

Medical Writers' Circle

a series of articles

written by medical
professionals about
the management
and treatment of
Hepatitis C

José Azócar, MD

Medical Director
Northgate Medical,
Springfield, MA

Adult Onset Diabetes Mellitus in Hepatitis C Virus Infection

Since the hepatitis C virus (HCV) was identified, numerous epidemiological studies have reported a higher prevalence of type 2 diabetes mellitus (DM2) in subjects infected by HCV (1-3). Although the initial associations of diabetes and liver disease were made in subjects with advanced liver disease (1-4), more recent reports have described an increase in DM2 before the development of advanced liver cirrhosis (5). Furthermore, the epidemiological link has been established between DM2 and HCV infection, rather than other causes of liver diseases, such as hepatitis B viral infection (HBV) and alcohol abuse (6). The increase in the number of cases of DM2 among people infected by HCV has been reported to be as much as four times higher than in the general population (7). Other factors, such as obesity, which is characterized by a high body mass index (BMI); advanced age and family history of diabetes, are also associated

with the higher incidence of diabetes in the HCV-infected population (8-10).

In addition to infection by HCV, other viral agents such as coxsackie virus, congenital rubella and cytomegalovirus have been proposed as being capable of triggering the development of diabetes mellitus type 1 (DM1) or juvenile diabetes mellitus (11-13). It is unclear as to why some patients with HCV infection develop diabetes. However, it is tempting to speculate that the HCV infection is able to trigger autoimmune mechanism(s) against the insulin producing pancreatic beta cells in susceptible individuals.

The mechanisms proposed for the development of DM1 following viral infection are generally based on findings of specific humoral and cellular immunity against viral antigens as well as insulin producing pancreatic cells in some diabetic children (11-15). In HCV infection, the use of interferon alfa, a well-known immune enhancer for the treatment of HCV infection,

has been observed to be associated with the development of diabetes (16, 17). Contrary to DM1 that occurs mainly in children, the diabetes associated with HCV infection has so far been observed mainly in adults (1-3). This may be due to the low incidence of HCV infection in children since the mechanisms of infection by HCV are associated with adult lifestyle. For example, sharing needles by intravenous drug users, tattooing and sexually transmitted diseases (18-20). Furthermore, risks for transmission of HCV infection in children, such as blood transfusion, have been dramatically reduced since the introduction of the screening tests for HCV antibodies in blood donors.

Presently, it is unknown what may make an individual susceptible to the development of diabetes after a viral infection. A genetic susceptibility for the development of DM1 has been well documented in some individuals (21). Whatever the trigger mechanism(s) for the development of diabetes in

susceptible individuals, DM1 or insulin dependent diabetes has been associated with genetic markers known as human histocompatibility antigens (HLA). Resistance to the development of diabetes has also been associated with HLA antigens.

A better understanding of the immunogenetics of HCV infection is needed. During the last few years, we have learned that the viral and clinical outcome of HCV infection is associated with the HLA type of the individual. Most HCV infected individuals develop chronic HCV infection, which is characterized by the presence of the HCV ribonucleic acid (RNA) in the blood and a high probability for the development of chronic liver disease including liver cirrhosis and liver cancer. However, some 20-30% of the infected individuals develop an immune response that is able to spontaneously overcome the infection (22, 23). These individuals become negative for HCV RNA and do not develop HCV-associated liver diseases. All of the above findings suggest that the genetic makeup of an individual is a determining factor in the outcome of the HCV infection, in which the development of diabetes is one of the possible outcomes.

References:

1. Taliani G, Poliandri G, Clementi G et al. Chronic Hepatitis C and diabetes mellitus. *J Hepatol* 1992 16 (Suppl): S116
2. Allison M E, Wreghitt T, Palmer CR et al. Evidence for a link be-

tween hepatitis C infection and diabetes mellitus in a cirrhotic population. *J Hepatol* 1994; 21: 1135-9.

3. Knobler H, Stagnaro-Green A, Wallestein S. Higher incidence of diabetes in liver transplant recipients with hepatitis C. *J Clin Gastroenterol* 1998; 26: 30-3.
4. Bigan DL, Pennington JJ, Carpenter A, et al. Hepatitis C-related cirrhosis: a predictor of diabetes after liver transplantation *Hepatology* 2000; 32:87-90.
5. Knobler H, Schihmanter R, Zifroni A et al. Increased risk of type 2 diabetes in noncirrhotic patients with chronic hepatitis C virus infection. *Mayo Clin Proc.* 2000; 75:355-9.
6. Fraser G, Harman I, Meller N, et al. Diabetes mellitus is associated with chronic hepatitis C but not chronic hepatitis B infection. *Isr J Med Sci* 1996; 32:526-30.
7. Custro N, Carroccio A, Ganci A et al. Glycemic homeostasis in chronic viral hepatitis and liver cirrhosis. *Diabetes Metab.* 27(4 Pt 1):476-81.
8. Kruzynska YT, Home PI, McIntyre N. Relationship between insulin sensitivity, insulin secretion and glucose intolerance in cirrhosis. *Hepatology* 1991; 14:1093-111
9. Monto A, Alonzo J, Watson JJ, et al. Steatosis in chronic hepatitis C: Relative contributions of obesity, diabetes mellitus, and alcohol. *Hepatology*; 36:729-36.
10. Petit JM, Bour JB, Galland-Jos C, et al. Risk factors for diabetes mellitus and early insulin resistance in chronic hepatitis C. *J Hepatol.* 2001; 35:279-83.
11. Gamble DR, Kinsley ML, Fitzgerald MG et al. Viral antibodies in diabetes mellitus. *BMJ* 1969; 1:627-30.
12. Banatvala JE, Bryant J, Scherthaner G, et al. Coxsackie B, mumps, rubella and cytomegalovirus specific IgM responses in patients with juvenile-onset insulin-dependent diabetes mellitus in Britain, Austria and Australia. *Lancet* 1985; 1:1409-12.
13. Woon JW, Austin M, Onodera T et al. Isolation of a virus from the pancreas of a child with diabetic ketoacidosis. *N Eng J Med.* 1979; 300: 1173-9.
14. Lonnrot M, Korpela K, Knip M et al. Enterovirus infection as a risk factor for beta-cell autoimmunity in a prospectively observed birth cohort: the Finnish Diabetes Predic-

tion and Prevention Study. *Diabetes.* 2000; 49:1314-8.

15. Atkinson MA, Bowman MA, Campbell L et al. Cellular immunity to a determinant common to glutamate decarboxylase and coxsackie virus in insulin-dependent diabetes. *J Clin Invest.* 1994; 94:2125-9.
16. Uto H, Matsuoka H, Murata M et al. A case of chronic hepatitis C developing insulin-dependent diabetes mellitus associated with various autoantibodies during interferon therapy. *Diabetes Res Clin Pract.* 2000; 49:101-6.
17. Fabris P, Betterle C, Greggio NA et al. F. Insulin-dependent diabetes mellitus during alpha-interferon therapy for chronic viral hepatitis. *J Hepatol.* 1998; 28:514-7. Review.
18. Haley RW, Fischer RP. Commercial tattooing as a potentially important source of hepatitis C infection. *Clinical epidemiology of 626 consecutive patients unaware of their hepatitis C serologic status. Medicine (Baltimore)* 2001; 80(2):134-51.
19. Conry-Cantilena C, VanRaden M, Gible J et al. Routes of infection, viremia, and liver disease in blood donors found to have hepatitis C virus infection. *N Engl J Med* 1996; 334:1691-6.
20. Alter MJ, Coleman PJ, Alexander WJ et al. Importance of heterosexual activity in the transmission of hepatitis B and non-A, non-B hepatitis. *Jama* 1989; 262:1201-5.
21. Todd JA, Mijovic C, Fletcher J, et al. Identification of susceptibility loci for insulin-dependent diabetes mellitus by trans-racial gene mapping. *Nature.*1989; 13:587-9.
22. Thio CL, Thomas DL, Goedert JJ et al. Racial differences in HLA class II associations with hepatitis C virus outcomes. *J Infect Dis* 2001; 184:16-21.
23. Azocar J, Clavijo O, Yunis EJ. MHC Class II Genes in HCV viral clearance of Hepatitis C Infected Hispanic patients. *Hum Immun.* In Press.

Medical Writers' Circle

is a program of the Hepatitis C Support Project.

The Mission of the Hepatitis C Support Project is to offer support to those who are affected by the hepatitis C Virus (HCV) and HIV/HCV coinfection.

Support is provided broadly, through information and education, as well as access to support groups. The (Project) seeks to serve the HCV community as well as the general public.

Visit our web site at www.hcvadvocate.org