

Glucose Abnormalities in Patients with Hepatitis C Virus Infection

Epidemiology and pathogenesis

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Hepatitis C virus (HCV) infection is a major cause of chronic liver disease, affecting ~3% of the world's population (1,2). The disease is characterized by silent onset in most infected individuals (3), and recent studies indicate that the rate of progression to advanced liver disease might be lower than previously assumed (4–6). If we consider that most HCV-infected persons are <50 years of age, the burden of disease associated with HCV infection is likely to increase during the next 10–20 years as this cohort reaches the age at which complications of chronic liver disease typically occur (7).

The prevalence of type 2 diabetes in people living in the developed world ranges from 2.0 to 9.4% (8), rising to 12.3% in U.S. adults between 40 and 74 years of age (9). The decline in mortality of people with diabetes, together with the rapidly increasing frequency of obesity and the sedentary lifestyle of the population portends a dramatic increase in the prevalence rates of type 2 diabetes (10–11). Therefore, both HCV liver disease and type 2 diabetes are two already prevalent diseases that will probably continue to increase in the next decades.

HCV mainly affects the liver, but also several tissues outside the liver have been reported to be involved, resulting in a wide spectrum of extrahepatic manifestations (12–14). During the last decade, it

has been hypothesized that diabetes could be one more of these extrahepatic conditions attributable to HCV infection. This raises the intriguing question of whether the rise in HCV infection is contributing to the increasing prevalence of type 2 diabetes.

In this review, the available information concerning the epidemiological association between HCV infection and diabetes is summarized. In addition, the physiopathological mechanisms related to the association between HCV and diabetes are also discussed.

PREVALENCE OF HCV ANTIBODIES IN DIABETIC POPULATION

— The prevalence of HCV antibodies in the type 2 diabetic population ranges between 1.78 and 12.1% (15–22) (more detailed information is shown in Table 1 of the online appendix [available at <http://care.diabetesjournals.org>]). Several cross-sectional studies have found a higher prevalence of HCV antibodies in type 2 diabetic patients than expected in the general population (15–17,21). In addition, all studies in which a control group of nondiabetic subjects had been included found a significantly higher prevalence of HCV antibodies in type 2 diabetic patients (17–19,22). By contrast, the prevalence of anti-HCV antibodies in type 1 diabetes does not exceed the rate of

prevalence expected in the general population (15,17,18,20,23). The clinical consequence of the high prevalence of HCV infection in the type 2 diabetic population is that mild elevations of serum transaminases should not be automatically attributed to fatty liver disease, and, therefore, testing for HCV infection in diabetic patients with an abnormal liver function tests should be mandatory (17).

Several studies have shown that the higher prevalence of HCV infection in diabetic patients is not related to the main risk factors associated with HCV seropositivity (17,18,22,24). In addition, the prevalence of chronic hepatitis B virus (HBV) infection, which shares similar epidemiological factors of transmission with HCV, has not been found higher in type 2 diabetic patients than in the general population (19,21,22,25,26). There is insufficient information concerning the duration of HCV infection and diabetes to enable us to assess their temporal relationship. In a previous study we reported that all patients with HCV infection and type 2 diabetes who had a history of prior blood transfusion had received their transfusions 10–20 years before the onset of diabetes (17). Similarly, Grimbirt et al. (27) reported that diabetes occurred 18 years after HCV infection. Supporting this data, Mason et al. (19) found that 52% of persons with both HCV infection and type 2 diabetes had risk factors for HCV infection before the onset of diabetes, whereas none had risk factors for HCV infection after the onset of diabetes. In addition, Knobler et al. (28) reported that when the temporal sequence was characterized in anti-HCV-positive diabetic patients, the diagnosis of HCV preceded the diagnosis of diabetes in 73% of cases. The absence of any particular epidemiologic factor for HCV infection among the diabetic population and the evidence suggesting that HCV infection antedates diabetes supports the idea that HCV might cause or predispose infected individuals to diabetes. However, no definitive conclusion can be made until a prospective study has been conducted.

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Abbreviations: GADA, GAD antibody; HBV, hepatitis B virus; HCV, hepatitis C virus; HOMA, homeostasis model assessment; IFG, impaired fasting glucose; IL, interleukin; OGTT, oral glucose tolerance test; PTDM, posttransplantation diabetes mellitus; TNF, tumor necrosis factor.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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Table 1—Prevalence of diabetes among people with HCV infection in comparison with other liver diseases not HCV, taking into account the degree of liver damage (chronic hepatitis or cirrhosis)

	Chronic hepatitis				P
	HCV infection (n)	Prevalence of diabetes	Other liver diseases not HCV (n)	Prevalence of diabetes	
Özyilkan et al. (42)	86	25.5	114 HCV (–)	7.8	0.001
Mangia et al. (43)*†	102	4.9	22 HBV, 14 OH	0.0	NS
Mason et al. (19)†‡	212	18.4	144 HBV	9.7	0.02
Knobler et al. (28)*†	45	33	88 HBV	12	0.004
Ryu et al. (21)‡§	68	23.5	157 HBV	8.2	0.002
Lecube et al. (39)*†	380	17	92 HCV (–)	7	0.03

	Cirrhosis				P
	HCV infection (n)	Prevalence of diabetes	Other liver diseases not HCV (n)	Prevalence of diabetes	
Allison et al. (44)¶#	34	50	66 HCV (–)	9	<0.0001
Özyilkan et al. (42)	50	38.0	133 HCV (–)	12.0	0.00006
del Olmo et al. (45)**	112	23.3	75 OH, 51 HBV	25.3, 27.5	NS, NS
Mangia et al. (43)*	157	34.3	38 HBV, 49 OH	31.5, 28.5	NS, NS
Guerrero et al. (46)‡#	28	28.6	47 HCV (–)	10.6	<0.05
Mason et al. (19)‡	145	33.1	88 HBV	20.5	0.04
Caronia et al. (47)**	1151	23.6	181 HBV	9.4	0.0002
Zein et al. (37)‡¶	64	25	78 CLD, 53 OH	1.3, 19	0.0001, NS
Bigam et al. (48)*¶	110	29	53 HBV, 115 CLD	6, 4	<0.001, <0.001
Ryu et al. (21)‡	28	25	102 HBV, 43 OH	13.7, 30.2	NS, NS
Garrido et al. (49)*#	50	36	50 HCV (–)	18	<0.05
Thuluvath et al. (32)*¶#	97	19.6	194 HCV (–)	11.5	NS
Parolin et al. (50)¶	36	36.11	70 HCV (–)	25.71	NS
Lecube et al. (39)*†	118	40	52 HCV (–)	36	NS

Data are percent, unless otherwise indicated. Diagnosis of type 2 diabetes according to *fasting plasma glucose >126 mg/dl, †fasting plasma glucose >140 mg/dl; ‡fasting plasma glucose >216 mg/dl, **treatment with hypoglycemic agents or insulin. Diagnosis of liver damage according to †liver biopsy, §not specified, ¶end-stage liver disease in pretransplant situation. #Both groups equipared by age, sex, and Child-Pugh degree. CLD, cholestasis liver disease; HBV, chronic HBV infection; OH, alcohol hepatic disease.

PREVALENCE OF TYPE 2 DIABETES AMONG HCV-INFECTED PATIENTS

— The Third National Health and Nutrition Examination Survey (NHANES III) showed that among persons ≥ 40 years of age, those with HCV infection were more than three times more likely than those without HCV infection to have type 2 diabetes (adjusted odds ratio [OR] 3.77) (26,29). No association between type 1 diabetes and HCV infection was detected. In addition, hepatitis B virus (HBV) infection did not increase the risk for type 2 diabetes. Another large community-based study also found that anti-HCV positivity was strongly associated with type 2 diabetes in those aged 35–49 years (OR 3.3 [95% CI 1.4–8.0]) (30). HCV status has also been independently related to the diagnosis of diabetes in American Indian women who were receiving prenatal care (31).

Ageing, obesity, family history of diabetes, African-American origin, and HIV coinfection are recognized influencing factors associated with diabetes

development among HCV-infected patients (32–35). By contrast, the relationship between type 2 diabetes and HCV genotypes remains controversial (18,19,24,28,36–39), and larger studies are needed to definitively answer the question of whether there is any specific HCV genotype that predisposes to or protects from diabetes development in HCV-infected patients. Since glucose abnormalities are more frequent in patients with advanced liver disease (40), the extent of liver damage should be carefully considered when evaluating the prevalence of diabetes among HCV-infected patients. Therefore, although it seems that community-identified HCV infection is not usually associated with cirrhosis (41), the lack of liver biopsy is a significant limiting factor in all the large community studies mentioned above.

Chronic hepatitis

The prevalence of type 2 diabetes in patients with chronic HCV infection with-

out cirrhosis ranges from 4.9 to 33% (19,21,24,28,39,42,43) (Table 1). An increased prevalence of diabetes among HCV-infected patients with chronic hepatitis compared with either subjects with other chronic liver disease or the general population has been consistently reported (19,21,28,39,42,43).

To further explore the link between HCV infection and diabetes, we have recently evaluated the prevalence not only of diabetes but also the impaired fasting glucose (IFG) in a large cohort of HCV-infected patients, taking into account the degree of liver damage (39). In HCV-positive patients with chronic hepatitis, we observed a threefold increase in the prevalence of glucose abnormalities in comparison with HCV-negative subjects with other liver diseases (32 vs. 12%). Both diabetes and IFG were significantly more prevalent among anti-HCV-positive patients (17 vs. 7%, $P = 0.03$ and 15 vs. 5%, $P = 0.009$, respectively). By contrast, differences were not observed

between cirrhotic patients with or without HCV infection. In addition, a multivariate analysis showed that HCV infection was independently related to glucose abnormalities in patients with chronic hepatitis (OR 4.26 [95% CI 2.03–8.93]) but not in cirrhotic patients (39). These findings suggest that the genuine connection between HCV infection and diabetes is initiated at the early stages of hepatic disease. In this regard, it should be emphasized that in HCV-infected patients with chronic hepatitis and normal transaminases, we detected a fivefold-higher prevalence of diabetes than that found among anti-HCV-negative patients (24 vs. 5%, $P = 0.003$) (39).

Liver cirrhosis

When HCV-infected patients with cirrhosis are evaluated, the prevalence of type 2 diabetes is higher than reported in patients with chronic hepatitis, and it ranges from 19.6 to 50% (19,21,32,37,39,42–50) (Table 1). However, differences between anti-HCV-positive and -negative patients are not always present. Discrepancies among studies may be explained by the selection of the control population. In this regard, it should be noted that although patients with cirrhosis due to HCV or HBV infection, as well as those patients with alcoholic liver cirrhosis, have increased risk of the development of diabetes, this is not the same for patients with cholestatic liver disease (Table 1). Although cirrhotic patients without cholestatic liver diseases have higher prevalence of diabetes than patients with chronic hepatitis, it was not significantly different between cirrhotic patients with or without HCV infection (21,32,37,39,43,45,50). Therefore, it seems that the presence of advanced liver disease is an even stronger diabetogenic factor than HCV infection itself. In other words, diabetes associated with HCV infection is less of a determinate than the effect of hepatic cirrhosis on glucose metabolism.

HCV infection as a risk factor for posttransplant diabetes

Posttransplantation diabetes mellitus (PTDM) is a common medical condition arising during the follow-up of renal and liver transplant recipients, which has increased in incidence over the last decade (51). A number of risk factors related to the recipient, the immunosuppressive agents used to prevent and treat rejection, and donor source have

been described as independent risk factors for the development of PTDM (52–55). Chronic HCV infection is currently one of the leading indications of orthotopic liver transplantation (56). The prevalence of PTDM in HCV-infected liver transplantation recipients ranges from 40 to 64%, significantly higher than the prevalence reported in transplanted patients for other causes of liver failure (37,48,55,57). In addition, HCV has been found to be an independent risk factor for diabetes development after transplantation (37,55). Furthermore, Baid et al. (55) reported a close temporal relationship between the recurrence of HCV hepatitis in the allograft and the onset of PTDM in approximately half of the HCV-positive patients with PTDM.

HCV infection may reach an incidence of 50% in patients with end-stage renal disease (58), and it has also been identified as an independent risk factor for predicting the development of PTDM after renal transplantation (58–60). The unadjusted OR for developing PTDM in HCV-infected renal transplant recipients ranges between 1.58 and 16.5 across published studies (61).

All these data reinforce the hypothesis that HCV is the cause rather than the consequence of diabetes. In addition, the link between HCV and diabetes may contribute substantially to the detrimental role of HCV on patient and graft survival after liver transplantation and/or renal transplantation (62).

HCV-infected patients as a high-risk group for type 2 diabetes development

The high prevalence of both diabetes and IFG found in HCV-infected patients suggests that they should be considered a high-risk group for diabetes development, and, therefore, a screening for diabetes should be recommended. Although the criteria recommended by the Expert Committee on the Diagnosis and Classification of Diabetes are mainly based on fasting blood glucose, there are some high-risk groups for type 2 diabetes development in which an oral glucose tolerance test (OGTT) is recommended for the diagnosis of glucose abnormalities. We performed an OGTT on 50 anti-HCV-positive patients and 50 anti-HCV-negative patients with chronic hepatitis in whom diabetes had not been diagnosed using the fasting blood glucose. Both groups were matched by age, BMI, and

sex. OGTT enabled us to diagnose 18% new cases of diabetes and 30% of impaired glucose tolerance in anti-HCV-positive patients in comparison with the criteria using baseline glucose, these figures being significantly higher than those obtained in anti-HCV-negative patients (4 and 18%, respectively) (39). These findings suggest that OGTT should be adopted as the primary screening test for diabetes in HCV-infected patients with chronic hepatitis.

PATHOGENIC MECHANISMS INVOLVED IN THE DIABETOGENIC ACTION OF HCV

HCV as a trigger of β -cell autoimmunity

HCV infection has been associated with immunologic disorders such as cryoglobulinemia, glomerulonephritis, thyroiditis, and Sjögren syndrome (12–14). It might be then thought that HCV could trigger an immune reaction against the β -cell that leads to diabetes. In this case, a possible pathogenic mechanism could be molecular mimicry, because HCV shares regional amino acid homology with GAD autoantibody (GADA), one of the main islet cell antigens (63).

Although the behavior of diabetes associated with HCV chronic hepatitis is similar to type 2 diabetes, HCV could contribute to latent autoimmune diabetes in adults, a slowly evolving autoimmune insulinitis that represents between 4 and 34% of all diagnosed diabetes in adults (64). However, none of the few studies that have examined the presence of islet cell antibodies in HCV-infected patients have found an increased frequency. Hieronimus et al. (65) found only one positive case of GADA among 47 HCV-infected patients. Mason et al. (19) detected GADA in 2 of 25 HCV-infected diabetic patients, but type 1 diabetic patients were also included in their study. We did not observe statistically significant differences in the prevalence of GADA, anti-tyrosine phosphatase autoantibody, or islet cell autoantibody among 26 HCV-infected diabetic patients, 277 HCV-infected nondiabetic patients, and 273 sex- and age-matched control subjects (66). Similarly, other investigators have not found any significant differences in the frequency of islet cell antibodies among diabetic patients with or without HCV infection (28,67–69).

Taken together, these results indicate a lack of association between HCV infection and β -cell autoimmunity. Therefore, autoimmunity can be ruled out as a mechanism involved in diabetes associated with HCV infection.

Direct damage to β -cell

Although HCV is an hepatotropic virus (70), it has also been identified in extra-hepatic tissues, including kidney, lung, testis, peripheral blood mononuclear cells, and also in the pancreas (71–73). Laskus et al. (72) documented the presence of HCV-RNA in the pancreas acinar cells and in the epithelial cells of the pancreatic duct. Recently, Masini et al. (74) detected virus-like particles in pancreatic β -cells from HCV-positive donors associated with morphological changes and a reduced in vitro glucose-stimulated insulin release. However, we have not found a decrease in β -cell function in nondiabetic anti-HCV-positive patients in comparison with anti-HCV-negative patients with chronic hepatitis. By contrast, in HCV-infected subjects, we observed an increase of insulin secretion assessed by homeostasis model assessment (HOMA)- β and the glucagon test (75). Moreover, as mentioned above, the clinical features of diabetes associated with HCV infection are similar to type 2 but not type 1 diabetes. Therefore, it seems that an impairment in insulin secretion due to β -cell damage by HCV itself is not a primary mechanism accounting for diabetes associated with HCV infection.

Iron overload

Type 2 diabetes is a condition that is frequently associated with elevated levels of serum ferritin (76,77). Indeed, high serum ferritin concentration is associated with insulin resistance and with increased risk of type 2 diabetes in healthy people (78,79). Given that several reports have shown an increase of ferritin levels in patients with HCV infection (80–83), it could be speculated that iron stores are the link between HCV infection and diabetes. In fact, hepatic iron deposition may cause insulin resistance by interfering with the ability of insulin to suppress hepatic glucose production (84). A descriptive analysis based on the Third National Health and Nutrition Examination Survey data found that subjects with anti-HCV

antibodies had a higher mean serum ferritin level than subjects without HCV antibodies (85). However, the magnitude of this association has not been fully established because most available studies are uncontrolled (80–82). In addition, the reported controlled studies are also difficult to interpret because they have not taken into account confounding factors such as sex distribution, alcohol consumption, severity of liver damage (cirrhosis versus chronic hepatitis), hemochromatosis gene mutations, or the presence of diabetes (49,86,87). It should be emphasized that serum ferritin is an acute-phase reactant that may be affected by inflammation (88,89), and there is accumulating evidence to suggest that in type 2 diabetes a low grade of inflammation does exist (90,91). After considering the confounding factors mentioned above, we have provided evidence that among HCV-infected patients, only anti-HCV-positive patients with diabetes have high ferritin concentrations (92). In fact, anti-HCV-positive patients without diabetes did not show higher ferritin concentrations than control subjects. Furthermore, diabetes but not HCV infection was independently related to ferritin levels in multiple regression analyses, thus suggesting that diabetes rather than HCV infection itself is the main factor associated with the increased ferritin concentration detected in patients with HCV infection. On this basis, it would seem that iron stores do not play a key role in the pathogenesis of diabetes associated with HCV infection. In this regard, Petit et al. (24) did not find any correlation between insulin resistance determined by the HOMA and hepatic iron histological grading.

Hepatic steatosis

Hepatic steatosis is more frequent in HCV than in HBV infection (93) and occurs in >50% of patients with chronic C hepatitis (94,95). Mild steatosis has been associated with high BMI and visceral obesity (95,96), whereas moderate to severe steatosis is more likely to be caused directly by the virus, especially the genotype 3 virus (97–99). Hepatic steatosis may contribute to HCV-associated diabetes by impairing the insulin's ability to lower hepatic glucose production (98,99) and favoring liver fibrosis (24,95,100). Alternatively, both insulin resistance and diabetes can adversely affect the course of chronic hepatitis C and lead to enhanced

steatosis, steatohepatitis, and liver fibrosis (95,101–103).

Proinflammatory cytokines

The relation between inflammation and insulin resistance in the pathogenesis of type 2 diabetes is well known (90,104). Cytokines such as tumor necrosis factor (TNF)- α and interleukin (IL)-6 have been related, both in the general population and in diabetic patients, not only to insulin resistance but also with the risk of developing type 2 diabetes (105–108).

TNF- α can induce insulin resistance by diverse mechanisms, particularly by inhibiting the tyrosine phosphorylation of the insulin receptor substrate-1 (IRS-1) (109), thus leading to impaired insulin action on peripheral tissues and hepatic glucose uptake (110). TNF- α signals through at least two known cell surface receptors (TNFR1 and TNFR2), and membranous shedding of these receptors reflects activation of the TNF system (111,112). Several reports have shown an increase in serum levels of TNF- α and its receptors in HCV-infected patients (38,113–118). In addition, high concentrations of TNFR1 and TNFR2 with a close relationship between the histological scores of hepatocellular damage and the degree of liver inflammation have been found in the livers of these subjects (114–117). Moreover, liver biopsy specimens from nondiabetic HCV patients have revealed significant impairments in the insulin signaling pathways (119), which are strikingly similar to TNF- α effects (120,121). Activation of the TNF- α system in HCV-infected patients could be related to the immune response that is characteristically mediated by the Th1-cells (122). These lymphocytes secrete γ -interferon as the predominant cytokine (123), which is able to enhance the production of TNF- α and its two receptors by macrophages (124), including those infiltrating the liver from systemic circulation and the Kupffer cells (125,126). Shintani et al. (127), using a transgenic mouse model that specifically expressed the HCV core protein in hepatocytes, have given direct experimental evidence of HCV infection in the development of insulin resistance, which finally leads to the development of type 2 diabetes. In addition, in this study the role of TNF- α in the pathogenesis of the HCV-associated insulin resistance state is strongly suggested.

IL-6 is a multifunctional cytokine produced by different cellular types including hepatocytes (128,129). It pro-

motes insulin resistance by inhibiting the transcription of the GLUT4, the IRS-1, and the peroxisome proliferator-activated receptor (130,131). In healthy subjects, IL-6 has been related to the risk of developing type 2 diabetes (107). In HCV-infected patients, IL-6 levels have been found to be higher than in the healthy population (132,133) and correlate with the histological severity of inflammation (132).

Recently, we have evaluated the initial mechanisms involved in diabetes development in HCV infection, and we have provided evidence that nondiabetic HCV-infected patients have higher insulin resistance than patients with other chronic liver diseases and that this was associated with the activation of the TNF- α system and high IL-6 levels (75). By contrast, as mentioned above, HOMA- β as well as insulin and C-peptide responses after the intravenous glucagons test were significantly higher in anti-HCV-positive patients than in anti-HCV-negative patients (75). Therefore, it seems that insulin resistance mediated by proinflammatory cytokines, but not a deficit in insulin secretion, is the main pathogenic mechanism involved in the pathogenesis of diabetes associated with HCV infection.

INSULIN RESISTANCE AND LIVER FIBROSIS

— An increase of the fasting insulin and a decrease in insulin sensitivity have been observed in HCV-infected subjects with a moderate or severe degree of hepatic fibrosis (75,134,135). However, HCV-infected patients without fibrosis (fibrosis stage 0) also present higher insulin resistance than patients with primary biliary cirrhosis with different degrees of hepatic fibrosis (fibrosis stages 1–3) and healthy individuals (36). These data suggest that HCV is capable of producing an increase in insulin resistance, even before a minimal degree of hepatic fibrosis is present. Alternatively, insulin resistance has been described as an independent factor in predicting the presence of hepatic fibrosis in HCV-infected patients (36). In fact, several studies have reported that both insulin resistance and diabetes can adversely affect the course of chronic hepatitis C leading to enhanced steatosis and liver fibrosis (24,28,95,96,100,101,134) and even increase the risk of hepatocellular carcinoma (136,137). Notably, Romero-Gómez et al. (138) and D'Souza et al. (139), have recently shown that insulin

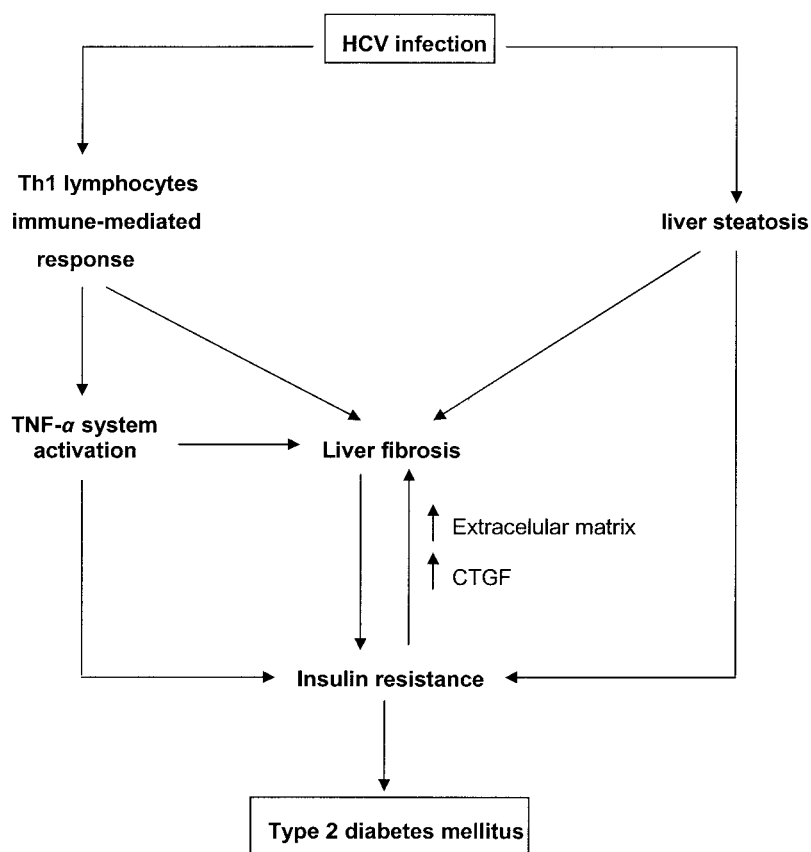


Figure 1— Mechanisms involved in the diabetogenic action of HCV. HCV infection induces an immune response characteristically mediated by Th1-cells. These lymphocytes secrete γ -interferon as the predominant cytokine, which is able to enhance the production of TNF- α by macrophages. At the same time, HCV directly causes liver fat deposition. All three events could be potential risk factors for liver fibrosis. Liver fibrosis, TNF system, and liver steatosis are also associated with the development of insulin resistance and type 2 diabetes. Alternatively, hyperinsulinemia can adversely affect the course of liver fibrosis through both the proliferation of stellate cells, thus enhancing the secretion of extracellular matrix, and the expression of the connective tissue growth factor (CTGF).

resistance is an independent predictor of a poor response to antiviral therapy in chronic hepatitis C infection.

Several mechanisms could explain the role of insulin resistance in the development of hepatic fibrosis (Fig. 1). Hyperinsulinemia per se stimulates the proliferation of stellate cells, thus enhancing the secretion of extracellular matrix (140). Moreover, both insulin and hyperglucemia are able to stimulate the expression of the connective tissue growth factor, a cytokine involved in the progression of fibrosis in the liver and other tissues (141,142).

CONCLUSIONS— HCV infection and type 2 diabetes are two common disorders with a high impact on health worldwide. A high prevalence of type 2 diabetes among HCV-infected patients

with chronic hepatitis has been consistently reported, and there is growing evidence to support the concept that HCV infection is a risk factor for developing type 2 diabetes. However, further studies to confirm this issue are needed. The specific mechanisms by which HCV leads to type 2 diabetes are not fully understood, but it seems that an increase of insulin resistance associated with both steatosis and the overproduction of proinflammatory cytokines could play a crucial role. These mechanisms are initiated in the early stages of hepatic disease. The knowledge of the pathogenic mechanisms involved in diabetes associated with HCV infection will enable us not only to further identify those patients at high risk of developing diabetes but also to select the best therapeutic option.

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