some of these unanswered questions, in particular, the last one, specifically in HCV genotype 4 (HCV-4) patients. They confirm previous work showing an independent effect of IR on viral dynamics and early viral suppression during antiviral therapy and, subsequently, on important outcomes such as end-of-treatment response and sustained virological response, and then eventually on fibrosis stage. They clearly show that in all these three aspects, IR negatively affects HCV patients. The study has the strength of being prospective and of studying patients with HCV-4, the dominant genotype in Egypt and the Middle East, a genotype that is significantly under-represented in most HCV treatment studies. In addition, the study excluded patients with obesity and those with overt diabetes. This is an important strength of this study because many of the previously observed negative effects of IR on HCV and other associated diseases may be more related to the metabolic and immunological consequences of diabetes and obesity rather than IR per se.

On the other hand, a potential limitation in this study is that although the authors formulated the reasonable plan of dividing patients into IR and non-IR groups, and then prospectively studying them, there were the inevitable significant differences between the two groups. Many of these factors are well known to affect fibrosis progression and response to antiviral therapy. Although the multivariate analyses attempted to control for these differences, these factors could potentially decrease the robustness of the conclusions.

It is worth noting that some of the findings of Ziada et al have been reported by previous studies in other genotypes and in HCV-4-infected patients as well. The prevalence of steatosis in HCV-4-infected patients has been documented in a few previous studies reporting a prevalence of approximately 40% (3-5). In the study by AlQaraawi et al (3), for example, 43% of patients showed mild, 42% moderate and 15% severe steatosis (3). These numbers are generally similar to what has been reported in HCV genotype 1 patients. If a specific HCV genotype is more associated with fatty liver, it is probably genotype 3 (1). However, the study by Ziada et al is probably the first to clearly examine IR markers as well as effects on antiviral treatment response in an integrated manner rather than just steatosis prevalence in patients with HCV-4. Previous studies involving HCV-4 patients have shown that variables such as age, gamma-glutamyl transferase levels, platelet count, body mass index, liver fibrosis stage, HOMA-IR, serum lipids and extent of hepatic inflammation are associated with steatosis grade or score (1-5). The presence of liver steatosis was also reported to be associated with a decreased chance of achieving SVR in two previous studies (3,6). Therefore, although Ziadi et al are not the first to report these observations in HCV-4, their prospective and careful study documenting the inter-relationships among HCV, IR and fatty liver, offers arguably the most complete picture to date.

With accumulating evidence in HCV-4 (this study and previous ones), it seems that the story of IR and fatty liver negatively affecting various aspects of HCV outcomes is not genotype dependent after all, and it can be seen across all genotypes. Whether HCV genotype 3 is associated with steatosis and IR by mechanisms different from the others remains unsettled and was not the focus of this particular article. In the meantime, pathogenic mechanisms of IR and fatty liver in HCV-4 and other genotypes remain to be elucidated by further clinical and basic research.

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