

# Metabolic Manifestations and Complications Associated With Chronic Hepatitis C Virus Infection

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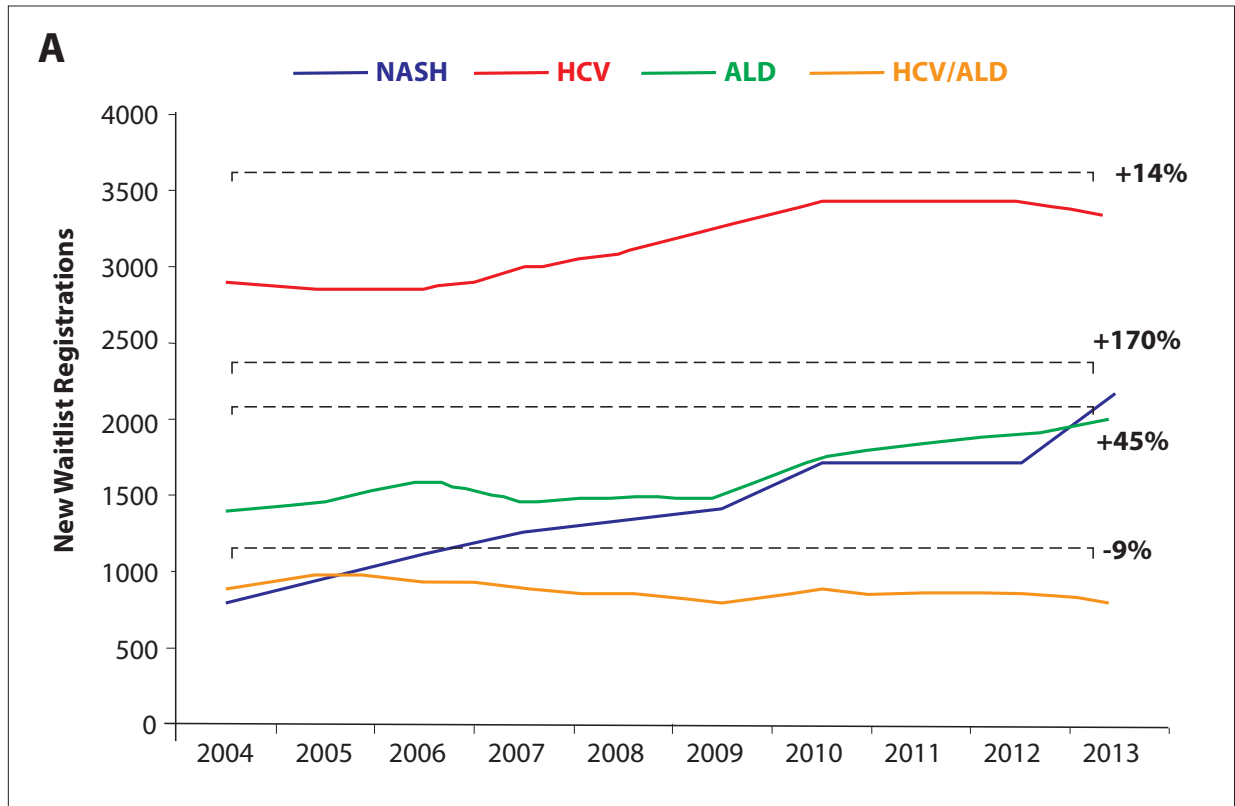
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**Abstract:** Chronic hepatitis C virus (HCV) infection is associated with many extrahepatic manifestations that contribute to morbidity and mortality. It is especially important to be aware of metabolic manifestations and serious complications that affect other organs and cancer risks. Chronic HCV infection itself contributes to de novo development of insulin resistance and hepatic steatosis, both of which increase the risk of cardiovascular diseases. Through these metabolic pathways (as well as through other hypothesized mechanisms that involve lipid metabolism, systemic inflammatory signals, and endothelial dysfunction), chronic HCV infection also contributes to significant systemic cardiovascular morbidity and mortality. While chronic HCV infection contributes to incident development of metabolic complications, the presence of concurrent metabolic diseases also contributes to disease progression, such as higher risks of hepatocellular carcinoma and progression to advanced fibrosis, among patients with chronic HCV infection. The implications of these observations are particularly important given the rising prevalence of obesity and metabolic syndrome in the United States and worldwide. Furthermore, concurrent nonalcoholic fatty liver disease, either as a result of underlying metabolic syndrome or as a direct result of HCV-induced fatty liver disease, further complicates the management of chronic HCV-infected patients. Greater awareness is needed toward the systemic manifestations of chronic HCV infection, with focused attention on the associated metabolic manifestations and complications. Successful treatment and cure of chronic HCV infection with the currently available, highly effective antiviral therapies will significantly improve long-term outcomes among these patients. It is also important to recognize and address the associated metabolic manifestations and complications to reduce cardiovascular-related morbidity and mortality.

## Keywords

Insulin resistance, metabolic syndrome, cardiovascular diseases, fatty liver, chronic hepatitis C virus infection, diabetes mellitus

Chronic hepatitis C virus (HCV) infection is a leading cause of morbidity and mortality, with studies estimating a prevalence of 3 to 7 million persons affected in the United States.<sup>1-4</sup> There have been major recent advances in antiviral

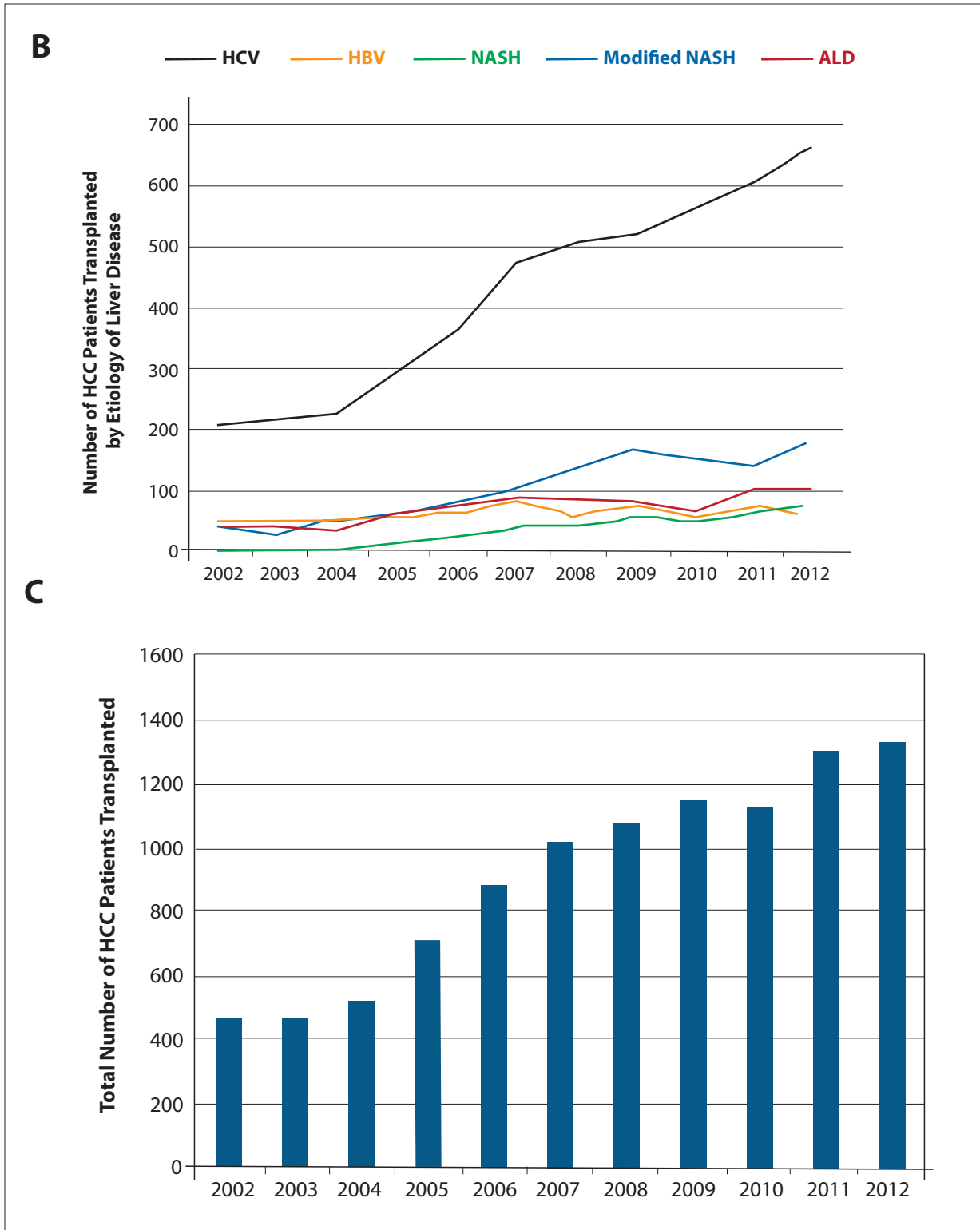


**Figure.** Trends in the etiology of liver disease leading to liver transplantation waitlist registration (A). (Figure continues on the following page.)

therapy for the management of chronic HCV infection, with the majority of current therapies achieving sustained virologic response (SVR) in over 95% of chronic HCV-infected patients. Despite these improvements, the long-term impact of these therapies on viral clearance and prevention of disease progression to cirrhosis and cirrhosis-related complications (eg, hepatocellular carcinoma [HCC], liver failure) will take time to determine. Currently, chronic HCV infection remains the leading cause of HCC and decompensated cirrhosis requiring liver transplantation in the United States (Figure).<sup>5-7</sup> While the impact of chronic HCV infection on liver-related complications and outcomes has been well studied, extrahepatic sequelae and complications of chronic HCV infection that result from the systemic effects of persistent viral infection are less well emphasized.<sup>8</sup> The early recognition of systemic effects of chronic HCV infection provides an opportunity to advocate for early initiation of antiviral therapy in which SVR may be achieved, as well as to treat all patients, thereby preventing further, and potentially permanent, hepatic and extrahepatic consequences of chronic HCV infection. This review highlights the metabolic manifestations and complications associated with chronic HCV infection.

## Insulin Resistance

The association between chronic HCV infection and metabolic manifestations primarily involves the potential diabetogenic effect of persistent viral infection. Several studies have investigated and demonstrated the association between chronic HCV infection and insulin resistance.<sup>9-14</sup> Using data from the third National Health and Nutrition Examination Survey (1988-1994), Mehta and colleagues performed a cross-sectional study of adults in the United States.<sup>14</sup> Among a study cohort of 9841 individuals, there was an 8.4% prevalence of diabetes mellitus and a 2.1% prevalence of individuals who were anti-HCV antibody-positive. After adjusting for multiple factors (including age, body mass index, and socioeconomic status), the authors demonstrated that adults age 40 years or older with HCV infection were nearly 4 times more likely to have concurrent diabetes than those without HCV infection.<sup>14</sup> However, as the authors acknowledged, while this study and previous cross-sectional studies have demonstrated the association of chronic HCV infection with insulin resistance, it remains unclear whether chronic HCV infection preceded the development of diabetes or whether HCV infection itself contributed to incident diabetes.



**Figure (continued).** Trends in the etiology of liver disease leading to HCC requiring liver transplantation (**B**) and the total number of HCC patients transplanted (**C**).

ALD, alcoholic liver disease; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; modified NASH, nonalcoholic steatohepatitis plus a cryptogenic or unknown etiology with a body mass index of at least 30; NASH, nonalcoholic steatohepatitis.

Figure A is adapted from Wong RJ et al.<sup>5</sup> Figures B and C are adapted from Wong RJ et al.<sup>6</sup>

To better address this question, Mehta and colleagues performed a follow-up study using data from the Atherosclerosis Risk in Communities Study.<sup>15</sup> In this prospective case-control study of men and women between the ages of 44 and 65 years, 1084 adults without diabetes at baseline were evaluated to determine the association between antecedent chronic HCV infection and the development of diabetes. After risk stratification adjustments based on factors such as age and body mass index, the authors demonstrated that among individuals at high risk for developing diabetes, the presence of chronic HCV infection was associated with a greater than 11-fold higher risk of developing diabetes over 9 years of follow-up (hazard ratio [HR], 11.58; 95% CI, 1.39-96.6).<sup>15</sup> Further supporting the increased risk of chronic HCV infection on insulin resistance, additional studies have demonstrated that successful clearance of HCV infection with antiviral therapy can lead to improved insulin resistance.<sup>16-24</sup> In a study by Romero-Gomez and colleagues, 1059 patients with chronic HCV infection were evaluated to determine the impact of achieving SVR on insulin resistance as measured by the homeostasis model assessment of insulin resistance.<sup>24</sup> The authors demonstrated that achieving SVR was an independent predictor of impaired fasting glucose or diabetes.<sup>24</sup>

However, another study by Giordanino and colleagues evaluated 202 chronic HCV-infected patients without pretreatment glucose abnormalities to determine whether antiviral treatment response affected the incidence of developing glucose abnormalities.<sup>25</sup> After a median follow-up period of 8 years, the authors found no significant difference between patients who achieved long-term virologic response and those who were non-responders with respect to their incidence of developing glucose abnormalities.<sup>25</sup> Another study of 2842 chronic HCV-infected patients treated with interferon monotherapy or in combination with ribavirin evaluated the impact of antiviral treatment on incident diabetes.<sup>23</sup> The investigators demonstrated a two-thirds reduction in the risk of developing incident diabetes associated with interferon treatment. Despite this seemingly conflicting study, the majority of studies continue to demonstrate the association of chronic HCV infection and insulin resistance, further emphasizing the potential metabolic benefit of achieving and maintaining viral clearance.

## Cardiovascular Diseases

The association between chronic HCV infection and cardiovascular diseases has been well studied, and while potential mechanisms have been hypothesized, the current literature demonstrates variations in the degree of this association.<sup>26-34</sup> Mechanistically, the potential increased risk of cardiovascular diseases among patients with chronic

HCV infection may stem from insulin resistance, hepatic steatosis contributing to increased systemic inflammatory markers, and/or endothelial dysfunction.<sup>31,35-39</sup> In addition, insulin resistance and hepatic steatosis are tightly linked and may further contribute to the development of other metabolic syndrome components such as hypertension and dyslipidemia.<sup>39-41</sup> However, a recent systematic review that evaluated published studies from 1995 to 2013 included a total of 5 studies that met inclusion and exclusion criteria.<sup>26</sup> The authors found 1 cohort study of US veterans that demonstrated a significantly increased risk of cardiovascular disease among patients with chronic HCV infection (HR, 1.27; 95% CI, 1.22-1.31); however, additional studies that also used US Veterans Affairs data, although from an earlier period, demonstrated a protective effect of chronic HCV infection on the development of cardiovascular disease.<sup>30,32</sup> The remaining studies included in this systematic review did not demonstrate a clear clinical association between chronic HCV infection and cardiovascular disease, leading the authors to conclude that more prospective studies are needed to better evaluate this association before more definitive statements regarding chronic HCV infection and its impact on cardiovascular disease can be made.<sup>26</sup>

The difficulties in evaluating cardiovascular associations of chronic HCV infection are multifold. Different studies utilize varying definitions, categorizations, and surrogates of cardiovascular disease (eg, carotid artery intima-media thickness, subclinical atherosclerosis, congestive heart failure) and span large periods of time, during which antiviral treatment regimens have significantly improved with better efficacy and fewer side effects.<sup>26</sup> Furthermore, while several hypotheses have been discussed, it is likely that chronic HCV infection and clearance of HCV infection with treatment impart a multitude of systemic metabolic changes that may affect cardiovascular disease risk in multidirectional ways. For example, as previously discussed, clearance of HCV infection improves insulin resistance, which may contribute to reducing cardiovascular disease risk.<sup>16-24</sup> However, studies have also postulated that chronic HCV infection itself may be associated with lower serum lipid levels, and patients who achieve SVR may develop a significant rebound rise in lipid levels in the blood that may contribute to increased cardiovascular disease risks.<sup>39-41</sup> Thus, the cumulative impact of persistent viral infection and subsequent viral clearance with antiviral therapy is a complex interplay of different mechanistic pathways, and while not all studies demonstrate clear and convincing evidence supporting the association between chronic HCV infection and cardiovascular diseases, it cannot be argued that viral clearance has an overall beneficial effect. Large prospective studies that include multivariate

analysis and sensitivity testing would permit a more refined understanding of this issue.

### Nonalcoholic Fatty Liver Disease

The interplay between chronic HCV infection and non-alcoholic fatty liver disease (NAFLD) is complex. As discussed above, chronic HCV infection can contribute to metabolic derangements (including insulin resistance and dyslipidemia) that subsequently increase the risk of developing concurrent NAFLD. In addition, several studies have reported that chronic HCV infection itself may contribute to the development of hepatic steatosis, the presence of which feeds into the cycle of metabolic diseases contributing to disease progression and complications among patients with chronic HCV infection.<sup>31,35,37,42</sup> The strong association between chronic HCV infection and de novo hepatic steatosis is seen most prominently in patients with HCV genotype 3 infection.<sup>35,42-45</sup> In a large meta-analysis, Leandro and colleagues evaluated 3068 patients with histologically confirmed chronic HCV infection from 10 centers in Italy, Switzerland, France, Australia, and the United States, among whom 50.9% had histologic evidence of hepatic steatosis.<sup>43</sup> Hepatic steatosis was more commonly found, and was more severe, in patients with HCV genotype 3 infection. Interestingly, subsequent studies demonstrated that hepatic steatosis was significantly improved, and in some cases completely resolved, after antiviral therapy in patients with HCV genotype 3 infection.<sup>42,45-47</sup> However, patients with non-genotype 3 infection did not demonstrate the same improvement in hepatic steatosis, even among those who achieved SVR with antiviral therapy.<sup>45-47</sup> While the exact etiologies underlying these observations are not clear, several hypotheses have been raised. Studies have described the potential de novo lipogenic role of chronic HCV infection through activation of *in vitro* sterol regulatory element-binding proteins 1c and 2, both of which are transcription factors involved in lipogenesis.<sup>48</sup> Further studies observed an inhibition of fatty acid oxidation by HCV infection, contributing to triglyceride accumulation.<sup>49-51</sup> Other hypotheses have implicated impaired assembly and secretion of very low-density lipoprotein.<sup>52,53</sup> Although the exact mechanisms of HCV-induced fatty liver disease are likely multifactorial and involve multiple systemic pathways, the implications of HCV-induced fatty liver are paramount to fully appreciating the systemic metabolic effects of chronic HCV infection. While clearance of chronic HCV infection with antiviral treatment will be important not only to address the hepatic and extrahepatic manifestations associated with persistent viral replication, increased awareness of associated metabolic derangements is also critical to prevent complications such as diabetes and cardiovascular diseases.

### Impact of Metabolic Diseases on the Natural History of Chronic Hepatitis C Virus Infection

Understanding whether chronic HCV infection increases the risk of developing metabolic complications deserves greater attention. However, it is also important to understand the impact of underlying metabolic diseases on the natural history of chronic HCV infection. Recognizing the impact of obesity and insulin resistance on disease progression among patients with chronic HCV infection is especially important given the rising prevalence of obesity and metabolic syndrome observed in the United States.<sup>54,55</sup>

In a recent systematic review evaluating the impact of metabolic diseases on disease progression among patients with chronic HCV infection, Dyal and colleagues looked at literature from 2001 to 2014 and identified 20 cohort studies that met inclusion criteria.<sup>56</sup> Focusing primarily on obesity, diabetes mellitus, and hepatic steatosis, the authors evaluated the association of these concurrent risk factors with the development of advanced fibrosis in patients with chronic HCV infection.<sup>56</sup> The authors demonstrated that the presence of concurrent diabetes among patients with chronic HCV infection was associated with a significantly higher risk of developing advanced fibrosis, with effect measures ranging from odds ratios (ORs) of 2.25 to 9.24. The presence of hepatic steatosis was also significantly associated with an increased risk of developing advanced fibrosis, with effect measures ranging from ORs of 1.80 to 14.3.<sup>56</sup> While the authors found 7 studies showing an increased risk of advanced fibrosis associated with obesity, 4 additional studies in the systematic review failed to show a significant association between the 2 conditions.

Disease progression to advanced fibrosis and cirrhosis is an important outcome among chronic HCV-infected patients. The development of HCC is another feared complication of chronic HCV infection. In a follow-up study, Dyal and colleagues performed a systematic review to evaluate the impact of obesity, diabetes mellitus, and hepatic steatosis on the risk of HCC among patients with chronic HCV infection.<sup>57</sup> A total of 9 studies from 2001 to 2014 met inclusion criteria and were included in the analysis. The authors demonstrated that concurrent diabetes was significantly associated with higher risk of HCC among chronic HCV-infected patients, with effect measures ranging from a HR of 1.73 to a risk ratio of 3.52.<sup>57</sup> The study also demonstrated an increased risk of HCC associated with obesity and hepatic steatosis, although the evidence supporting these associations were less robust, and larger studies with longer-term follow-up are needed to further explore these associations.

Both of the aforementioned systematic reviews attempted to better clarify the impact of concurrent metabolic diseases on disease progression and the natural



history of chronic HCV infection; however, several limitations must be acknowledged when interpreting these results. The ideal method for exploring the impact of metabolic diseases on disease progression would be to identify patients with antecedent metabolic diseases who subsequently acquired HCV infection. However, many of these studies were observational in nature and either utilized a case-control or retrospective cohort study design, which inherently limit the true ability to understand causation.<sup>56,57</sup> Furthermore, the study period of the included studies spanned a period during which significant advancements in HCV therapies were introduced. Thus, improved therapies may have been a potential confounder or effect modifier that affected disease progression in chronic HCV-infected patients. Despite the general agreement that increasing rates of metabolic diseases undoubtedly contribute to worse outcomes such as cardiovascular diseases, the current studies suffer from heterogeneity in definitions of obesity and insulin resistance, and often do not take into account more accurate measures of metabolic risk such as waist circumference as a measure of visceral adiposity, which may be especially important when evaluating for metabolic diseases in ethnically diverse populations.<sup>6,26,54,58</sup> Nevertheless, greater awareness of underlying metabolic diseases among patients with chronic HCV infection is paramount in that targeted treatment of these diseases can translate not only into improved management of liver disease but into overall health, including cardiovascular diseases.

In the current era of highly effective direct-acting antiviral therapies for chronic HCV infection, the ability to eradicate HCV will not only improve HCV-related liver disease, but will likely impact the incidence and prevalence of HCV-related metabolic diseases, given the association between the 2 conditions. However, greater awareness is also needed for metabolic diseases unrelated to chronic HCV infection, including NAFLD and NAFLD-related complications.

## Conclusion

Despite the improvements in diagnosis, linkage to care, treatment, and eradication of chronic HCV infection, this condition will continue to pose a major disease burden for the near future. Chronic HCV infection contributes to significant hepatic disease and complications; however, it is important to understand and appreciate the systemic effects of chronic HCV infection as it relates to metabolic manifestations and complications. The associations between chronic HCV infection and metabolic disease and between chronic HCV infection and cardiovascular diseases are especially important in light of the increasing prevalence of obesity and metabolic syndrome and their costs to patients, the health care system, and society.

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