

# Severe Insulin Resistance in a Treatment-Naive Chronic Hepatitis C Patient

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The association between diabetes mellitus (DM), insulin resistance, and chronic hepatitis C (CHC) has been noted but, as of yet, is not fully understood. Much of this discussion has centered on the relationship between type II DM and CHC infection that is presumed to be secondary to interferon therapy for CHC. We report the case of a man with CHC infection, DM, and the sudden, severe worsening of glycemic control. Here, we discuss a case of severe insulin resistance as a complication of CHC infection and review the associated literature.

## Case Report

A 43-year-old man with a history of type II DM, hypertension, normocytic anemia, depression, past cocaine abuse, and ongoing alcohol abuse began experiencing markedly increased insulin requirements and simultaneously began to suffer frequent florid episodes of diabetic ketoacidosis (DKA). During the ensuing year, he was hospitalized more than 10 times with florid acidemia due to ketonemia. Insulin requirements over the course of that year were exceptional; even after resolution of his diabetic ketoacidotic state, the patient required in excess of 1,500 units daily of a short-acting insulin administered via a sliding-scale system. Multiple attempts to introduce intermediate- or long-acting insulin preparations were unsuccessful and resulted in additional medical attention for symptomatic hypoglycemia. Due to a history of nonadherence, it was felt that the patient was not an appropriate candidate for an insulin pump. Prior to his first episode of DKA, the patient had been controlled on less than 100 units daily of an intermediate-acting insulin for approximately 4 years prior.

During the same year that the patient's DM became difficult to control, he was diagnosed with CHC infection, with an initial viral load of 517,000 copies. On the

assumption that his severe insulin resistance was associated with the underlying CHC infection, the patient was initiated on plasmapheresis. Although plasmapheresis resulted in a modest and transient improvement in blood sugar control, procedure-associated hypotension prevented the ongoing use of this therapy. The patient did not undergo liver biopsy, though he did have sonographic findings consistent with cirrhotic liver disease. He was not considered a candidate for antiviral therapy secondary to a history of alcohol and cocaine abuse and poor support system.

An anti-insulin receptor antibody level was obtained and found to be negative. HIV testing and hepatitis B testing, additionally, were negative. However, the patient, in several instances, tested positive for cocaine metabolites on toxicology screening.

## Discussion

Although advanced liver disease of any etiology may alter glucose metabolism, evidence is accruing to support a particular association between CHC and DM.<sup>1-3</sup> In the case of our patient, it remains unclear why the requirement for insulin increased so dramatically, particularly in the absence of interferon therapy. The majority of reported cases of DM in association with CHC appear to be of the noninsulin-dependent variety and occur during or after treatment with interferon therapy.<sup>4</sup> Our patient represents an unusual and, as of yet, unreported example of a severely insulin-resistant, treatment-naive CHC patient. To the best of our knowledge, this case report is the first reported case of severe insulin resistance seen in a patient with concurrent DM and CHC without interferon administration.

Several mechanisms have been suggested for the reported association between DM and CHC, including increased levels of tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) as well as changes at the cellular level induced by the hepatitis C virus. Increased activity of TNF- $\alpha$  results in a number of metabolic changes at the molecular level, including inhibition of insulin-stimulated tyrosine phosphorylation of insulin receptor and insulin receptor substrate-1 (IRS-

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1); stimulation of lipolysis; increased hepatic insulin resistance; and interference with beta-cell function.<sup>5</sup> The primary source of increased TNF- $\alpha$  appears to be due to hepatic macrophages that are upregulated as part of the immune response to the hepatitis C virus.<sup>6</sup> No TNF- $\alpha$  studies were conducted on this patient.

Further discussion has centered upon the intrinsic effect of the hepatitis C virus and subsequent mutation at the genetic level. Evidence has shown that the virus core may induce the suppressor of cytokine signaling-3 gene (SOCS3) to promote proteasomal degradation of IRS-1 and -2, thereby resulting in downregulation of insulin receptors.<sup>7</sup> Another proposed mechanism may include changes in the sterol regulatory element-binding protein synthesis pathway that may further alter insulin signaling.<sup>8</sup> Finally, extrahepatic effects of the virus may include injury to islet cells, leading to beta-cell dysfunction.<sup>9</sup> Whether this dysfunction is due to the effect of the virus itself or to the autoimmune reaction induced by the virus is unclear. Genetic studies were not conducted on this patient.

There is ongoing discussion regarding the factors that may influence the level of insulin resistance. Postulated factors include the extent of the level of liver injury and the genotype of the virus.<sup>1,2</sup> The patient underwent virologic and biochemical assessments, but he did not have histologic assessment of his liver injury.

In conclusion, there are multiple mechanisms under discussion that may explain insulin resistance in CHC infection. It appears likely that the hepatitis C virus has direct effects on hepatic genetic machinery, resulting in changes in glucose metabolism. Most current discussion has focused on interferon-induced type II DM, but in this treatment-naïve patient, the severe insulin resistance most likely appears to be due to effects of the hepatitis C virus itself. Although the patient's confirmed cocaine and alcohol abuse could have certainly contributed to his altered glucose handling, the degree and sustained nature of his insulin requirements make the attribution of his hyperglycemia and ketonemia to drug abuse alone appear to be less likely.

## References

1. Yazicioglu G, Isitan F, Altunbas H. Insulin resistance in chronic hepatitis C. *Int J Clin Pract.* 2004;58:1020-1022.
2. Hui JM, Sud A, Farrell GC. Insulin resistance is associated with chronic hepatitis C virus infection and fibrosis progression. *Gastroenterology.* 2003;125:1695-1704.
3. Shintani Y, Fujie H, Miyoshi H. Hepatitis C virus infection and diabetes: direct involvement of the virus in the development of insulin resistance. *Gastroenterology.* 2004;126:840-848.
4. Mehta SH, Brancati FL, Sulkowski MS, Strathdee SA, Szklo M, Thomas DL. Prevalence of type 2 diabetes mellitus among persons with hepatitis C virus infection in the United States. *Ann Intern Med.* 2000;133:592-599.
5. Greenberg AS, McDaniel ML. Identifying the links between obesity, insulin resistance and beta-cell function: potential role of adipocyte-derived cytokines in the pathogenesis of type 2 diabetes. *Eur J Clin Invest.* 2002;32:24-34.
6. Rehermann B. Interaction between the hepatitis C virus and the immune system. *Semin Liver Dis.* 2000;20:127-141.
7. Kawaguchi T, Yoshida T, Harada M. Hepatitis C virus downregulates insulin receptor substrates 1 and 2 through up-regulation of suppressor of cytokine signaling 3. *Am J Pathol.* 2004;165:1499-1508.
8. Su AI, Pezacki JB, Wodicka L, Brideau AD, Suppekova L, et al. Genomic analysis of hepatitis C infection. *Proc Natl Acad Sci.* 2002;99:15669-15674.
9. Narita R, Abe S, Kihara Y. Insulin resistance and insulin secretion in chronic hepatitis C virus infection. *J Hepatol.* 2004;41:132-138.

## Review

### Hepatitis C Virus and Insulin Resistance/Diabetes Mellitus

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The significance of insulin resistance with or without type II diabetes mellitus (DM) in the setting of hepatitis C virus infection is clear. Insulin resistance is associated with the progression of liver disease as well as a decreased responsiveness to therapy with pegylated interferon and ribavirin.<sup>1-5</sup> A recent multivariate analysis showed DM to be associated with progression of fibrosis.<sup>6</sup> The question of whether insulin resistance or DM is an extraintestinal manifestation of hepatitis C virus infection is less clear and does not fit into a simple cause-and-effect scenario. This complex relationship is further complicated by high baseline prevalence of obesity, metabolic syndrome, and DM in the general population, all of which are factors that can lead to chronic liver disease in the form of nonalcoholic steatohepatitis independent of hepatitis C virus infection.

Khokhar and Fischer describe a patient with preexisting DM who was found to have increasing insulin resistance with 10 hospital admissions for diabetic ketoacidosis over a 1-year period.<sup>7</sup> The patient was unable to tolerate

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long-acting insulin secondary to hypoglycemia, though his short-acting insulin requirement topped 1,500 units daily. During the course of these hospital admissions, the patient was diagnosed with chronic hepatitis C (CHC) infection and eventually cirrhosis via ultrasound. His clinical course was notably complicated by alcohol and cocaine abuse, which made treatment for his CHC prohibitive. Interestingly, he was given a trial of plasmapheresis in an effort to improve his glycemic control, which the authors speculated was secondary to his hepatitis C virus infection. The description of a "modest and transient improvement" in blood sugar control was attributed to the results of this entirely experimental procedure, and any efficacy was limited by the patient's inability to tolerate plasmapheresis secondary to hypotension.

Although this case report describes severe insulin resistance in the setting of DM and CHC infection without interferon therapy, it is not the first report to do so. Oliveira and coworkers recently compared 15 type II diabetic patients with CHC to 15 type II diabetic patients without CHC and demonstrated that insulin resistance is much higher in those patients with CHC, independent of age, body mass index (BMI), or gender.<sup>8</sup> Collectively, these studies highlight the known complex relationship between hepatitis C virus and host metabolism, a relationship that extends beyond a simple cause-and-effect paradigm with distinct differences between genotypes 1 and 4 versus genotypes 2 and 3.

Genotypes 1 and 4 comprise the majority of patients with CHC and have shown the greatest association with insulin resistance. Animal models using genotype 1 constructs have shown that hepatitis C virus infection without weight gain causes insulin resistance.<sup>9</sup> This finding was supported by a recent prospective study of 500 CHC patients compared to chronic hepatitis B patients, which demonstrated, on multivariate analysis, a significant correlation between genotype 1 or 4 infection and insulin resistance, both in the presence and absence of DM.<sup>5</sup> Interestingly, patients with genotype 2 or 3 hepatitis C virus infection showed only a 22% rate of insulin resistance versus the 40.1% seen in genotype 1 or 4 infected patients, despite similar BMIs, supporting other previous studies that showed low rates of insulin resistance in genotype 2 or 3 infected patients.<sup>1</sup>

The correlation of genotype 1 hepatitis C virus infection and insulin resistance (as well as hepatic steatosis) was also demonstrated by Vidali and colleagues.<sup>10</sup> This study highlighted the known differences between nongenotype 3 and genotype 3 infection, as the association of insulin resistance with CHC infection was seen only in nongenotype 3 patients on multivariate analysis. This difference is thought to be secondary to the direct metabolic effects of genotype 1 infection that result in hepatic steatosis/insu-

lin resistance versus the more viral cytopathic effects of genotype 3 infection.

Unraveling the intricate web of pathways involved in the development of insulin resistance is difficult. Increased circulating tumor necrosis factor- $\alpha$  and viral-mediated induction of suppressor of cytokine signaling (SOCS) 3 with subsequent downregulation of insulin receptor substrates 1 and 2 are potential mechanisms by which hepatitis C virus infection is thought to promote insulin resistance. Although far from straightforward, the association of insulin resistance with genotype 1 infection may partially explain the lower rates of sustained virologic response when compared to genotype 3 CHC, though certainly more evidence is required before this can be concluded.

The presence of advanced fibrosis or cirrhosis such as that seen in the patient treated by Khokhar and Fischer also has host metabolic effects that must be taken into account when assessing the effect of hepatitis C virus on insulin resistance. Cirrhosis, independent of hepatitis C virus, has been shown to adversely affect glucose homeostasis, and there is a clear association of cirrhosis with diabetes.<sup>11</sup> In fact, some studies show that upwards of 96% of patients with cirrhosis have insulin resistance with or without DM.<sup>12</sup> However, certain causes of cirrhosis are more often associated with insulin resistance, as shown by a study conducted by Zein and associates in which diabetes rates were 25% in patients with hepatitis C virus cirrhosis, 19% in patients with alcoholic liver disease, but only 1.3% in patients with cholestatic liver disease.<sup>13</sup> These findings would suggest that mechanisms leading to cirrhosis, and not the cirrhosis itself, are the cause of insulin resistance.

Both preexisting, insulin-requiring diabetes and cirrhosis existed in the patient treated by Khokhar and Fischer, though a stable insulin requirement of less than 100 units daily was noted prior to the diagnosis of hepatitis C virus infection. As the patient appeared to have recurring risk factors for hepatitis C virus infection, it is impossible to date his onset of infection. He certainly could have had long-term CHC that progressed to cirrhosis and led to increased insulin resistance/worsening of his diabetes, or a newer onset of infection could have tipped the scales, so to speak, into diabetic ketoacidosis requiring large volumes of insulin. Regardless of the cause, this patient's overall prognosis remains poor.

In summary, the number of patients infected with hepatitis C virus worldwide is increasing, as is the prevalence of obesity and metabolic syndrome. Hepatitis C virus infection, particularly of genotypes 1 and 4, may cause insulin resistance or may exacerbate preexisting insulin resistance. In turn, this may lead to more advanced liver disease and decreased responsiveness to therapy with

pegylated interferon and ribavirin. The mechanisms leading to insulin resistance in the setting of hepatitis C virus infection are currently under study and may lead to the development of new and improved therapies for CHC.

*The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or reflecting the view of the Department of the Army or the Department of Defense.*

## References

- Hui JM, Sud A, Farrell GC, Bandara P, Byth K, et al. Insulin resistance is associated with chronic hepatitis C virus infection and fibrosis progression. *Gastroenterology*. 2003;125:1695-1704.
- Hickman IJ, Powell EE, Prins JB, Clouston AD, Ash S, et al. In overweight patients with chronic hepatitis C, circulating insulin is associated with hepatic fibrosis: implications for therapy. *J Hepatol*. 2003;39:1043-1048.
- Romero-Gómez M, Del Mar Viloria M, Andrade RJ, Salmerón J, Diago M, et al. Insulin resistance impairs sustained response rate to peginterferon plus ribavirin in chronic hepatitis patients. *Gastroenterology*. 2005;128:636-641.
- Poustchi H, Negro F, Hui J, Cua IH, Brandt LR, et al. Insulin resistance and response to therapy in patients infected with chronic hepatitis C virus genotypes 2 and 3. *J Hepatol*. 2008;48:28-34.
- Moucari R, Asselah T, Cazals-Hatem D, Voitot H, Boyer N, et al. Insulin resistance in chronic hepatitis C: association with genotypes 1 and 4, serum hepatitis C virus RNA level, and liver fibrosis. *Gastroenterology*. 2008;134:416-423.
- Kita Y, Mizukoshi E, Takamura T, Sakurai M, Takata Y, et al. Impact of diabetes mellitus on prognosis of patients infected with hepatitis C virus. *Metabolism*. 2007;56:1682-1688.
- Khokhar O, Fischer J. Severe insulin resistance in a treatment-naive chronic hepatitis C patient. *Gastroenterol Hepatol*. 2008;4:567-568.
- Oliveira BR, Magalhães O, Furlanetto TW, Bertoluci MC. Increased insulin resistance and hyperinsulinemia in patients with type 2 diabetes and chronic hepatitis C. *Diabetes Res Clin Pract*. 2008;79:e11-e12.
- Shintani Y, Fujie H, Miyoshi H, Tsutsumi T, Tsukamoto K, et al. Hepatitis C virus infection and diabetes: direct involvement of the virus in the development of insulin resistance. *Gastroenterology*. 2004;126:840-848.
- Vidali M, Tripodi MF, Ivaldi A, Zampino R, Occhino G, et al. Interplay between oxidative stress and hepatic steatosis in the progression of chronic hepatitis C. *J Hepatol*. 2008;48:399-406.
- Hickman IJ, Macdonald GA. Impact of diabetes on the severity of liver disease. *Am J Med*. 2007;120:829-834.
- Holstein A, Hinze S, Thiessen E, Plaschke A, Egberts EH. Clinical implications of hepatogenous diabetes in liver cirrhosis. *J Gastroenterol Hepatol*. 2002;17:677-681.
- Zein NN, Abdulkarim AS, Wiesner RH, Egan KS, Persing DH. Prevalence of diabetes mellitus in patients with end-stage liver cirrhosis due to hepatitis C, alcoholic or cholestatic disease. *J Hepatol*. 2000;32:209-217.