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 transmision 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, Grimbert 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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Received for publication 18 October 2005 and accepted in revised form 14 February 2006.

Additional information for this article can be found in an online appendix at http://care.diabetesjournals.org.

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.

DOI: 10.2337/dc05-1995

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				
	HCV infection (*n*)	Prevalence of diabetes	Other liver diseases not HCV (*n*)	Prevalence of diabetes	*P*
Özylilkan 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				
	HCV infection (*n*)	Prevalence of diabetes	Other liver diseases not HCV (*n*)	Prevalence of diabetes	*P*
Allison et al. (44)¶#	34	50	66 HCV (−)	9	<0.0001
Özylilkan 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, cholostatic 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, hepitidis 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 without 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 than 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 cryoglobulinemia, glomerulonephritis, thyroiditis, and Sjöegren 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 extrahepatic 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 hepatocelular 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.

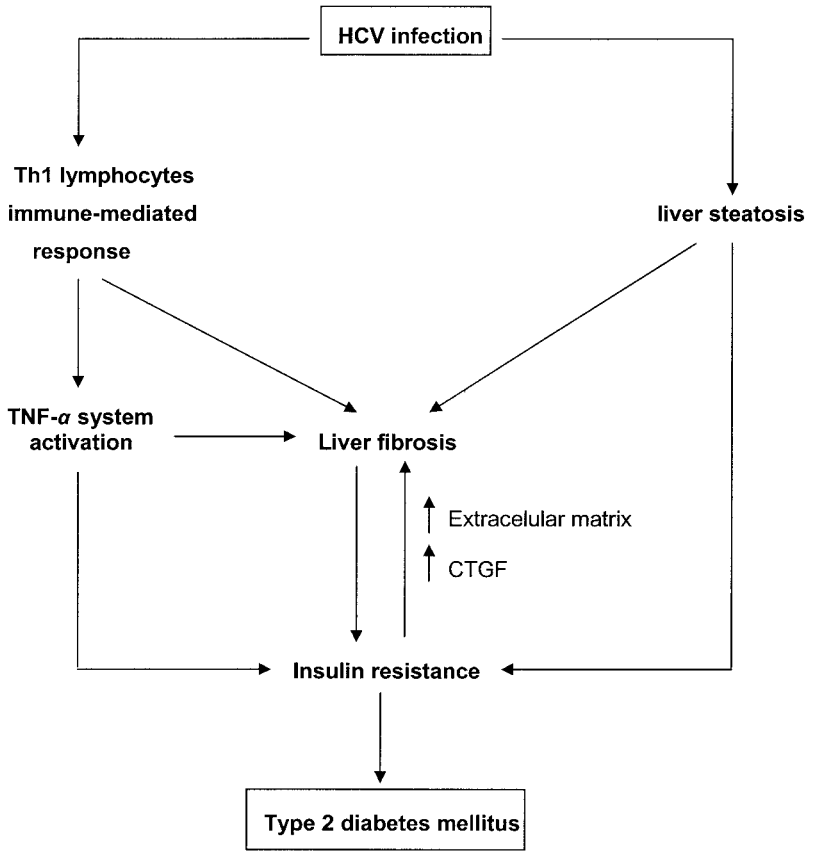

Figure 1— *Mechanisms involved in the diabetogenic action of HCV. HCV infection induces an immune response characteristically mediated by Th1-cells. These lymphocytes secrete γ-interferon as the predominant cytokine, which is able to enhance the production of TNF-α by macrophages. At the same time, HCV 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 extracelular matrix, and the expression of the connective tissue growth factor (CTGF).*

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 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 extracelular 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.

Acknowledgments— This study was supported by grants from the Fundació La Marató TV3 (99/2,610), Novo Nordisk Pharma (01/0,066), and the Instituto de Salud Carlos III (G03/212, C03/08, and C03/02).

References

1. World Health Organization and Viral Hepatitus Prevention Board: Global surveillance and control of hepatitis C: Report of a WHO Consultation organized in collaboration with the Viral Hepatitis Prevention Board, Antwerp, Belgium. *J Viral Hepat* 6:35–47, 1999
2. Ray Kim W: Global epidemiology and burden of hepatitis C. *Microbes Infect* 4: 1219–1225, 2000
3. Alberti A, Chemello L, Benvegnù L: Natural history of hepatitis C. *J Hepatol* 31 (Suppl. 1):17–24, 1999
4. Seeff LB, Miller RN, Rabkin CS, Buskell-Bales Z, Straley-Eason KD, Smoak BL, Johnson LD, Lee SR, Kaplan EL: 45-year follow-up of hepatitis C virus infection in healthy young adults. *Ann Intern Med* 132:105–111, 2000
5. Alter HJ, Seeff LB: Recovery, persistence, and sequelae in hepatitis C virus infection: a perspective on long-term outcome. *Semin Liv Dis* 20:17–35, 2000
6. Salomon JA, Weinstein MC, Hammitt JK, Goldie SJ: Empirically calibrated model of hepatitis C virus infection in the United States. *Am J Epidemiol* 156: 761–773, 2002
7. Alter MJ, Kruszon-Moran D, Nainan OV, McQuillan GM, Gao F, Moyer LA, Kaslow RA, Margolis HS: The prevalence of hepatitis C virus infection in the United States, 1988 through 1994. *N Engl J Med* 341:556–562, 1999
8. King H, Aubert RE, Herman WH: Global burden of diabetes, 1995–2025: prevalence, numerical estimates, and projections. *Diabetes Care* 21:1414–1431, 1998
9. Harris MI, Flegal KM, Cowie CC, Eberhardt MS, Goldstein DE, Little RR, Wiedmeyer HM, Byrd-Holt DD: Prevalence of diabetes, impaired fasting glucose, and impaired glucose tolerance in U.S. adults: the Third National Health and Nutrition Examination Survey, 1988–1994. *Diabetes Care* 21:518–524, 1998
10. Kuzmarski RJ, Flegal KM, Campbell SM, Johnson CL: Increasing prevalence of overweight among US adults: the National Health and Nutrition Examination Surveys, 1960 to 1991. *JAMA* 272:205–211, 1994
11. Wild S, Roglic G, Green A, Sicree R, King H: Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care* 27:1047–1053, 2004
12. Gumbert SC, Chopra S: Hepatitis C: a multifaceted disease: Review of extrahepatic manifestations (Review). *Ann Intern Med* 123:615–620, 1995
13. Cacoub P, Poynard T, Ghillani P, Charlotte F, Olivi M, Piette JC: Extrahepatic manifestations of chronic hepatitis C: MULTIVIRC Group: multidepartment Virus C. *Arthritis Rheum* 42:2204–2212, 1999
14. Nocente R, Ceccanti M, Bertazzoni G, Cammarota G, Silveri NG, Gasbarrini G: HCV infection and extrahepatic manifestations (Review). *Hepatogastroenterology* 50:1149–1154, 2003
15. Özyilkan E, Erbas T, Simsek H, Telatar F, Kayhan B, Telatar H: Increased prevalence of hepatitis C virus antibodies in patients with diabetes mellitus. *J Intern Med* 235:283–284, 1994
16. Gray H, Wreghitt T, Stratton IM, Alexander GJ, Turner RC, O'Rahilly S: High prevalence of hepatitis C infection in Afro-Caribbean patients with type 2 diabetes and abnormal liver function test. *Diabet Med* 12:244–249, 1995
17. Simó R, Hernández C, Genescà J, Jardí R, Mesa J: High prevalence of hepatitis C virus infection in diabetic patients. *Diabetes Care* 19:998–1000, 1996
18. Rudoni S, Petit JM, Bour JB, Aho LS, Castaneda A, Vaillant G, Verges B, Brun JM: HCV infection and diabetes mellitus: influence of the use of finger stick devices on nosocomial transmission. *Diabetes Metab* 25:502–505, 1999
19. Mason AL, Lau JY, Hoang N, Qian K, Alexander GJ, Xu L, Guo L, Jacob S, Regenstein FG, Zimmerman R, Everhart JE, Wasserfall C, Maclaren NK, Perrillo RP: Association of diabetes mellitus and chronic hepatitis C virus infection. *Hepatology* 29:328–333, 1999
20. Sotiropoulos A, Peppas TA, Skliros E, Apostolou O, Kotsini V, Pappas SI: Low prevalence of hepatitis C virus infection in Greek diabetic patients. *Diabet Med* 16:250–252, 1999
21. Ryu JK, Lee SB, Hong SJ, Lee S: Association of chronic hepatitis C virus infection and diabetes mellitus in Korean patients. *Korean J Intern Med* 16:18–23, 2001
22. Okan V, Araz M, Aktaran S, Karsligil T, Meram I, Bayraktaroglu Z, Demirci F: Increased frequency of HCV but not HBV infection in type 2 diabetic patients in Turkey. *Int J Clin Pract* 56:175–177, 2002
23. Cerutti F, Palomba E, Sacchetti C, Gay V, Versace A, Tovo PA: Anti-HCV antibodies in a population of insulin-dependent diabetic children and adolescents. *Diabetes Care* 22:1587–1588, 1999
24. Petit JM, Bour JB, Galland-Jos C, Minello A, Verges B, Guiguet M, Brun JM, Hillon P: Risk factors for diabetes mellitus and early insulin resistance in chronic hepatitis C. *J Hepatol* 35:279–283, 2001
25. Boluda Monzo S, Mesa Manteca J, Obiols Alfonso G, Simó Canonge R: [Surface antigen of hepatitis B in diabetes mellitus] (Letter). *Med Clin (Barc)* 92:397, 1989 [article in Spanish]
26. 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* 133:592–599, 2000
27. Grimbert S, Valensi P, Levy-Marchal C, Perret G, Richardet JP, Raffoux C, Trinchet JC, Beaugrand M: High prevalence of diabetes mellitus in patients with chronic hepatitis C: a case-control study. *Gastroenterol Clin Biol* 20:544–548, 1996
28. 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* 75:355–359, 2000
29. 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 (Letter). *Hepatology* 33:1554, 2001
30. Wang CS, Wang ST, Yao WJ, Chang TT, Chou P: Community-based study of hepatitis C virus infection and type 2 diabetes: an association affected by age and hepatitis severity status. *Am J Epidemiol* 158:1154–1160, 2003
31. Wilson C: Hepatitis C infection and type 2 diabetes in American-Indian women. *Diabetes Care* 27:2116–2119, 2004
32. Thuluvath PJ, John PR: Association between hepatitis C, diabetes mellitus, and race: a case-control study. *Am J Gastroenterol* 98:438–441, 2003
33. Mehta SH, Brancati FL, Strathdee SA, Pankow JS, Netski D, Coresh J, Szklo M, Thomas DL: Hepatitis C virus infection and incident type 2 diabetes. *Hepatology* 38:50–56, 2003
34. Mehta SH, Moore RD, Thomas DL, Chaisson RE, Sulkowski MS: The effect of HAART and HCV infection on the developement of hyperglycemia among HIV-infected persons. *J Acquir Immune Defic Syndr* 33:577–584, 2003
35. Butt AA, Fultz SL, Kwoh CK, Kelley D, Skanderson M, Justice AC: Risk of diabetes in HIV infected veterans pre- and post-HAART and the role of HCV coinfection. *Hepatology* 40:115–119, 2004
36. Hui JM, Sud A, Farrell GC, Bandara P, Byth K, Kench JG, McCaughan GW, George J: Insulin resistance is associated with chronic hepatitis C virus infection and fibrosis progression. *Gastroenterol-*

ogy 125:1695–1704, 2003
37. 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, alcohol, or cholestatic disease. *J Hepatol* 32: 209–217, 2000
38. Knobler H, Zhornicky T, Sandler A, Haran N, Ashur Y, Schattner A: Tumor necrosis factor-alpha-induced insulin resistance may mediate the hepatitis C virus-diabetes association. *Am J Gastroenterol* 98:2751–2756, 2003
39. Lecube A, Hernández C, Genescà J, Esteban JI, Jardí R, Simó R: High prevalence of glucose abnormalities in patients with hepatitis C virus infection: a multivariate analysis considering the liver injury. *Diabetes Care* 27:1171–1175, 2004
40. Kruszynska YT, Home PD, McIntyre N: Relationship between insulin sensitivity, insulin secretion and glucose tolerance in cirrhosis. *Hepatology* 14:103–111, 1991
41. Rodger A, Roberts S, Lanigan A, Bowden S, Brown T, Crofts N: Assessment of long-term outcomes of community-acquired hepatitis C infection in a cohort with sera stored from 1971 to 1975. *Hepatology* 32:582–587, 2000
42. Özylilkan E, Arslan M: Increased prevalence of diabetes mellitus in patients with chronic hepatitis C virus infection. *Am J Gastroenterol* 91:1480–1481, 1996
43. Mangia A, Schiavone G, Lezzi G, Marmo R, Bruno F, Villani MR, Cascavilla I, Fantasia L, Andriulli A: HCV and diabetes mellitus: evidence for a negative association. *Am J Gastroenterol* 93:2363–2367, 1998
44. Allison ME, Wreghitt T, Palmer CR, Alexander GJ: Evidence for a link between hepatitis C virus infection and diabetes mellitus in a cirrhotic population. *J Hepatol* 21:1135–1139, 1994
45. del Olmo JA, Serra MA, Rodrigo JM: Liver cirrhosis and diabetes mellitus (Letter). *J Hepatol* 24:645, 1996
46. Guerrero Igea FJ, Garrido Serrano A, Lepe Jiménez JA, Palomo Gil S: [High prevalence of diabetes mellitus in patients with chronic hepatitis C virus infection] (Letter). *Med Clin (Barc)* 111:676–677, 1998 [article in Spanish]
47. Caronia S, Taylor K, Pagliaro L, Carr C, Palazzo U, Petrick J, O'Rahilly S, Shore S, Tom BD, Alexander GJ: Further evidence for an association between non-insulin-dependent diabetes mellitus and chronic hepatitis C virus infection. *Hepatology* 30:1059–1063, 1999
48. Bigam DL, Pennington JJ, Carpentier A, Wanless IR, Hemming AW, Croxford R, Greig PD, Lilly LB, Heathcote JE, Levy GA, Cattral MS: Hepatitis C-related cirrhosis: a predictor of diabetes after liver transplantation. *Hepatology* 32:87–90, 2000
49. Garrido Serrano A, Guerrero Igea FJ, Lepe Jiménez JA, Palomo Gil S, Grilo Reina A: Hyperinsulinemia in cirrhotic patients infected with hepatitis C virus infection. *Gastroenterol Hepatol* 24:127–131, 2001
50. Parolin MB, Zaina FE, Araujo MV, Kupka E, Coelho JC: Prevalence of type 2 diabetes mellitus in Brazilian liver transplant candidates: negative association with HCV status. *Transplant Proc* 36:2774–2775, 2004
51. Cosio FG, Pesavento TE, Osei K, Henry ML, Ferguson RM: Post-transplant diabetes mellitus: increasing incidence in renal allograft recipients transplanted in recent years. *Kidney Int* 59:732–737, 2001
52. Boudreaux JP, McHugh L, Canafax DM, Ascher N, Sutherland DE, Payne W, Simmons RL, Najarian JS, Fryd DS: The impact of cyclosposporine and combination immunosuppression on the incidence of posttransplant diabetes in renal allograft recipients. *Transplantation* 44: 376–381, 1987
53. Vesco L, Busson M, Bedrossian J, Bitker MO, Hiesse C, Lang P: Diabetes mellitus after renal transplantation: characteristics, outcome, and risk factors. *Transplantation* 61:1475–1478, 1996
54. Kasiske BL, Snyder JJ, Gilbertson D, Matas AJ: Diabetes mellitus after kidney transplantation in the United States. *Am J Tranplant* 3:178–185, 2003
55. Baid S, Cosimi AB, Farrell ML, Schoenfeld DA, Feng S, Chung RT, Tolkoff-Rubin N, Pascual M: Posttransplant diabetes mellitus in liver transplant recipients: risk factors, temporal relationship with hepatitis C virus allograft hepatitis, and impact on mortality. *Transplantation* 72:1066–1072, 2001
56. Gilbert JR, Pascual M, Rubin RH, Delmonico FL, Cosimi AB: Evolving trends in liver transplantation: an outcome and charge analysis. *Transplantation* 67:246–253, 1999
57. Knobler H, Stagnaro-Green A, Wallenstein S, Schwartz M, Roman SH: Higher incidence of diabetes in liver transplant recipients with hepatitis C. *J Clin Gastroenterol* 26:30–33, 1998
58. Gentil MA, Rocha JL, Pereira P, Algarra GR, Lopez R: High incidence of diabetes mellitus after kidney transplant in patients with hepatitis C (Letter). *Nephron* 82:85, 1999
59. Gursoy M, Guvener N, Koksal R, Karavelioglu D, Baysal C, Ozdemir N, Boyacioglu S, Bilgin N, Erdal R: Impact of HCV infection on development of post-transplantation diabetes mellitus in renal allograft recipients. *Transplant Proc* 32:561–562, 2000
60. Yildiz A, Tütüncu Y, Yazici H, Acalla V, Kayacan SM, Sever MS, Carin M, Karsidag K: Association between hepatitis C virus infection and development of post-transplantation diabetes mellitus in renal transplant recipients. *Transplantation* 74:1109–1113, 2002
61. Fabrizi F, Lampertico P, Lunghi G, Mangano S, Aucella F, Martin P: Review article: hepatitis C virus infection and type-2 diabetes mellitus in renal diseases and transplantation (Review). *Aliment Pharmacol Ther* 21:623–632, 2005
62. Abbott KC, Lentine KL, Bucci JR, Agodoa LY, Koff JM, Holtzmuller KC, Schnitzler MA: Impact of diabetes and hepatitis after kidney transplantation on patients who are affected by hepatitis C virus. *J Am Soc Nephrol* 15:3166–3174, 2004
63. Honeyman MC, Stone NL, Harrison LC: T-cell epitopes in type 1 diabetes autoantigen tyrosine phosphatase IA2: potential for mimicry with rotavirus and other envirommental agents. *Mol Med* 4:231–239, 1998
64. Turner R, Stratton I, Horton V, Manley S, Zimmet P, Mackay IR, Shattock M, Bottazzo GF, Holman R: UKPDS 25: autoantibodies to islet-cell cytoplasm and glutamic acid decarboxilase for prediction of insulin requirement in type 2 diabetes: UK Prospective Diabetes Study Group. *Lancet* 350:1288–1293, 1997
65. Hieronimus S, Fredenrich A, Tran A, Benzaken S, Fenichel P: Antibodies to GAD in chronic hepatitis C patients (Letter). *Diabetes Care* 20:1044, 1997
66. Piquer S, Hernández C, Enríquez J, Ross A, Esteban JI, Genesca J, Bonifacio E, Puig-Domingo M, Simó R: Islet cell and thyroid antibody prevalence in patients with hepatitis C virus infection: effect of treatment with interferon. *J Lab Clin Med* 137:38–42, 2001
67. Ando H, Nagai Y, Yokohama M, Takamura T, Kobayashi K: Antibodies to GAD in diabetic patients with chronic hepatitis C (Letter). *Diabet Med* 15:797, 1998
68. Harman-Boehm I, Zingman L, Hilzenrat N: No evidence for anti-islet autoimmunity in diabetes mellitus associated with chronic hepatitis C infection (Letter). *Hepatology* 30:342, 1999
69. Betterle C, Fabris P, Zanchetta R, Pedini B, Tositti G, Bosi E, de Lalla F: Autoimmunity againts pancreatic islets and other tissues before and after interferon-alpha therapy in patients with hepatitis C virus chronic infection. *Diabetes Care* 23:1177–1181, 2000
70. Nouri-Aria KT, Sallie R, Sangar D, Alexander GJ, Smith H, Byrne J, Portmann B, Eddleston AL, Williams R: Detection of genomic and intermediate replicative strands of hepatitis C virus in liver tissue by in situ hybridization. *J Clin Invest* 91: 2226–2234, 1993

71. Muller HM, Pfaff E, Goeser T, Kallinowski B, Solbach C, Theilmann L: Peripheral blood leukocytes serve as a possible extrahepatic site for hepatitis C virus replication. *J Gen Virol* 74:669–676, 1993
72. Laskus T, Radkowski M, Wang LF, Vargas H, Rakela J: Search for hepatitis C virus extrahepatic replication sites in patients with acquired immunodeficiency syndrome: specific detection of negative-strand viral RNA in various tissues. *Hepatology* 28:1398–1401, 1998
73. Yan FM, Chen AS, Hao F, Zhao XP, Gu CH, Zhao LB, Yang DL, Hao LJ: Hepatitis C virus may infect extrahepatic tissues in patients with hepatitis C. *World J Gastroenterol* 6:805–811, 2002
74. Masini M, Campani D, Boggi U, Menicagli M, Funel N, Pollera M, Lupi R, Del Guerra S, Bugliani M, Torri S, Del Prato S, Mosca F, Filipponi F, Marchetti P: Hepatitis C virus infection and human pancreatic β-cell dysfunction (Brief Report). *Diabetes Care* 28:940–941, 2005
75. Lecube A, Hernández C, Genescà J, Simó R: Proinflammatory cytokines, insulin resistance, and insulin secretion in chronic hepatitis C patients: a case-control study. *Diabetes Care* 29:1096–1101, 2006
76. Kaye TB, Guay AT, Simonson DC: Non-insulin-dependent diabetes mellitus and elevated serum ferritin level. *J Diabetes Complications* 7:246–249, 1993
77. Ford ES, Cogswell ME: Diabetes and serum ferritin concentration among U.S. adults. *Diabetes Care* 22:1978–1983, 1999
78. Salonen JT, Tuomainen TP, Nyyssönen K, Lakka HM, Punnonen K: Relation between iron stores and non-insulin dependent diabetes in men: case-control study. *BMJ* 317:727, 1998
79. Jiang R, Manson JE, Meigs JB, Ma J, Rifai N, Hu FB: Body iron stores in relation to risk of type 2 diabetes in apparently healthy women. *JAMA* 291:711–717, 2004
80. Di Biesceglie AM, Axiotis CA, Hoofnagle JH, Bacon BR: Measurements of iron status in patients with chronic hepatitis. *Gastroenterology* 102:2108–2113, 1992
81. Farinati F, Cardin R, De Maria N, Della Libera G, Marafin C, Lecis E, Burra P, Floreani A, Cecchetto A, Naccarato R: Iron storage, lipid peroxidation and glutathione turnover in chronic anti-HCV positive hepatitis. *J Hepatol* 22:449–456, 1995
82. Riggio O, Montagnese F, Fiore P, Folino S, Giambartolomei S, Gandin C, Merli M, Quinti I, Violante N, Caroli S, Senofonte O, Capocaccia L: Iron overload in patients with chronic viral hepatitis: how common is it? *Am J Gastroenterol* 92:1298–1301, 1997
83. Giannini E, Mastracci L, Botta F, Romagnoli P, Fasoli A, Risso D, Faravelli F, Ceppa P, Lantieri PB, Icardi GC, Testa R: Liver iron accumulation in chronic hepatitis C patients without HFE mutations: relationships with histological damage, viral load and genotype and alpha-glutathione S-transferase levels. *Eur J Gastroenterol Hepatol* 13:1355–1361, 2001
84. Mendler MH, Turlin B, Moirand R, Jouanolle AM, Sapey T, Guyader D, Le Gall JY, Brissot P, David V, Deugnier Y: Insulin resistance-associated hepatic iron overload. *Gastroenterology* 117:1155–1163, 1999
85. Paris R: Association of hepatitis C and diabetes mellitus. *Ann Intern Med* 135:141–142, 2001
86. Arber N, Konikoff FM, Moshkowitz M, Baratz M, Hallak A, Santo M, Halpern Z, Weiss H, Gilat T: Increased serum iron and iron saturation without liver iron accumulation distinguish chronic hepatitis C from other chronic liver diseases. *Dig Dis Sci* 39:2656–2659, 1994
87. Barbaro G, Di Lorenzo G, Ribersani M, Soldini M, Giancaspro G, Bellomo G, Belloni G, Grisorio B, Barbarini G: Serum ferritin and hepatic glutathione concentrations in chronic hepatitis C patients related to the hepatitis C virus genotype. *J Hepatol* 30:774–782, 1999
88. Konijn AM, Hershko C: Ferritin synthesis in inflammation. I. Pathogenesis of impaired iron release. *Br J Haematol* 37:7–16, 1977
89. Fernández-Real JM, López-Bermejo A, Ricart W: Cross-talk between iron metabolism and diabetes. *Diabetes* 51:2348–2354, 2002
90. Fernández-Real JM, Ricart W: Insulin resistance and inflammation in an evolutionary perspective: the contribution of cytokine genotype/phenotype to thriftiness. *Diabetologia* 42:1367–1374, 1999
91. Fernández-Real JM, Ricart W: Insulin resistance and chronic cardiovascular inflammatory syndrome. *Endocr Rev* 24:278–301, 2003
92. Lecube A, Hernandez C, Genesca J, Esteban JI, Jardi R, Garcia L, Simo R: Diabetes is the main factor accounting for the high ferritin levels detected in chronic hepatitis C virus infection. *Diabetes Care* 27:2669–2675, 2004
93. Rozario R, Ramakrishna B: Histopathological study of chronic hepatitis B and C: a comparison of two scoring systems. *J Hepatol* 38:223–229, 2003
94. Ramalho F: Hepatitis C virus infection and liver steatosis. *Antiviral Res* 60:125–127, 2003
95. Camma C, Bruno S, Di Marco V, Di Bona D, Rumi M, Vinci M, Rebucci C, Cividini A, Pizzolanti G, Minola E, Mondelli MU, Colombo M, Pinzello G, Craxi A: Insulin resistance is associated with steatosis in nondiabetic patients with genotype 1 chronic hepatitis C. *Hepatology* 43:64–71, 2006
96. Adinolfi LE, Gambardella M, Andreana A, Tripodi MF, Utili R, Ruggiero G: Steatosis accelerates the progression of liver damage of chronic hepatitis C patients and correlates with specific HCV genotype and visceral obesity. *Hepatology* 33:1358–1364, 2001
97. Rubbia-Brandt L, Fabris P, Paganin S, Leandro G, Male PJ, Giostra E, Carlotto A, Bozzola L, Smedile A, Negro F: Steatosis affects chronic hepatitis C progression in a genotype specific way. *Gut* 53:406–412, 2004
98. Castera L, Chouteau P, Hezode C, Zafrani ES, Dhumeaux D, Pawlotsky JM: Hepatitis C virus-induced hepatocellular steatosis. *Am J Gastroenterol* 100:711–715, 2005
99. Abid K, Pazienza V, de Gottardi A, Rubbia-Brandt L, Conne B, Pugnale P, Rossi C, Mangia A, Negro F: An in vitro model of hepatitis C virus genotype 3a-associated triglycerides accumulation. *J Hepatol* 42:744–751, 2005
100. Hourigan LF, Macdonald GA, Purdie D, Whitehall VH, Shorthouse C, Clouston A, Powell EE: Fibrosis in chronic hepatitis C correlates significantly with body mass index and steatosis. *Hepatology* 29:1215–1219, 1999
101. Castera L, Hezode C, Roudot-Thoraval F, Bastie A, Zafrani ES, Pawlotsky JM, Dhumeaux D: Worsening of steatosis is an independent factor of fibrosis progression in untreated patients with chronic hepatitis and paired liver biopsies. *Gut* 52:288–292, 2003
102. Ohata K, Hamasaki K, Toriyama K, Matsumoto K, Saeki A, Yanagi K, Abiru S, Nakagawa Y, Shigeno M, Miyazoe S, Ichikawa T, Ishikawa H, Nakao K, Eguchi K: Hepatic steatosis is a risk factor for hepatocellular carcinoma in patients with chronic hepatitis C virus infection. *Cancer* 97:3036–3043, 2003
103. Fartoux L, Poujol-Robert A, Guechot J, Wendum D, Poupon R, Serfaty L: Insulin resistance is a cause of steatosis and fibrosis progression in chronic hepatitis C. *Gut* 54:1003–1008, 2005
104. Pickup JC, Crook MA: Is type II diabetes mellitus a disease of the innate immune system? *Diabetologia* 41:1241–1248, 1998
105. Fernandez-Real JM, Broch M, Ricart W, Casamitjana R, Gutierrez C, Vendrell J, Richart C: Plasma levels of the soluble fraction of tumor necrosis factor receptor 2 and insulin resistance. *Diabetes* 47:1757–1762, 1998
106. Pickup JC, Chusney GD, Thomas SM, Burt D: Plasma interleukin-6, tumour necrosis factor alpha and blood cytokine production in type 2 diabetes. *Life Sci* 67:291–300, 2000
107. Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM: C-reactive protein, inter-

leukin 6, and risk of developing type 2 diabetes mellitus. *JAMA* 286:327–334, 2001
108. Vozarova B, Weyer C, Hanson K, Tataranni PA, Bogardus C, Pratley RE: Circulating interleukin-6 in relation to adiposity, insulin action, and insulin secretion. *Obes Res* 9:414–417, 2001
109. Hotamisligil GS, Peraldi P, Budavari A, Ellis R, White MF, Spiegelman BM: IRS-1-mediated inhibition of insulin receptor tyrosine kinase activity in TNF-alpha and obesity-induced insulin resistance. *Science* 271:665–668, 1996
110. Lang CH, Dobrescu C, Bagby GJ: Tumor necrosis factor impairs insulin action on peripheral glucose disposal and hepatic glucose uptake. *Endocrinology* 130:43–52, 1992
111. Aderka D, Engelmann H, Maor Y, Brakebusch C, Wallach D: Stabilization of the bioactivity of tumor necrosis factor by its soluble receptors. *J Exp Med* 175:323–329, 1992
112. Díez-Ruiz A, Tilz GP, Zangerle R, Baier-Bitterlich G, Wachter H, Fuchs D: Soluble receptors for tumour necrosis factor in clinical laboratory diagnosis. *Eur J Haematol* 54:1–8, 1995
113. Fabris C, Soardo G, Falleti E, Toniutto P, Vitulli D, Federico E, Del Forno M, Mattiuzzo M, Gonano F, Pirisi M: Relationship among hepatic inflammatory changes, circulating levels of citokines, and response to IFN-alpha in chronic hepatitis C. *J Interferon Cytokine Res* 18: 705–709, 1998
114. Kallinowski B, Haseroth K, Marinos G, Hanck C, Stremmel W, Theilmann L, Singer MV, Rossol S: Induction of tumour necrosis factor (TNF) receptor type p55 and p75 in patients with chronic hepatitis C virus (HCV) infection. *Clin Exp Immunol* 111:269–277, 1998
115. Zylberberg H, Rimaniol AC, Pol S, Masson A, De Groote D, Berthelot P, Bach JF, Brechot C, Zavala F: Soluble tumor necrosis factor receptors in chronic hepatitis C: a correlation with histological fibrosis and activity. *J Hepatol* 30:185–191, 1999
116. Itoh Y, Okanoue T, Ohnishi N, Sakamoto M, Nishioji K, Nakagawa Y, Minami M, Murakami Y, Kashima K: Serum levels of soluble tumor necrosis factor receptors and effects of interferon therapy in patients with chronic hepatitis C virus infection. *Am J Gastroenterol* 94:1332–1340, 1999
117. Dumoulin FL, Wennrich U, Nischalke HD, Leifeld L, Fisher HP, Sauerbruch T, Spengler U: Intrahepatic mRNA levels of interferon gamma and tumor necrosis factor alpha and response to antiviral treatment of chronic hepatitis C. *J Hum Virol* 4:195–199, 2001
118. Knobler H, Schattner A: TNF-alpha, chronic hepatitis C and diabetes: a novel triad. *QJM* 98:1–6, 2005
119. Aytug S, Reich D, Sapiro LE, Bernstein D, Begum N: Impaired IRS-1/PI3-kinase signaling in patients with HCV: a mechanism for increased prevalence of type 2 diabetes. *Hepatology* 38:1384–1392, 2003
120. 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* 32 (Suppl. 3):24–34, 2002
121. Ruan H, Lodish HF: Insulin resistance in adipose tissue: direct and indirect effects of tumor necrosis factor-alpha. *Cytokine Growth Factor Rev* 14:447–455, 2003
122. Napoli J, Bishop GA, McGuinness PH, Painter DM, McCaughan GW: Progressive liver injury in chronic hepatitis C infection correlates with increased intrahepatic expression on Th1-associated cytokines. *Hepatology* 24:759–765, 1996
123. Rehermann B: Interaction between the hepatitis C virus and the immune system. *Semin Liver Dis* 20:127–141, 2000
124. Del Prete G, Maggi E, Romagnani S: Human Th1 and Th2 cells: functional properties, mechanisms of regulation, and role in disease. *Lab Invest* 70:299–306, 1994
125. Burgio VL, Ballardini G, Artini M, Caratozzolo M, Bianchi FB, Levrero M: Expression of co-stimulatory molecules by Kupffer cells in chronic hepatitis of hepatitis C etiology. *Hepatology* 27:1600–1606, 1998
126. McGuinness PH, Painter D, Davies S, McCaughan GW: Increases in intrahepatic CD68 positive cells, MAC387 positive cells, and proinflammatory cytokines (particularly interleukin 18) in chronic hepatitis C virus infection. *Gut* 46:260–269, 2000
127. Shintani Y, Fujie H, Miyoshi H, Tsutsumi T, Tsukamoto K, Kimura S, Moriya K, Koike K: Hepatitis C virus infection and diabetes: direct involvement of the virus in the development of insulin resistance. *Gastroenterology* 126:840–848, 2004
128. Papanicolau DA, Wilder RL, Manolagas SC, Chrousos GP: The pathophysiologic roles of interleukin-6 in human disease. *Ann Intern Med* 128:127–137, 1998
129. Fried SK, Bunkin DA, Greenberg AS: Omental and subcutaneous adipose tissues of obese subjects release interleukin-6: depot difference and regulation by glucocorticoid. *J Clin Endocrinol Metab* 83:847–850, 1998
130. Rotter V, Nagaev I, Smith U: Interleukin-6 (IL-6) induces insulin resistance in 3T3–L1 adipocytes and is, like IL-8 and tumor necrosis factor-alpha, overexpressed in human fat cells from insulin-resistant subjects. *J Biol Chem* 278: 45777–45784, 2003
131. Klover PJ, Zimmers TA, Koniaris LG, Mooney RA: Chronic exposure to interleukin-6 causes hepatic insulin resistance in mice. *Diabetes* 52:2784–2789, 2003
132. Malaguarnera M, Di Fazio I, Romeo MA, Restuccia S, Laurino A, Trovato BA: Elevation of interleukin 6 levels in patients with chronic hepatitis due to hepatitis C virus. *J Gastroenterol* 32:211–215,1997
133. Cotler SJ, Reddy KR, McCone J, Wolfe DL, Liu A, Craft TR, Ferris MW, Conrad AJ, Albrecht J, Morrissey M, Ganger DR, Rosenblate H, Blatt LM, Jensen DM, Taylor MW: An analysis of acute changes in interleukin-6 levels after treatment of hepatic C with consensus interferon. *J Interferon Cytokine Res* 21:1011–1019, 2001
134. Konrad T, Zeuzem S, Toffolo G, Vicini P, Teuber G, Briem D, Lormann J, Lenz T, Hermann G, Berger A, Cobelli C, Usadel K: Severity of HCV-induced liver damage alters glucose homeostasis in noncirrhotic patients with chronic HCV infection. *Digestion* 62:52–59, 2000
135. Sougleri M, Labropoulou-Karatza C, Paraskevopoulou P, Fragopanagou H, Alexandrides T: Chronic hepatitis C virus infection without cirrhosis induces insulin resistance in patients with alpha-thalassaemia major. *Eur J Gastroenterol Hepatol* 13:1195–1199, 2001
136. 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* 96:2462–2467, 2001
137. Tazawa J, Maeda M, Nakagawa M, Ohbayashi H, Kusano F, Yamane M, Sakai Y, Suzuki K: Diabetes mellitus may be associated with hepatocarcinogenesis in patients with chronic hepatitis C. *Dig Dis Sci* 47:710–715, 2002
138. Romero-Gómez M, Del Mar Viloria, Andrade RJ, Salmeron J, Diago M, Fernandez-Rodriguez CM, Corpas R, Cruz M, Grande L, Vazquez L, Munoz-De-Rueda P, Lopez-Serrano P, Gila A, Gutierrez ML, Perez C, Ruiz-Extremera A, Suarez E, Castillo J: Insulin resistance impairs sustained response rate to peginterferon plus ribavirin in chronic hepatitis C patients. *Gastroenterology* 128:636–641, 2005
139. D'Souza R, Sabin A, Foster GR: Insulin resistance plays a significant role in liver fibrosis in chronic hepatitis C and in the response to antiviral therapy. *Am J Gastroenterol* 100:1509–1515, 2005
140. Svegliati-Baroni G, Ridolfi F, Di Sario A, Casini A, Marucci L, Gaggiotti G, Orlandoni P, Macarri G, Perego L, Benedetti A, Folli F: Insulin and insulin-like growth factor-1 stimulate proliferation and type I collagen accumulation by human hepatic stellate cells: differential

effects on signal transduction pathways. *Hepatology* 29:1743–1751, 1999
141. Paradis V, Dargere D, Vidaud M, De Gouville AC, Huet S, Martinez V, Gauthier JM, Ba N, Sobesky R, Ratziu V, Bedossa P: Expression of connective tissuegrowth factor in experimental rat and human liver fibrosis. *Hepatology* 30: 968–976, 1999
142. Paradis V, Perlemuter G, Bonvoust F, Dargere D, Parfait B, Vidaud M, Conti M, Huet S, Ba N, Buffet C, Bedossa P: High glucose and hyperinsulinemia stimulate connective tissue growth factor expression: a potential mechanism involved in progression to fibrosis in nonalcoholic steatohepatitis. *Hepatology* 34:738–744, 2001