Hepatitis Monthly 2009; 9(2): 92-94

EDITORIAL

On Diabetes Mellitus and Hepatitis C Infection: Should the Patients be Screened?

Bagher Larijani, Fatemeh Bandarian

Endocrinology and Metabolism Research Center, Tehran University of Medical Sciences, Tehran, Iran
emrc@tums.ac.ir

The relationship between diabetes mellitus (DM) and hepatitis C virus (HCV) infection has been challenging in recent decade in the world and has been studied from several aspects. Despite of these efforts, yet there is no general consensus on patient screening. The majority of studies have focused on the development of DM in patients with chronic HCV infection and a few of them have investigated the incidence rate of HCV infection in patients with DM. The prevalence of hepatitis C is almost 3% among the world's population; the infection would progress to chronic hepatitis in 55%–80% of them [1]. In Iran, the seroprevalence of HCV among blood donors has been reported as 0.12% [2]; the rate however is 30% among imprisoned intravenous drug abusers [3]. The incidence of type II DM among HCV infected patients with chronic disease has been reported variously from 23% to 62% [4-8].

Studies have revealed that the prevalence of insulin resistance in patients infected with the genotype 3 virus is less than other genotypes [5-9]. Insulin resistance and diabetes are more likely to develop in patients infected with HCV genotype 4 which is the predominant genotype in the Middle Eastern countries [10]. In spite of this report, in Iran, subtypes 1a and 3a are the predominant subtypes, whereas subtypes 1b and 4 are less common [11]. Therefore, we anticipate less prevalence of insulin resistance and diabetes in HCV-infected patents in Iran.

The prevalence of DM among HCV-infected patients has been reported as 18.3% in Iran [12]. In that study, family history of DM, chronic hepatitis and cirrhosis were the only independent risk factors of DM as confirmed in previous studies [13]. Furthermore, other studies found that male gender, fibrosis stage and body mass index (BMI) are other risk factors for development of DM in patients with chronic hepatitis C [13, 14]. The prevalence of DM in general population of Iran has been estimated to be 4.6%–10% [15-18]. It is obvious that the prevalence of DM in HCV-infected patients is more than that in the general population—even in our population which has a low incidence of DM in HCV-infected patients. This difference, however, was not confirmed in some studies [19, 20]. It has been shown that HCV-infected patients have a two-fold risk for development of DM [21]. This risk was estimated to be 3.8 in HCV-positive individuals older than 40 years in National Health and Nutrition Examination Survey III (NHANES III) [22]. This risk also increases further in HCV-infected patients with known DM risk factors [23]. The seroprevalence of hepatitis C among type 2 diabetic patients ranges from 1.4% to 36% in various studies [19, 20, 24-27].

Although it remains to be determined whether HCV infection leads to DM or *vice versa*, based on the current available evidence, it seems that this is the HCV infection which causes DM. As the main type of diabetes in patients with chronic hepatitis C is type 2 DM, it seems that insulin resistance might

have a significant role in this process [5]. Several ongoing studies attempt to investigate the molecular mechanisms involved in diabetogenic effects of HCV. Multiple pathways have been suggested for these effects. HCV by increasing tumor necrosis factor alpha (TNF-α) levels—which is an important factor in the inflammatory process in HCV infection—and changing the insulin signaling pathways could result in insulin resistance [28-30]. TNF-α has a significant role in the development of insulin resistance in these patients. HCV also could inhibit the insulin signaling pathway through up regulation of "suppressor of cytokine signaling 3" (SOC3) [31] and reduction in "signal transducer and activator of transcription 3" (STAT-3), which has a key role in glucose homeostasis and insulin sensitivity [32].

Other possible mechanisms include direct cytotoxic effects of HCV on pancreatic islet cells [33], immune-mediated mechanisms [34], elevated levels of monocyte chemotactic protein 1 and CXCL10 [35, 36]. In addition, HCV-infected islet cells could induce an immune response (through CXCL10 gene) that finally results in islet cell dysfunction [33]. Hepatic steatosis which is observed in more than half of HCV-infected patients may further cause insulin resistance. Furthermore, insulin resistance and diabetes, by themselves, can result in steatosis and liver fibrosis in patients with chronic HCV infection [37].

However, as hyperglycemia and diabetes are independent risk factors for the response to treatment [20] in patients with chronic HCV infection, early diagnosis and control of DM in these patients could result in better care and outcome of HCV patients [8]. So, early screening of patients with chronic HCV infection for detection of diabetes and glucose metabolism disorders is recommended to improve patients' outcome although better control of HCV could prevent development of DM in these patients. Routine screening for HCV in diabetic patients, however, is not recommended due to its low incidence, but it should be considered in case of raise in liver enzymes.

References

1. NIH Consensus Statement on Management of Hepatitis C: 2002. *NIH Consens State Sci Statements*. 2002;**19**(3):1-46.
2. Alavian SM, Gholami B, Masarrat S. Hepatitis C risk factors in Iranian volunteer blood donors: a case-control study. *J Gastroenterol Hepatol*. 2002;**17**(10):1092-7.
3. Alizadeh AH, Alavian SM, Jafari K, Yazdi N. Prevalence of hepatitis C virus infection and its related risk factors in drug abuser prisoners in Hamedan—Iran. *World J Gastroenterol*. 2005;**11**(26):4085-9.
4. Caronia S, Taylor K, Pagliaro L, *et al*. Further evidence for an association between non-insulin-dependent diabetes mellitus and chronic hepatitis C virus infection. *Hepatology*. 1999;**30**(4):1059-63.
5. Mason AL, Lau JY, Hoang N, *et al*. Association of diabetes mellitus and chronic hepatitis C virus infection. *Hepatology*. 1999;**29**(2):328-33.
6. Grimbert S, Valensi P, Levy-Marchal C, *et al*. High prevalence of diabetes mellitus in patients with chronic hepatitis C. A case-control study. *Gastroenterol Clin Biol*. 1996;**20**(6-7):544-8.
7. Chehadeh W, Abdella N, Ben-Nakhi A, Al-Arouj M, Al-Nakib W. Risk factors for the development of diabetes mellitus in chronic hepatitis C virus genotype 4 infection. *J Gastroenterol Hepatol*. 2009;**24**(1):42-8.
8. Aytaman A, McFarlane SI. Uncovering glucose abnormalities in people with hepatitis C infection: should oral glucose tolerance test become a standard of care? *Am J Gastroenterol*. 2008;**103**(8):1941-3.
9. Knobler H, Schihmanter R, Zifroni A, Fenakel G, Schattner A. Increased risk of type 2 diabetes in noncirrhotic patients with chronic hepatitis C virus infection. *Mayo Clin Proc*. 2000;**75**(4):355-9.
10. Ray SC, Arthur RR, Carella A, Bukh J, Thomas DL. Genetic epidemiology of hepatitis C virus throughout egypt. *J Infect Dis*. 2000;**182**(3):698-707.
11. Samimi-Rad K, Nategh R, Malekzadeh R, Norder H, Magnius L. Molecular epidemiology of hepatitis C virus in Iran as reflected by phylogenetic analysis of the NS5B region. *Journal of medical virology*. 2004;**74**(2):246-52.
12. Alavian SM, Hajarizadeh B, Nematizadeh F, Larijani B. Prevalence and determinants of diabetes mellitus among Iranian patients with chronic liver disease. *BMC Endocr Disord*. 2004;**4**(1):4.
13. Fabrizi F, Messa P, Martin P, Takkouche B. Hepatitis C virus infection and post-transplant diabetes mellitus among renal transplant patients: a meta-analysis. *Int J Artif Organs*. 2008;**31**(8):675-82.
14. Sanchez-Perez B, Aranda Narvaez JM, Santoyo Santoyo J, *et al*. Influence of immunosuppression and effect of hepatitis C virus on new onset of diabetes mellitus in liver transplant recipients. *Transplant Proc*. 2008;**40**(9):2994-6.
15. Larijani B, Abolhasani F, Mohajeri-Tehrani MR, Tabtabaie O. Prevalence of diabetes mellitus in iran in 2000. *Iranian Journal of Diabetes & Lipid Disorders*. 2005;**4**(3):75-83
16. Azizi F, Rahmani M, Emami H, *et al*. Cardiovascular risk factors in an Iranian urban population: Tehran lipid and glucose study (phase 1). *Soz Praventivmed*. 2002;**47**(6):408-26.
17. Azizi F, Navai L. Study of the prevalence of diabetes and impaired glucose tolerance in rural areas of Tehran province. *Hakim* 2001;**2**(4):112-8.
18. Amini M, Afshin-Nia F, Bashardoost N, Aminorroaya A, Shahparian M, Kazemi M. Prevalence and risk factors of diabetes mellitus in the Isfahan city population (aged 40 or over) in 1993. *Diabetes Res Clin Pract*. 1997;**38**(3):185-90.
19. Costa LM, Mussi AD, Brianeze MR, Souto FJ. Hepatitis C as a risk factor for diabetes type 2: lack of evidence in a hospital in central-west Brazil. *Braz J Infect Dis*. 2008;**12**(1):24-6.
20. Gulcan A, Gulcan E, Toker A, Bulut I, Akcan Y. Evaluation of risk factors and seroprevalence of hepatitis B and C in diabetic patients in Kutahya, Turkey. *J Investig Med*. 2008;**56**(6):858-63.
21. White DL, Ratziu V, El-Serag HB. Hepatitis C infection and risk of diabetes: a systematic review and meta-analysis. *J Hepatol*. 2008;**49**(5):831-44.
22. 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**(8):592-9.
23. Mehta SH, Brancati FL, Strathdee SA*, et al*. Hepatitis C virus infection and incident type 2 diabetes. *Hepatology*. 2003;**38**(1):50-6.
24. Simo R, Hernandez C, Genesca J, Jardi R, Mesa J. High prevalence of hepatitis C virus infection in diabetic patients. *Diabetes Care*. 1996;**19**(9):998-1000.
25. Aytaman A, Bahtiyar G, McFarlane S. Interferon-a therapy and Type 1 diabetes mellitus in patients with hepatitis C: pathophysiologic insights. *Therapy*. 2005;**2**(3):439-46.
26. Shah IA, Shah SWA, Hayat Z, Haq NU, Noor M. Impaired glucose tolerance in HCV/HBV cirrhosis. *J Postgrad Med Inst*. 2000;**14**(1):68-72.
27. Ali SS, Ali IS, Aamir AH, Jadoon Z, Inayatullah S. Frequency of hepatitis C infection in diabetic patients. *J Ayub Med Coll Abbottabad*. 2007;**19**(1):46-9.
28. Kawaguchi T, Yoshida T, Harada M*, et al*. Hepatitis C virus down-regulates insulin receptor substrates 1 and 2 through up-regulation of suppressor of cytokine signaling 3. *Am J Pathol*. 2004;**165**(5):1499-508.
29. Noto H, Raskin P. Hepatitis C infection and diabetes. *J Diabetes Complications*. 2006;**20**(2):113-20.
30. Knobler H, Schattner A. TNF-{alpha}, chronic hepatitis C and diabetes: a novel triad. *QJM*. 2005;**98**(1):1-6.
31. Inoue H, Ogawa W, Ozaki M*, et al*. Role of STAT-3 in regulation of hepatic gluconeogenic genes and carbohydrate metabolism in vivo. *Nat Med*. 2004;**10**(2):168-74.
32. Hui JM, Sud A, Farrell GC*, et al*. Insulin resistance is associated with chronic hepatitis C virus infection and fibrosis progression [corrected]. *Gastroenterology*. 2003;**125**(6):1695-704.
33. Masini M, Campani D, Boggi U*, et al*. Hepatitis C virus infection and human pancreatic beta-cell dysfunction. *Diabetes Care*. 2005;**28**(4):940-1.
34. Antonelli A, Ferri C, Fallahi P*, et al*. Type 2 diabetes in hepatitis C-related mixed cryoglobulinaemia patients. *Rheumatology (Oxford)*. 2004;**43**(2):238-40.
35. Antonelli A, Ferri C, Ferrari SM, Colaci M, Sansonno D, Fallahi P. Endocrine manifestations of hepatitis C virus infection. *Nat Clin Pract Endocrinol Metab*. 2009;**5**(1):26-34.
36. Antonelli A, Ferri C, Ferrari SM, Colaci M, Fallahi P. Immunopathogenesis of HCV-related endocrine manifestations in chronic hepatitis and mixed cryoglobulinemia. *Autoimmun Rev*. 2008;**8**(1):18-23.
37. El-Serag HB, Richardson PA, Everhart JE. The role of diabetes in hepatocellular carcinoma: a case-control study among United States Veterans. *Am J Gastroenterol*. 2001;**96**(8):2462-7.