

# Viral hepatitis infection and insulin resistance: A review of the pathophysiological mechanisms

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## Abstract

Viral hepatitis is a common cause of morbidity in Mexico. Insulin resistance (IR) is related to the liver damage caused by some viral infections, especially chronic infections. Chronic viral infection is an important risk factor for the development of type 2 diabetes mellitus, disease that is currently among the 10 main causes of morbidity and the most common cause of mortality. Although several studies have reported an association between IR and hepatitis B virus or hepatitis C virus (HCV) infection, the pathophysiology has been studied thoroughly only for the association between IR and HCV infection. It is thought that HCV infection causes direct damage through the action of the core proteins, which induces an inflammatory state characterized by secretion of proinflammatory cytokines that interfere with normal insulin signaling and disturb glucose, lipid and protein metabolism. This review summarizes the mechanisms by which viral infection is thought to induce IR.

Key words: insulin resistance; hepatitis B virus; hepatitis C virus.

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## Resumen

Las hepatitis virales son una causa común de morbilidad en México. La resistencia a la insulina (RI) ha sido relacionada con el daño hepático causado por infecciones virales crónicas, haciendo de ellas un factor de riesgo para el desarrollo de diabetes mellitus tipo 2, problema de salud que se encuentra entre las primeras 10 causas de morbilidad y es la primera de mortalidad. Aunque varios estudios han reportado una asociación entre la RI y la infección con virus de la hepatitis B y virus de la hepatitis C, sólo con el último se ha estudiado su fisiopatología. Se ha sugerido que produce daño directo a través de proteínas de su núcleo e induce un estado inflamatorio que interfiere con la señalización normal de insulina, resultando en una alteración del metabolismo de glucosa, lípidos y proteínas. Esta revisión resume los mecanismos por los que se sugiere que estas infecciones inducen RI.

Palabras clave: resistencia a la insulina; virus de hepatitis B; virus de hepatitis C.

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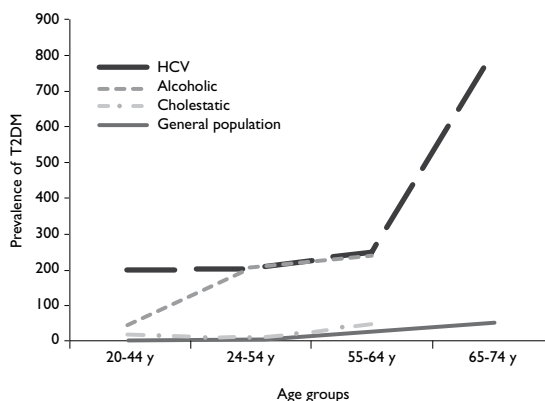
Many agents are capable of causing liver damage, including drugs, toxins, infections, and metabolic alterations, any of which may lead to liver failure. Viral infection is a frequent cause of liver damage. Viral infections considered to be hepatotropic include viral hepatitis caused by hepatitis viruses A, B, C, D, E, and F,<sup>1</sup> while the non-hepatotropic are Cytomegalovirus, Herpes Virus, and Epstein–Barr Virus. Most produce an acute infection, and only hepatitis viruses B, C, D, and E cause chronic liver disease. Several studies have shown that the damage or metabolic changes induced by these viruses have a significant impact on several organs of the body besides the liver. In recent years, insulin resistance (IR) and the metabolic syndrome have become more important and are linked to liver diseases, especially chronic diseases. The pathophysiological basis of the metabolic syndrome is IR, which is defined as an increased need for insulin in the peripheral tissues (muscle and adipose) to achieve normal blood glucose levels and to reduce the glucose output in the liver,<sup>2</sup> and may lead to type 2 diabetes mellitus (T2DM). In this paper, we explain the pathophysiology of IR caused by infection with viral agents responsible for liver damage.

### Epidemiology

Viral hepatitis infection is common in Mexico and its prevalence has been increasing. In 2008, 1 107 cases of infection with hepatitis B virus (HBV) and 2 226 cases of hepatitis C virus (HCV) were reported, giving incidence rates of 1.04 and 2.09 per 100 000 inhabitants, respectively.<sup>3</sup> The number of cases is expected to continue increasing in the coming decades.<sup>4</sup>

Overweight and obesity are major public health issues and are considered risk factors for the development of IR and the metabolic syndrome, which are the physiological bases of T2DM, another pathological entity whose prevalence has been increasing. In 2008, 396 374 new cases were reported, giving an incidence rate of 371.4 per 100 000 inhabitants; most patients are older than 45 years.<sup>3</sup>

Recent studies have confirmed a close relationship between IR and other liver diseases. IR and T2DM are associated with complications similar to those associated with chronic hepatitis caused by HBV and HCV infection, such as cirrhosis and hepatocellular carcinoma. Zein and colleagues reported that T2DM occurs with a high prevalence in cirrhotic patients in both Western and Eastern countries. The prevalence of T2DM is especially high in cirrhotic patients whose etiology is HCV infection rather than alcohol or cholestatic disease, etiologies in which is also noted a greater incidence of T2DM than in the general population (figure 1).<sup>5</sup> The



**FIGURE 1: PREVALENCE OF T2DM IN PATIENTS WITH LIVER CIRRHOSIS CAUSED BY DIVERSE ETIOLOGIES.<sup>5</sup> NOTICE THE HIGHER PREVALENCE AMONG HCV-INFECTED PATIENTS. HCV: HEPATITIS C VIRUS**

prevalence rates of T2DM in HCV infection is high: up to 33% in the USA,<sup>6</sup> 23% in Spain,<sup>7</sup> 20% in Japan<sup>8</sup> and 22% in Saudi Arabia<sup>9</sup> have been reported. A cross-sectional study performed by our group in a university hospital in Mexico City found a similar prevalence of this association of 22.7%.<sup>10</sup> The prevalence rates of T2DM in HBV infection is of 12% in the USA,<sup>11</sup> 11.9% in Japan,<sup>8</sup> and 16.7% in Mexico.<sup>10,12,13</sup>

The relationship between chronic liver diseases and T2DM is strong enough to be called “hepatogenous diabetes”, which is now recognized by the World Health Organization as an independent entity involving the development of T2DM caused by cirrhosis.<sup>14</sup> It has been suggested that 17–30% of cirrhotic patients are clinically diabetic and that this entity is caused by two abnormalities that occur simultaneously: IR in muscle and the inadequate response of  $\beta$ -cells, which secrete insufficient insulin to overcome the defect in insulin action. The IR induced by liver cirrhosis is greater than that caused by T2DM and leads to faster onset of and more severe metabolic complications.<sup>15</sup>

### Liver-related IR

Figure 2 shows the mechanisms of IR related to the liver. Two factors may explain IR of liver origin. One pathway is through the production of free fatty acids; an increase in their concentration inhibits the insulin-induced suppression of endogenous glucose production,<sup>16</sup> and the stimulation of gluconeogenesis<sup>17</sup> associated with activation of protein kinase C $\delta$ .<sup>18</sup>

Another pathway associated with IR in the liver is mutation of fructose 2,6-bisphosphonate, which leads to a decrease in fructose 2,6-bisphosphonate, which causes three changes: a less suppression of hepatic glucose production (increased gluconeogenesis), disruption of glucose flux, and a decrease in the insulin-induced Akt phosphorylation in the liver.<sup>19</sup>

Phosphorylation of the IRS-2 in the cascade of insulin activation also influences glycogen synthesis. This phosphorylation inhibits Glycogen Synthase Kinase 3 (GSK-3), which, in normal situations, induces glycogen synthesis and uptake of plasma glucose. In pathological situations, glycogen synthesis is interrupted and glucose is not taken up, leading to the development of IR.

### Viral hepatitis and IR

As noted above, several studies have shown that some viral infections promote IR. This association has been established mostly in chronic hepatitis because acute infections promote liver damage rather than metabolic changes because of the duration of the damage. This is why studies have focused on HCV and HBV infections, the most common causes of chronic liver disease. The association between IR or T2DM and hepatitis caused by hepatitis A virus (HAV), cytomegalovirus, or other acute viral infections has not been studied, and we focus the rest of this review on other chronic entities.

### HCV infection and IR

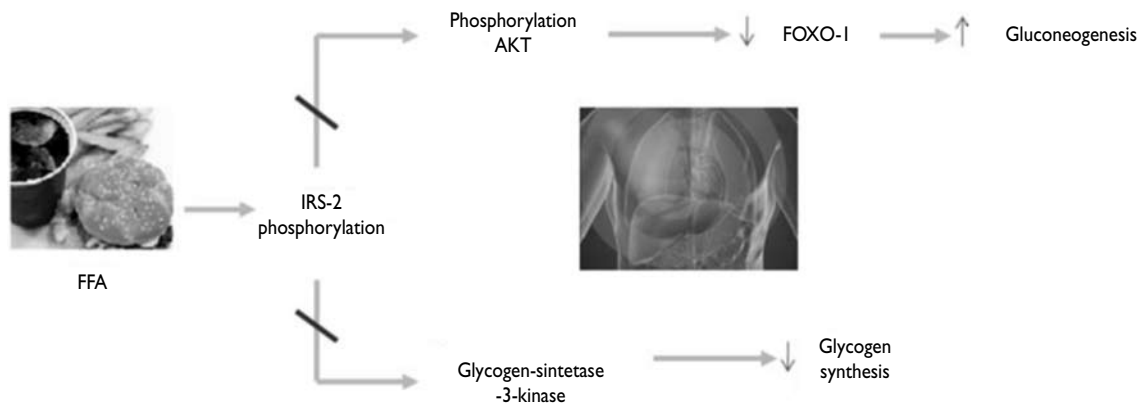
Infection with HCV is a leading cause of chronic liver disease. According to the World Health Organization, more than 3% of the world's population (around 170

million people) are infected and about 130 million are at risk of cirrhosis.<sup>20</sup> Most infected people (60–80%) develop chronic hepatitis C, which is associated with progressive fibrosis and a 3–9% chance of developing cirrhosis within the next 50 years.<sup>4,21</sup>

HCV infection is associated with the development of IR and, eventually, T2DM; thus, HCV can be considered a metabolic disease. It has been suggested that HCV core proteins directly damage the pancreatic tissue, inducing  $\beta$ -pancreatic cell dysfunction and, therefore, altering the insulin response to hyperglycemia, which eventually leads to IR.<sup>22</sup> Some authors consider that T2DM may be an extrahepatic manifestation of HCV infection.<sup>23</sup> In addition, the presence of IR itself predicts a faster progression to fibrosis, cirrhosis, liver failure, and hepatocellular carcinoma, and a poor response to antiviral therapy against HCV.<sup>12</sup>

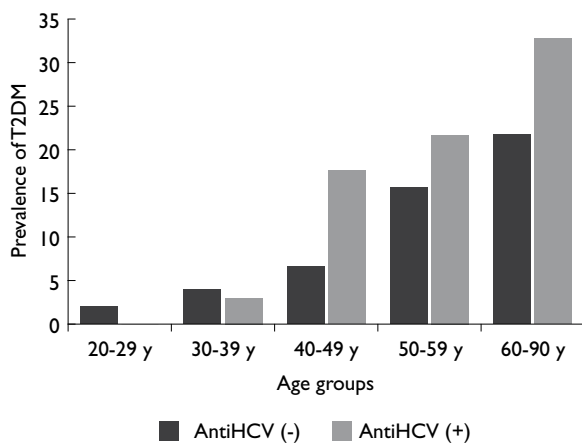
In 1994, Allison *et al* described for the first time the correlation between HCV and T2DM,<sup>24</sup> although this relationship was found only in cirrhotic patients with HCV. Later studies reported this association in cirrhotic patients with HBV (although in a lower percentage of patients).<sup>25</sup> Subsequent studies found that cirrhosis is not necessary for the development of T2DM because several HCV-infected patients without cirrhosis presented T2DM<sup>26–29</sup> (figure 3). These studies also demonstrated that fasting insulin and HOMA-IR levels are higher in HCV-infected patients than in other groups.<sup>30</sup>

Some authors have suggested that the disturbance of glucose homeostasis is related to the reduced glucose uptake, portosystemic shunting, impaired glucagon metabolism and increase in the production of proinflammatory cytokines such as TNF- $\alpha$ , IL-6, and TGF- $\beta$ .



FFA: free fatty acids, IRS: insulin receptor substrate

**FIGURE 2: MECHANISMS OF LIVER-RELATED INSULIN RESISTANCE**



**FIGURE 3: PREVALENCE OF T2DM IN PATIENTS WITH AND WITHOUT HCV INFECTION. THESE ARE THE RESULTS REPORTED IN THE STUDY BY MEHTA AND COLLEAGUES.<sup>33</sup> THE RIGHT BARS DEMONSTRATE CLEARLY THAT THE INCIDENCE OF T2DM IS HIGHER IN PATIENTS WITH HCV INFECTION THAN IN UNINFECTED PEOPLE**

NS3 and NS5A are structural proteins of the HCV that act as key mediators in the induction of oxidative stress and inflammation. It is thought that NS5A associates with the endoplasmic reticulum (ER) within cells and induces protein phosphatase 2A expression, which stimulates the production of mitochondrial reactive oxygen species (ROS) by releasing calcium from the ER. This protein also activates the Toll-like receptor-4 and the NF- $\kappa$ B pathway, which increase the production of TNF- $\alpha$  and IL-6. By contrast, NS3 has shown to be able to activate NADPH oxidase 2, which then generates ROS. Consequently, both mechanisms promote inflammation and other changes such as the proliferation of hepatic stellate cells, which promote hepatic fibrosis.<sup>31</sup>

The mechanisms by which HCV produces IR are not entirely clear. It has been suggested that the induction of IR occurs through the serine phosphorylation on the IRS-1 and impairment of the Akt signaling pathway. The mechanisms by which these are altered differ between genotypes, making IR genotype specific. As seen in the pathogenesis of steatosis, where genotype 1 is associated with the metabolic syndrome and genotype 3 is associated with the cytopathic effect of the virus, the IR is also related with the genotype. Although all HCV genotypes can induce IR, some genotypes seem to induce a more severe form of IR. People with genotype 1 or 4 are more prone than those with genotype 3 to develop IR.<sup>6</sup> Another study found that the severity of IR is greater in genotype 2a compared with 1.<sup>22</sup> Paziienza

and colleagues demonstrated that the core protein of genotype 3a downregulates peroxisome proliferator-activated receptor- $\gamma$  (PPAR $\gamma$ ) and upregulates the suppressor of cytokine signal 7 (SOCS-7), whereas the core protein of genotype 1b activates mTOR and SOCS-3; all these mechanisms cause the phosphorylation of the IRS-1 (figure 4). This discovery shows that the degradation of the IRS-1 in IR development is genotype specific.<sup>15,32</sup> Enhanced production of SOCS is related to phosphorylation of the Akt and Phosphatidylinositol 3 Kinase (PI3K) pathways, which inhibits the production of GLUT-4 and, therefore, glucose uptake. Furthermore, this family of suppressor cytokines has also been linked to the development of interferon resistance.<sup>31</sup>

### Hepatitis B infection and IR

Even though the introduction of a vaccine against the HBV has diminished the number of cases of HBV infection considerably, the burden of the disease continues to be high worldwide. About 350 million people worldwide are infected and at risk for progression of the disease.<sup>33</sup>

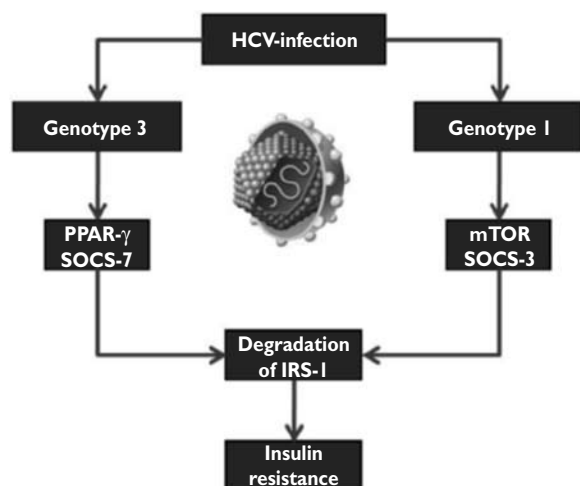
The reports on the relationship between T2DM and HBV infection are inconsistent. Some authors have found glycemic abnormalities in HBV-infected patients similar to those associated with HCV infection.<sup>34</sup> However, others have reported that IR and HBV infection are not related<sup>35,36</sup> and that HBV infection may be protective against the development of IR.<sup>37,38</sup> These inconsistencies indicate the need for prospective studies.

The association between HBV and the development of hepatic steatosis is also somewhat controversial. Wang and coworkers affirmed that HBV infection is not related to the development of liver steatosis,<sup>36</sup> whereas others have suggested that the accumulation of lipids in the liver occurs through several mechanisms that eventually activate SREBP-1 and PPAR $\gamma$ .<sup>39</sup> This last point is interesting because the pathogenesis of HCV-associated IR occurs through the inhibition of PPAR $\gamma$  and, as noted, HBV infection produces the exact opposite effect on PPAR $\gamma$ . Although other mechanisms responsible for IR development have not been studied thoroughly, this last point may explain the purported protective effect of HBV infection.

### Other chronic viral hepatitis infections and IR

The other two hepatotropic viruses that may cause chronic hepatitis are hepatitis D virus (HDV) and hepatitis E virus (HEV).

HDV infection has two epidemiological patterns: an endemic pattern in Mediterranean countries and a



PPAR $\gamma$ : peroxisome proliferator activator receptor- $\gamma$ , SOCS: suppressor of cytokine signaling, mTOR: mammalian target of rapamycin, IRS: insulin receptor substrate

**FIGURE 4: THE PHYSIOLOGY OF GENOTYPE-SPECIFIC INSULIN RESISTANCE**

nonendemic pattern in the USA and northern Europe. The effects of HDV infection are synergistic with those of HBV infection. Most of the time, HDV superinfection promotes an acute event of HBV infection; sometimes both infections can be sustained chronically. No studies have shown an association between HDV alone and IR, although it is known that HDV may accelerate HBV progression and damage.<sup>1</sup>

Little is known about the pathophysiology of HEV infection. It is known that this infection may cause both acute infection, similar to that of HAV infection, or chronic infection. It was believed that this infection was endemic in developing countries; however, recent studies have shown it to be an emerging disease in developed countries. HEV infection occurs mostly in immunosuppressed patients, especially in patients who have received a transplant, in HIV coinfecting patients, and in individuals undergoing chemotherapy for any reason. There are no reports of an association between HEV infection and IR, although as it causes liver damage through the chronic secretion of proinflammatory cytokines, it is possible that it also leads to the development of IR. Further study is needed to confirm this association.<sup>40</sup>

## Conclusion

Mexican population is facing a major health issue because of the increasing prevalence of T2DM. Several studies have shown a high incidence and prevalence, indicating that Mexican population is prone to developing the disease and that the impact has been increasing each year. Because some forms of chronic hepatitis are worsened by IR, chronic liver diseases will become an increasing problem in this population.

Only the chronic forms of viral hepatitis have been studied thoroughly in relation to their association with IR and T2DM. Although some studies have reported an association between HBV infection and IR, it seems more likely that they are not related and that the infection may even provide some protection against the metabolic alterations. Nevertheless, it is clear that prospective studies are needed. It is clear that HCV infection and IR are related, and that their effects are synergistic. IR may complicate HCV infection, possibly by causing interferon resistance (associated with failure of the hepatitis treatment) and progression of liver damage. On the other way around HCV infection may contribute to the development of T2DM and its complications.

The relationship between T2DM and the development of cirrhosis and hepatocellular carcinoma has been increasing worldwide<sup>41</sup> and in Mexico. Recent reports show that both, T2DM and cirrhosis are among the three most frequent causes of mortality.<sup>42</sup> This is why we encourage all physicians, regardless of their specialty, to consider screening for IR and hyperglycemia in all patients with viral hepatitis infection.

*Declaration of conflicts of interest:* The authors declare no conflict of interest.

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