Online Submissions: wjg.wjgnet.com
wjg@wjgnet.com
doi:10.3748/wjg.15.1537

World J Gastroenterol 2009 April 7; 15(13): 1537-1547
World Journal of Gastroenterology ISSN 1007-9327

EDITORIAL

Hepatitis C virus and type 2 diabetes

Francesco Negro, Mahnaz Alaei

Francesco Negro, Mahnaz Alaei, Division of Gastroenterology, Hepatology and Clinical Pathology, University Hospitals, 24 rue Micheli-du-Crest, 1211 Geneva 14, Switzerland
Francesco Negro, Division of Clinical Pathology, University Hospitals, 24 rue Micheli-du-Crest, 1211 Geneva 14, Switzerland
Author contributions: Negro F conceived and wrote the manuscript; Alaei M did a literature search and participated in the writing of the manuscript; both authors approved its final version.
Supported by Grant No. 320000-116544 from the Swiss National Science Foundation and by a research award from the Leenaards Foundation
Correspondence to: Francesco Negro, MD, Associate Professor, Division of Gastroenterology, Hepatology and Clinical Pathology, University Hospitals, 24 rue Micheli-du-Crest, 1211 Geneva 14,
Switzerland. francesco.negro@hcuge.ch
Telephone: +41-22-3795800 Fax: +41-22-3729366
Received: December 18, 2008 Revised: January 21, 2009
Accepted: January 28, 2009
Published online: April 7, 2009

Abstract

This review focuses on the relationship between hepatitis C virus (HCV) infection and glucose metabolism derangements. Cross-sectional and longitudinal studies have shown that the chronic HCV infection is associated with an increased risk of developing insulin resistance (IR) and type 2 diabetes (T2D). The direct effect of HCV on the insulin signaling has been analyzed in experimental models. Although currently available data should be considered as preliminary, HCV seems to affect glucose metabolism *via* mechanisms that involve cellular pathways that have been implicated in the host innate immune response. IR and T2D not only accelerate the histological and clinical progression of chronic hepatitis C, but also reduce the early and sustained virological response to interferon-alpha-based therapy. Thus, a detailed knowledge of the mechanisms underlying the HCV-associated glucose metabolism derangements is warranted, in order to improve the clinical management of chronic hepatitis C patients.

Key words: Hepatitis C; Fibrosis; Insulin resistance; Insulin signaling; Type 2 diabetes

Peer reviewer: Atsushi Nakajima, Professor, Division of Gastroenterology, Yokohama City University Graduate School of Medicine, 3-9 Fuku-ura, Kanazawa-ku, Yokohama 236-0004, Japan

Negro F, Alaei M. Hepatitis C virus and type 2 diabetes. *World J Gastroenterol* 2009; 15(13): 1537-1547 Available from: URL: http://www.wjgnet.com/1007-9327/15/1537.asp DOI: http://dx.doi.org/10.3748/wjg.15.1537

INTRODUCTION

Hepatitis C virus (HCV) infection is a frequent cause of acute and chronic hepatitis, and leads to the development of cirrhosis and hepatocellular carcinoma. It is estimated that about 150 to 200 million people have been in contact with HCV worldwide, and approximately 85% are chronically infected. The spectrum of severity of liver disease associated with HCV varies widely, as does the rate of progression towards the cirrhotic stage. The latter seems to depend on several, mostly host-related cofactors, such as age, sex, level of alcohol consumption, overweight, immune status and co-infections[1,2]. One of these cofactors is type 2 diabetes (T2D), which has been recognized to modify the course of hepatitis C even at the stage of insulin resistance (IR), a condition that precedes the development of T2D[3,4]. Although individuals may develop IR independently of HCV, a considerable amount of clinical and experimental data suggest that HCV contributes to its pathogenesis. This aspect is important, because IR seems not only to accelerate the course of chronic hepatitis C, but also to influence the response to antiviral therapy[5]. The scope of this review is to discuss the current level of evidence in favor of a causal association between HCV and T2D/IR, its clinical impact, and some directions for management.

ASSOCIATION BETWEEN HCV AND T2D

T2D is a common complication of all liver diseases, independently of the etiology, especially at the advanced stage. However, clinical and experimental data suggest a direct role of HCV in the perturbation of glucose metabolism. The first observation that cirrhotic patients infected with HCV may present with T2D more often than patients with cirrhosis of other

etiology was reported in 1994 by Allison *et al*[6]. Most studies using a cross-sectional design and comparing the prevalence of T2D in a population of chronic hepatitis C patients with that of a comparator group have confirmed these preliminary observations[7-14], with rare exceptions[15]. Comparator groups have included patients with chronic liver disease[7-9,12-14], drug users[10] or human immunodeficiency virus (HIV) mono-infected patients[11]. It can be argued that, in these studies, the two populations of patients-i.e. HCV-infected and uninfected-may have differed by relevant risk factors for T2D, notably age, gender distribution and stage of liver disease. It is noteworthy that, in the HIV-co-infected cohorts studied by Visnegarwala *et al*[11], the association between HCV and T2D was significant, as assessed by multivariate analysis, only among subjects < 50 years old. Similarly, in the study by Lecube *et al*[12], glucose abnormalities, including impaired fasting glucose (IFG), were significantly more prevalent (i.e. about three-fold) among HCV-positive patients attending a liver unit, compared to HCV-negative patients, only when they were at a pre-cirrhotic stage. These observations suggest that HCV interferes with glucose metabolism independently of age and stage of liver disease. At a later, cirrhotic stage, however, multiple factors contributing to IR may prevail and partially or completely mask the HCV-related effect. Further evidence has come *via* case-control studies in which all cases were represented by HCV-infected individuals[16-24], although in most cases, the prevalence of T2D among HCV-infected individuals compared to matched controls was, in general, lower than that seen in previous studies.

Several investigators have approached this issue from a different point of view, i.e. measuring the prevalence of HCV markers among populations of diabetic patients[8,15,25-33]. Most controlled studies have suggested a significant association, the proportion of HCV-positive persons among diabetics being two- to seven-fold compared to controls[8,15,29,32]. The prevalence of HCV markers among patients with T2D reported by uncontrolled studies was also claimed to be higher than that observed in the general population taken as a reference[25,27,30]. However, the study by Sotiropoulos *et al*[26] reported a rather low HCV prevalence (1.65%), especially if one considers that a field survey in the Greek general population gave a HCV seroprevalence of 1.25%[34]. Other controlled studies from Italy[28], Nigeria[31] and Turkey[33] have failed to find an excess prevalence of HCV infection among patients with T2D. The data have therefore proven inconclusive. It has been suggested that patients with T2D are at risk of blood-borne infections *via* repeated use of finger stick devices. However, a single study from France, evaluating the prevalence of HCV antibodies in 259 patients with T2D seen during 1998 at a diabetic unit, has failed to confirm this hypothesis[35]. One cannot exclude that iatrogenic transmission of HCV among diabetic patients may however have been significant in previous decades.

The potential ascertainment bias that may occur in clinic-based studies that target a specific disease group has been overcome in a vast (and hitherto unsurpassed) study conducted in the general population, the Third National Health and Nutrition Examination Survey (NANHES-III)[36]. This study, which included 9841 subjects aged ⩾ 20 years, showed that persons who were anti-HCV-positive and aged ⩾ 40 years had an odds ratio of 3.77 (95% CI: 1.80-7.87), after adjusting for sex, body mass index (BMI) and ethnicity, of having T2D compared to anti-HCV-negative individuals.

Thus, clinic-based studies and the general population-based NANHES-III study came to similar conclusions, which reinforce the hypothesis of a causal association between HCV infection and T2D. As a result of the cross-sectional nature of all these surveys, however, as hinted before, a temporal relationship between HCV infection and T2D cannot be established. This issue, i.e. did the HCV infection come before the occurrence of T2D or *vice versa*, has been addressed by longitudinal studies. A prospective, case-cohort study, performed in the United States, analyzed whether persons who developed T2D were more likely to have had precedent HCV infection when enrolled in a community-based cohort of 1084 persons aged 44-65 years (the Atherosclerosis Risk in Communities Study)[37]. The prevalence of HCV in this population was 0.8%. A total of 548 subjects developed *de novo* T2D over 9 years of follow-up. Prior to entry, subjects had been categorized as low-risk or high-risk for T2D based on age and BMI. Among those at high risk for T2D, persons with HCV infection were more than 11 times as likely as those without HCV infection to develop T2D (relative hazard, 11.58; 95% CI: 1.39-96.6). Among those at low risk, the incidence of T2D was not increased among HCV-infected subjects. The conclusion of this important survey was that pre-existing HCV infection may increase the incidence of T2D in persons with known risk factors. The second study[38], a community-based cohort survey performed in southern Taiwan, enrolled 4958 persons aged ⩾ 40 years, without T2D at entry. This study included 3486 seronegative persons, 812 anti-HCV-positive patients, 544 individuals with the hepatitis B surface antigen (HBsAg) and 116 with hepatitis B virus (HBV)/HCV co-infection. Over a follow-up of 7 years, 474 cases of incident T2D were recorded: overall, 14.3% of anti-HCV-positive, 7.5% of HBsAg-positive, and 8.6% of seronegative individuals developed T2D during the study. Compared to anti-HCV-negative individuals, anti-HCV-positive persons had a higher cumulative incidence of T2D ($P < 0.0001$). By multivariate analysis, the fact of being anti-HCV-positive, co-infection with HBV and HCV, overweight, obesity, and increasing age were all significantly associated with T2D, while sex and alcohol consumption, among other factors, were not. Interestingly, when patients were stratified by age and BMI, the risk of developing T2D among anti-HCV-positive individuals increased when age decreased and BMI levels increased. This study concluded that HCV infection is an independent predictor of T2D. The risk

was higher in patients with elevated BMI, but, at variance with the previous study, seemed to decrease with age.

Thus, cross-sectional and longitudinal studies both seem to converge towards the same conclusion, i.e. there exists an excess T2D risk in HCV-infected persons compared to controls infected with HBV,which suggests a direct role of HCV in inducing derangement of glucose metabolism. A recent, large meta-analysis, the first of this kind, has reached the same conclusion[39].

An additional, strong case in favor of an association between HCV and T2D comes from longitudinal studies performed in patients having received a liver or kidney transplant. T2D is a common complication of liver transplantation (LT). Apart from isolated negative reports[40], there is accumulating evidence that HCV is a strong predictor of new-onset T2D after LT[41]. A first study from Toronto, Canada[42], analyzed the prevalence of T2D among 278 LT recipients, whose indication for transplantation was liver failure caused by HCV (110 patients), HBV (53 patients) or cholestatic liver disease (115 patients). Multivariate analysis revealed that HCV-related cirrhosis ($P = 0.002$), pre-LT T2D ($P < 0.0001$) and male gender ($P = 0.019$) were independent predictors of the presence of T2D 1 year after LT. The high prevalence of T2D persisted among HCV-positive persons, with 41% being diabetic at 5 years. This observation was subsequently confirmed by other studies. In a series from Harvard[42], which compared 47 HCV-positive to 111 HCV-negative cases, HCV infection was an independent risk factor for the development of T2D after LT (hazard ratio 2.5, $P = 0.001$). These data were repeatedly confirmed by later studies[43-49], with one exception from the [University of California, Los Angeles (UCLA)] series, in which the lack of association may have been a consequence of the excess representation of HCV-positive patients[50]. Several predisposing factors were identified across the studies: impaired fasting glucose and a maximum lifetime BMI over 25 kg/m^2[49], age and male gender[48], serum HCV RNA level after LT[51], and use of tacrolimus[45] or steroid boluses[43]. On the other hand, use of cyclosporine[49] and rapid discontinuation of steroids[52] seem to reduce the incidence of T2D among HCV-positive persons.

A similarly increased risk of T2D has been reported after kidney transplantation (KT). After two early reports, underlining a rather strong association between ongoing HCV infection and post-KT T2D[53,54], a major retrospective analysis on 427 kidney recipients without T2D before KT[55] showed that, by multivariate logistic regression, HCV (adjusted OR 5.58; 95% CI: 2.63-11.83; $P = 0.0001$), weight at transplantation (adjusted OR 1.028; 95% CI: 1.00-1.05; $P = 0.001$), and tacrolimus (adjusted OR 2.85; 95% CI: 1.01-5.28; $P = 0.047$) were associated with newly onset T2D after KT. In this study, a significant interaction ($P = 0.0001$) was found between presence of HCV and use of tacrolimus, since in the HCV-positive group, T2D occurred more often in tacrolimus-treated than cyclosporine A-treated patients (57.8% *vs* 7.7%; $P < 0.0001$)[55]. Most subsequent studies confirmed this robust association[56-63], with some exceptions[21,64-66]. Thus, in a recent meta-analysis of 10 studies, the pooled relative risk for post-KT T2D was 2.73 (95% CI: 1.94-3.83)[67]. When only two large studies were considered, the pooled relative risk was still 1.36 (95% CI: 1.21-1.54). The existing publication bias did not change the results in a meaningful way, after a sensitivity analysis was performed[67]. In addition to ongoing HCV infection, risk factors for developing T2D after KT are family history of T2D[55,60], age[57,59,61,62], use of tacrolimus[55,59,60,62,63], smoking[61], overweight/obesity[62,63], African-American ethnicity[62] and pre-transplantation impaired fasting glucose[63]. Thus, there exists a significant increase of the risk of post-KT T2D in HCV-positive recipients, especially in the first 2 mo after transplantation[57]. Since T2D and its complications are a leading cause of mortality after KT, it is easy to understand that every effort should be made to clear HCV with antiviral therapy in the pre-KT period, whenever this is feasible.

Thus, HCV and T2D are associated more than just by chance, suggesting that HCV may alter glucose homeostasis by its direct action, or *via* indirect mechanisms such as through cytokine stimulation (see below). The association between HCV infection and glucose abnormalities holds true if, instead of looking at the occurrence of overt T2D, one considers pre-diabetes conditions, such as impaired glucose tolerance (IGT) or IR. The latter is defined as a condition in which higher than normal insulin concentration are needed to achieve normal metabolic responses or, alternatively, normal insulin concentration are unable to achieve normal metabolic responses[68]. It has to be stated clearly, however, that it is not clear whether IR associated with HCV infection invariably evolves towards T2D in all infected persons, especially those without other risk factors of T2D. There is a clear need of longitudinal studies that may clarify this issue.

In a classical paper, Hui and collaborators[4] compared fasting levels of serum insulin, C-peptide and IR [measured as homeostasis assessment (HOMA) score] in 121 HCV patients with stage 0 or 1 liver fibrosis and 137 healthy volunteers matched by sex, BMI, and waist-to-hip ratio. Results showed that such HCV-infected persons, not withstanding their early stage of liver disease, had higher levels of insulin, C peptide, and HOMA scores compared with controls. Besides, this study was the first to suggest that genotype 3 may have significantly lower HOMA scores than other genotypes (which were comparable when adjusted for the remaining independent predictors of IR). Thus, this work showed how HCV may induce IR irrespective of the stage of advancement of the underlying liver disease, an effect that seemed to be genotype specific. In a similar, more recent paper, Moucari *et al*[69] analyzed 600 consecutive patients (500 with chronic hepatitis C and 100 controls with chronic hepatitis B). IR was less frequent in chronic hepatitis B than in matched chronic hepatitis C cases (5% *vs* 35%, respectively, $P < 0.001$), again irrespective of the stage of liver disease (patients were divided

according to the presence or absence of liver cirrhosis). Furthermore, IR was associated with genotypes 1 and 4 and high serum HCV RNA levels, even suggesting a trend, among patients without features of the metabolic syndrome, between HCV replication level and HOMA score. These data further corroborated the hypothesis that HCV may have a direct involvement in glucose metabolism derangement. A correlation between HCV RNA levels and HOMA score has been reported also by other studies[70-72], especially in genotype 1[71] or after adjustment for age, gender and visceral adipose tissue area[72]. These results are not, however, confirmed by all investigators. In a recent paper, Anty *et al*[73] reported that lean patients with non-3 genotypes had higher glycemia and lower adiponectin levels than controls, at closer look it was evident that, considering only the 52 patients with F0/F1, then the HOMA scores were comparable to those of 22 controls (1.7 ± 1.6 *vs* 1.4 ± 1.5, P = NS). Negative results have also been reported from Japan, where two studies failed to identify HCV infection as independent predictor of IR[14,74]. Thus, further work is warranted in this field, and, more importantly, a thorough analysis, at the population level, of HCV sequences that may be directly involved in stimulating IR. Furthermore, it is impossible to determine whether HCV replication is responsible for increased IR or whether HCV replication is favored by hyperinsulinemia, as suggested by some *in vitro* data[75], and/or by the increased serum levels of free fatty acids[76] typically observed in IR and T2D[77]. Finally, the poor correlation between HCV RNA levels and HOMA score may also be caused by the fact that the overall level of IR also depends on the contribution from the adipose tissue and muscle, two extrahepatic compartments not infected by HCV.

Finally, if HCV is increasing the level of IR or predisposes to the development of glucose metabolism disturbances, including T2D, in high-risk individuals, then curing HCV should result in amelioration of the HOMA score and in a decreased incidence of T2D after the end of therapy. Kawaguchi *et al*[78], in their study on 89 patients, showed that eradication of HCV improved the HOMA score and the intrahepatic expression of the insulin receptor substrate (IRS) 1 and 2, two cellular transducers of the insulin signal (see below). Similar results have been reported in a cohort of 181 genotype 4 patients from Egypt[79]. Regarding the incidence of glucose metabolism derangements after sustained virological response (SVR), Romero-Gómez *et al*[80] assessed the effect of SVR and other host and viral factors on the incidence of impaired fasting glucose and T2D in 1059 patients with chronic hepatitis C treated with pegylated interferon (IFN)-α2a and ribavirin. Their data show that SVR reduces by half the incidence of T2D and/or IFG during a post-therapy follow-up of 27 ± 17 mo (range, 9.3-67 mo). Similar data have been reported in 234 patients followed in Barcelona for at least 3 years after the end of therapy[81]. However, in a cohort of 202 patients with a significantly longer follow-up (8.0 years, range 5-16)[82], the benefit of SVR (if any) was not observed, even after adjustment for several baseline risk factors of T2D.

In conclusion, HCV seems to increase the risk of incident T2D in predisposed individuals. As a result, the association between HCV and T2D is more evident among patients who are older and have higher BMI. When measuring IR before T2D has occurred, some HCV-infected patients are clearly less insulin sensitive than controls, matched for risk factors of T2D and stage of liver disease. This effect is probably associated with specific HCV sequences and/or subtypes, and shows some dose-dependence, i.e. may be correlated with HCV replication level. Curing HCV seems to have beneficial effects on the level of insulin sensitivity, although this may not be the rule. In the next chapter we will analyze the potential mechanisms of interference with the insulin signaling brought about by HCV.

MECHANISMS OF HCV INTERFERENCE WITH INSULIN SIGNALING

Experimental data are compatible with direct interference of HCV with the insulin signaling cascade. This was first suggested by a study in which liver specimens obtained from 42 non-obese, non-diabetic, HCV-infected individuals and 10 non-HCV-infected subjects matched for age and BMI were exposed *ex vivo* to insulin, and examined for the contents and phosphorylation/activation status of some insulin signaling molecules[83]. Insulin-stimulated IRS-1 tyrosine phosphorylation was decreased by two-fold in HCV-infected patients compared to non-HCV-infected ones, and this was paralleled by significant reductions in IRS-1/p85 phosphatidylinositol 3 (PI3)-kinase association, IRS-1-associated PI3-kinase enzymatic activity and insulin-stimulated Akt phosphorylation[83]. It was concluded that, in patients with chronic hepatitis C, direct interactions between HCV and insulin signaling components occur that may result in IR, which in turn, may progress to T2D in at-risk individuals. In the transgenic mouse model[84], the core-encoding region of HCV is sufficient to induce IR. This effect was reversed by treatment with anti-tumor necrosis factor (TNF)-antibodies, which suggested an increased level of serine phosphorylation of IRS-1 as induced by TNF-α. Thus, the core protein may induce IR indirectly *via* stimulation of the secretion of TNF-α. However, *in vitro* models suggest otherwise, hinting at a direct interaction of the core protein with the insulin signaling pathway. An increased proteasomal degradation of the IRS-1 and -2 *via* the activation of the suppressor of cytokine signaling (SOCS)-3 has been reported after transient expression of the core protein[85]. Direct but genotype-specific mechanisms have been advocated in another study[86], in which down-regulation of peroxisome proliferator-activated receptor-γ (PPAR-γ) and up-regulation of SOCS-7 was observed in cells transfected with the core protein of genotype 3,

whereas the core protein of genotype 1b activated the mammalian target of rapamycin, findings that were confirmed by using agonists for PPAR-γ (rosiglitazone) or short interfering RNAs for SOCS-7[87]. Among the indirect mechanisms, an increased endoplasmic reticulum stress has also been described that may lead to IR[87]. More recently, the role of c-Jun N-terminal kinase (JNK) has been emphasized[88]. The HCV core protein-mediated Ser (312) phosphorylation of IRS-1 was inhibited by a JNK inhibitor in an *in vitro* infection assay using cell-culture-grown HCV[88].

Studies on chronically infected patients have suggested that increased oxidative stress and intrahepatic inflammation may also play a role. Mitsuyoshi *et al*[89] evaluated 203 chronic hepatitis C patients with HCV genotypes 1 or 2 infection. HOMA and serum levels of thioredoxin, a marker of oxidative stress, were significantly correlated with each other, even after adjustment for BMI. However, in the human model, the indirect role of inflammatory mediators, such as TNF-α, seems more likely, in keeping with the transgenic mouse model. In fact, in chronic hepatitis C patients, an increased intrahepatic TNF-α response, which results in IR and a higher risk of developing T2D, has been described[90,91]. Further work is necessary in this field, and the availability of genotype-specific replicon assays may pave the way to more in-depth mechanistic analyses.

CLINICAL CONSEQUENCES OF IR/T2D IN CHRONIC HEPATITIS C

The clinical consequences of IR and T2D on chronic hepatitis C are dual: accelerated fibrogenesis and reduced response to IFN-based therapy. Since one of the most frequent consequences of IR/T2D on the liver is steatosis, many data can be inferred indirectly looking at past studies in which the impact of non-virus- and non-alcohol-induced fatty liver on fibrosis progression was evaluated[2]. In fact, in these cases, the most likely cause of fatty liver was IR, and this, rather than steatosis, seems to predict the stage of fibrosis and its progression over time[4]. More generally, accelerated liver fibrogenesis should be considered in the complex of the consequences of the metabolic syndrome on the liver. This view allows one to consider several pathogenetic mechanisms other than IR, such as oxidative stress, increased secretion of pro-inflammatory adipokines and cytokines, and the peculiar susceptibility to apoptosis that has been associated with steatosis. High serum glucose[92], hyperinsulinemia[93] and IR[4,71,94-97] are all associated with increased fibrosis in chronic hepatitis C, and more rapid progression of hepatitis C in diabetics has been reported also after LT[98] and KT[99]. However, claiming that the sole pathogenetic mechanism that underlies accelerated fibrogenesis in patients with chronic hepatitis C and IR is the hyperglycemic/hyperinsulinemic state is an oversimplification. First, it is not unknown whether patients with virus-induced IR alone, i.e. without the other components of the metabolic syndrome (especially in the absence of the visceral obesity and the inflammatory state associated with it), share the same risk of increased liver disease progression compared to patients with overt metabolic syndrome. Second, patients with central obesity have not only increased IR but also altered levels of a whole array of pro-inflammatory cytokines and adipokines, which may exert their unwanted effects on the liver and other extra-adipose tissues independently of the action of insulin. The relative contribution of these cytokines to liver fibrosis in chronic hepatitis C is starting to be unraveled, but it is far from being fully understood.

In non-alcoholic steatohepatitis, hyperglycemia/hyperinsulinemia may be directly stimulating hepatic stellate cells to produce connective tissue growth factor (CTGF), which leads to increased collagen fiber deposition[100]. Increased intrahepatic levels of CTGF have been reported to occur in chronic hepatitis C[101]. The reduction of IR consequent to body weight reduction and increased physical activity may lead to reduced fibrosis score over time and a diminished number of activate hepatic stellate cells[102].

Several pro-inflammatory cytokines and adipokines may be involved in the pathogenesis of liver injury in chronic hepatitis C. However, their relative contribution is under debate. A large, careful study has evaluated the role of TNF-α, interleukin 6, leptin and adiponectin in the pathogenesis of HCV-associated liver injury[103]. Only TNF-levels seemed to correlate with severity of portal and periportal inflammation, but none of the cytokines considered in this study were correlated with liver fibrosis. Several other studies have failed to pinpoint a clear correlation between the severity of fibrosis and serum levels of leptin[94,104-106], with only one positive report[107]. The role of adiponectin is quite controversial[103]. In addition, recent data have suggested a potential involvement of resistin in the pathogenesis of liver fibrosis[108]. However, these latter data await independent confirmation. Finally, increased liver cell apoptosis has been reported to be correlated with steatosis[109]. Hepatocyte apoptosis can be measured by caspase activity in serum[110]. In the presence of steatosis, apoptosis is correlated with activation of stellate cells and increased stage of fibrosis, in keeping with the hypothesis that a steatotic liver is more vulnerable to liver injury, and suggesting another mechanism of liver disease progression in patients with fatty liver and the metabolic syndrome[109].

Increasing levels of IR are associated with reduced rates of initial virological response[111-113] as well as SVR in chronic hepatitis C patients treated with a combination of pegylated IFN-α and ribavirin[114-119]. This negative association has been reported not only in patients infected with the HCV genotype 1[114,116,119], but also in those with the so-called "easy-to-treat" genotypes 2 and 3[118]. Furthermore, the negative impact of IR on the early response to anti-HCV therapy has been

recently confirmed among HIV-infected patients[120]. The molecular link between IR and lack of responsiveness to IFN-α seems to lie in the increased levels of SOCS-3 in the liver[117,121]. Interestingly, SOCS-3, as stated above, is not only promoting the proteasomal degradation of IRS-1, which leads to impaired insulin signaling and IR[85], but, together with other members of the SOCS family, is also a negative regulator in the transduction of the IFN-α signaling[122]. Thus, it is not too unlikely that HCV may have developed, from the evolutionary standpoint, the ability to activate SOCS-3 or other members[86] of the SOCS family as a mechanism to inhibit the IFN-α signaling, one of the main arms of the host innate immune response, simultaneously impairing the insulin signaling. This view seems to be supported by the recent finding that HCV may also activate the protein phosphatase 2A, again with the dual effect of interfering with the insulin[87] and IFN-α[123] signaling pathways. Whether these mechanisms may be exploited pharmacologically, i.e. with drugs aimed at reducing IR while improving the responsiveness to IFN-α, remains to be fully explored (see below).

PERSPECTIVES FOR CLINICAL MANAGEMENT

The treatment of IR and T2D in chronic hepatitis C patients has two goals, as far as the underlying liver disease is concerned: to reduce fibrogenesis (hence liver disease progression) and to increase the response to IFN-based therapy. As pointed out above, it is not known whether IR invariably increases liver fibrosis, i.e. in the context of the metabolic syndrome or in cases of purely virus-induced IR, without the remaining constellation of cytokine changes that accompany the metabolic syndrome. This distinction is important also when antiviral therapy has to be undertaken, because here therapy should be aimed at correcting IR based on the underlying molecular mechanisms, which may differ according to the viral genotype and the presence or absence of metabolic syndrome. At present, however, the approach that is being followed is rather empirical.

A single study[102] has analyzed the biochemical and histological consequences of a 3-mo program that comprises body weight reduction and increased physical activity. In 19 subjects with steatosis and chronic hepatitis C, the weight loss was paralleled by progressive reduction of serum alanine aminotransferase levels and of mean fasting insulin. In patients with paired liver biopsies, steatosis decreased, together with the fibrosis score and the number of activated stellate cells, despite the persistence of HCV. The authors concluded that weight reduction may provide an important adjunct management strategy for patients with chronic hepatitis C[102]. Lifestyle changes are the single most important measure to reduce the incidence of T2D in those at risk[124] and of the metabolic syndrome in patients with IGT[125]. Moreover, the metabolic syndrome may even regress following such intervention[125], more often than among patients treated with metformin. Therefore, lifestyle changes (weight reduction and increased physical activity) should constitute the mainstay of the clinical management of patients with chronic hepatitis C and initial glucose metabolism derangements (IR and IGT), with the aim of reducing their progression to overt T2D and possibly, their impact on liver fibrogenesis.

Alternatively, insulin sensitizing agents have been tested with the specific aim of improving the rate of response to IFN-α-based therapy. As said above, IR reduces the rate of response to antivirals in chronic hepatitis C. Thus, it was suggested that IR should be corrected in patients with chronic hepatitis C not responding to IFN-α-based treatment, in order to improve response upon re-treatment. The modalities of this intervention, however, have not been established. In addition, the optimal HOMA score to be reached has not been identified. The preliminary data from four independent studies[126-129] have not been encouraging. A first prospective, multicenter study aimed at investigating the efficacy and safety of the insulin sensitizer pioglitazone, 15 mg *qd*, added to pegylated IFN-2a, 180 g *qw*/ribavirin, 1000-1200 mg *qd* combination therapy in chronic hepatitis C patients who were previously non-responders to a pegylated IFN-α/ribavirin combination[126]. All patients had a baseline HOMA > 2, because this was the threshold that discriminated responders from non-responders in previous studies[114,118]. None of the first five patients enrolled into the trial had a sufficient virological response after 12 wk to warrant continuation of the trial, which was therefore prematurely terminated. Data from three additional trials have been presented at the 2008 meeting of the American Association for the Study of Liver Diseases. In an interim analysis of one of them, 30 mg *qd* pioglitazone was given for 4 wk as monotherapy, and then added for the first 4 wk of standard therapy of treatment-naïve, non-diabetic, chronic hepatitis C patients. The authors showed that the triple regimen that contained pioglitazone increased significantly the rate of virological response after 4 wk therapy, compared to pegylated IFN-α/ribavirin combination alone[127]. However, long-term data are awaited before any conclusion can be drawn, and some caution is required. In fact, in another randomized, double-blind, placebo-controlled study, adding pioglitazone 30 mg *qd* simultaneously to standard care increased the early and end-of-treatment virological response, but failed to increase the SVR[128]. Further data are needed before insulin sensitizers can be added to the panoply of drugs to treat hepatitis C.

Furthermore, the effects of PPAR agonists on serum lipids and their potential consequences on the HCV life cycle should be investigated in more detail. It is also unclear whether the treatment with the insulin sensitizer should be started at the same time as the antiviral retreatment or precede it, in order to start the pegylated IFN-α/ribavirin combination only when the HOMA

score has decreased to a level predictive of an increased SVR[114,118]. It is not clear whether the best approach is to use a PPAR agonist (and at what dose) or a biguanide such as metformin, whose mechanism of action is specifically directed against the hepatic AMP-activated protein kinase[130]. The final results of the TRIC-1 study[129] show that adding metformin to pegylated IFN-α/ribavirin combination afforded a marginal, non-significant gain as to the SVR rate, despite an increased rapid virological response after 4 wk of triple therapy. Thus, further clinical trials aimed at reducing the IR in chronic hepatitis C *via* different pharmacological interventions are warranted.

CONCLUSION

HCV and IR/T2D are associated to an extent that cannot be merely explained by chance, which suggests that HCV interferes directly (through one or more of its proteins) and/or indirectly (by modulating the production of specific cytokines, like TNF-α) with glucose metabolism. Independently of the mechanism, IR and T2D have important effects on the hepatitis C progression and response to antivirals, which warrants specific and effective measures to correct such metabolic anomalies. Although lifestyle interventions are certainly indicated in patients with chronic hepatitis C and the metabolic syndrome, in order to reduce the cardiovascular morbidity and mortality, it remains to be fully explored whether these measures will also have an impact on the underlying liver disease. Insulin sensitizers are currently being evaluated in clinical trials, but available data do not warrant their use in all chronic hepatitis C patients with IR, with the specific aim of increasing response to antivirals, at least outside of clinical trials.

REFERENCES

1 **Alberti A**, Vario A, Ferrari A, Pistis R. Review article: chronic hepatitis C--natural history and cofactors. *Aliment Pharmacol Ther* 2005; **22** Suppl 2: 74-78
2 **Asselah T**, Rubbia-Brandt L, Marcellin P, Negro F. Steatosis in chronic hepatitis C: why does it really matter? *Gut* 2006; **55**: 123-130
3 **Leandro G**, Mangia A, Hui J, Fabris P, Rubbia-Brandt L, Colloredo G, Adinolfi LE, Asselah T, Jonsson JR, Smedile A, Terrault N, Pazienza V, Giordani MT, Giostra E, Sonzogni A, Ruggiero G, Marcellin P, Powell EE, George J, Negro F. Relationship between steatosis, inflammation, and fibrosis in chronic hepatitis C: a meta-analysis of individual patient data. *Gastroenterology* 2006; **130**: 1636-1642
4 **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 [corrected]. *Gastroenterology* 2003; **125**: 1695-1704
5 **Negro F**. Insulin resistance and HCV: will new knowledge modify clinical management? *J Hepatol* 2006; **45**: 514-519
6 **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* 1994; **21**: 1135-1139
7 **Fraser GM**, Harman I, Meller N, Niv Y, Porath A. Diabetes mellitus is associated with chronic hepatitis C but not chronic hepatitis B infection. *Isr J Med Sci* 1996; **32**: 526-530
8 **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* 1999; **29**: 328-333
9 **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* 2000; **32**: 209-217
10 **Howard AA**, Klein RS, Schoenbaum EE. Association of hepatitis C infection and antiretroviral use with diabetes mellitus in drug users. *Clin Infect Dis* 2003; **36**: 1318-1323
11 **Visnegarwala F**, Chen L, Raghavan S, Tedaldi E. Prevalence of diabetes mellitus and dyslipidemia among antiretroviral naive patients co-infected with hepatitis C virus (HCV) and HIV-1 compared to patients without co-infection. *J Infect* 2005; **50**: 331-337
12 **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* 2004; **27**: 1171-1175
13 **Huang JF**, Dai CY, Hwang SJ, Ho CK, Hsiao PJ, Hsieh MY, Lee LP, Lin ZY, Chen SC, Hsieh MY, Wang LY, Shin SJ, Chang WY, Chuang WL, Yu ML. Hepatitis C viremia increases the association with type 2 diabetes mellitus in a hepatitis B and C endemic area: an epidemiological link with virological implication. *Am J Gastroenterol* 2007; **102**: 1237-1243
14 **Imazeki F**, Yokosuka O, Fukai K, Kanda T, Kojima H, Saisho H. Prevalence of diabetes mellitus and insulin resistance in patients with chronic hepatitis C: comparison with hepatitis B virus-infected and hepatitis C virus-cleared patients. *Liver Int* 2008; **28**: 355-362
15 **Qureshi H**, Ahsan T, Mujeeb SA, Jawad F, Mehdi I, Ahmed W, Alam SE. Diabetes mellitus is equally frequent in chronic HCV and HBV infection. *J Pak Med Assoc* 2002; **52**: 280-283
16 **Ozyilkan E**, Arslan M. Increased prevalence of diabetes mellitus in patients with chronic hepatitis C virus infection. *Am J Gastroenterol* 1996; **91**: 1480-1481
17 **Grimbert S**, Valensi P, Lévy-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* 1996; **20**: 544-548
18 **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* 1998; **93**: 2363-2367
19 **Caronia S**, Taylor K, Pagliaro L, Carr C, Palazzo U, Petrik 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* 1999; **30**: 1059-1063
20 **El-Serag HB**, Hampel H, Yeh C, Rabeneck L. Extrahepatic manifestations of hepatitis C among United States male veterans. *Hepatology* 2002; **36**: 1439-1445
21 **Hirakauva EY**, Ferraz ML, Perez RM, Ferreira AS, Silva AE, Hauache O, Pestana JO. Prevalence of diabetes mellitus in renal transplant patients with hepatitis B or C virus infection. *Transplant Proc* 2002; **34**: 3220-3222
22 **Zein CO**, Levy C, Basu A, Zein NN. Chronic hepatitis C and type II diabetes mellitus: a prospective cross-sectional study. *Am J Gastroenterol* 2005; **100**: 48-55
23 **Antonelli A**, Ferri C, Fallahi P, Pampana A, Ferrari SM, Goglia F, Ferrannini E. Hepatitis C virus infection: evidence for an association with type 2 diabetes. *Diabetes Care* 2005; **28**: 2548-2550
24 **Huang JF**, Yu ML, Dai CY, Hsieh MY, Hwang SJ, Hsiao PJ, Lee LP, Lin ZY, Chen SC, Hsieh MY, Wang LY, Shin SJ, Chang WY, Chuang WL. Reappraisal of the characteristics

of glucose abnormalities in patients with chronic hepatitis C infection. *Am J Gastroenterol* 2008; **103**: 1933-1940

25 **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 tests. *Diabet Med* 1995; **12**: 244-249

26 **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* 1999; **16**: 250-252

27 **Sangiorgio L**, Attardo T, Gangemi R, Rubino C, Barone M, Lunetta M. Increased frequency of HCV and HBV infection in type 2 diabetic patients. *Diabetes Res Clin Pract* 2000; **48**: 147-151

28 **Picerno I**, Di Pietro A, Spataro P, Di Benedetto A, Romano G, Scoglio ME. Is diabetes mellitus a risk factor for HCV infection? *Ann Ig* 2002; **14**: 473-477

29 **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* 2002; **56**: 175-177

30 **Fukui M**, Kitagawa Y, Nakamura N, Yoshikawa T. Hepatitis C virus and atherosclerosis in patients with type 2 diabetes. *JAMA* 2003; **289**: 1245-1246

31 **Balogun WO**, Adeleye JO, Akinlade KS, Kuti M, Otegbayo JA. Low prevalence of hepatitis-C viral seropositivity among patients with type-2 diabetes mellitus in a tertiary hospital. *J Natl Med Assoc* 2006; **98**: 1805-1808

32 **Chen HF**, Li CY, Chen P, See TT, Lee HY. Seroprevalence of hepatitis B and C in type 2 diabetic patients. *J Chin Med Assoc* 2006; **69**: 146-152

33 **Gulcan A**, Gulcan E, Toker A, Bulut I, Akcan Y. Evaluation of risk factors and seroprevalence of hepatitis B and C in diabetic patients in Kutahya, Turkey. *J Investig Med* 2008; **56**: 858-863

34 **Goritsas C**, Plerou I, Agaliotis S, Spinthaki R, Mimidis K, Velissaris D, Lazarou N, Labropoulou-Karatza C. HCV infection in the general population of a Greek island: prevalence and risk factors. *Hepatogastroenterology* 2000; **47**: 782-785

35 **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* 1999; **25**: 502-505

36 **Mehta SH**, Brancati FL, Sulkowski MS, Strathdee SA, Szklo M, Thomas DL. Prevalence of type 2 diabetes mellitus among persons with hepatitis C virus infection in the United States. *Ann Intern Med* 2000; **133**: 592-599

37 **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* 2003; **38**: 50-56

38 **Wang CS**, Wang ST, Yao WJ, Chang TT, Chou P. Hepatitis C virus infection and the development of type 2 diabetes in a community-based longitudinal study. *Am J Epidemiol* 2007; **166**: 196-203

39 **White DL**, Ratziu V, El-Serag HB. Hepatitis C infection and risk of diabetes: a systematic review and meta-analysis. *J Hepatol* 2008; **49**: 831-844

40 **Kishi Y**, Sugawara Y, Tamura S, Kaneko J, Matsui Y, Makuuchi M. New-onset diabetes mellitus after living donor liver transplantation: possible association with hepatitis C. *Transplant Proc* 2006; **38**: 2989-2992

41 **Ma Y**, Yan WW. Chronic hepatitis C virus infection and post-liver transplantation diabetes mellitus. *World J Gastroenterol* 2005; **11**: 6085-6089

42 **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* 2000; **32**: 87-90

43 **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* 2001; **72**: 1066-1072

44 **AlDosary AA**, Ramji AS, Elliott TG, Sirrs SM, Thompson DM, Erb SR, Steinbrecher UP, Yoshida EM. Post-liver transplantation diabetes mellitus: an association with hepatitis C. *Liver Transpl* 2002; **8**: 356-361

45 **Khalili M**, Lim JW, Bass N, Ascher NL, Roberts JP, Terrault NA. New onset diabetes mellitus after liver transplantation: the critical role of hepatitis C infection. *Liver Transpl* 2004; **10**: 349-355

46 **Parolin MB**, Zaina FE, Araújo MV, Kupka E, Coelho JC. Prevalence of new-onset diabetes mellitus in Brazilian liver transplant recipients: association with HCV infection. *Transplant Proc* 2004; **36**: 2776-2777

47 **Delgado-Borrego A**, Casson D, Schoenfeld D, Somsouk M, Terella A, Jordan SH, Bhan A, Baid S, Cosimi AB, Pascual M, Chung RT. Hepatitis C virus is independently associated with increased insulin resistance after liver transplantation. *Transplantation* 2004; **77**: 703-710

48 **Soule JL**, Olyaei AJ, Boslaugh TA, Busch AM, Schwartz JM, Morehouse SH, Ham JM, Orloff SL. Hepatitis C infection increases the risk of new-onset diabetes after transplantation in liver allograft recipients. *Am J Surg* 2005; **189**: 552-557; discussion 557

49 **Saliba F**, Lakehal M, Pageaux GP, Roche B, Vanlemmens C, Duvoux C, Dumortier J, Salamé E, Calmus Y, Maugendre D. Risk factors for new-onset diabetes mellitus following liver transplantation and impact of hepatitis C infection : an observational multicenter study. *Liver Transpl* 2007; **13**: 136-144

50 **Saab S**, Shpaner A, Zhao Y, Brito I, Durazo F, Han S, Farmer DG, Ghobrial RM, Yersiz H, Goldstein LI, Tong MJ, Busuttil RW. Prevalence and risk factors for diabetes mellitus in moderate term survivors of liver transplantation. *Am J Transplant* 2006; **6**: 1890-1895

51 **Delgado-Borrego A**, Liu YS, Jordan SH, Agrawal S, Zhang H, Christofi M, Casson D, Cosimi AB, Chung RT. Prospective study of liver transplant recipients with HCV infection: evidence for a causal relationship between HCV and insulin resistance. *Liver Transpl* 2008; **14**: 193-201

52 **Humar A**, Crotteau S, Gruessner A, Kandaswamy R, Gruessner R, Payne W, Lake J. Steroid minimization in liver transplant recipients: impact on hepatitis C recurrence and post-transplant diabetes. *Clin Transplant* 2007; **21**: 526-531

53 **Gentil MA**, Rocha JL, Pereira P, Algarra GR, López R. High incidence of diabetes mellitus after kidney transplant in patients with hepatitis C. *Nephron* 1999; **82**: 85

54 **Gürsoy M**, Güvener N, Köksal R, Karavelioğlu D, Baysal C, Ozdemir N, Boyacioğlu S, Bilgin N, Erdal R. Impact of HCV infection on development of posttransplantation diabetes mellitus in renal allograft recipients. *Transplant Proc* 2000; **32**: 561-562

55 **Bloom RD**, Rao V, Weng F, Grossman RA, Cohen D, Mange KC. Association of hepatitis C with posttransplant diabetes in renal transplant patients on tacrolimus. *J Am Soc Nephrol* 2002; **13**: 1374-1380

56 **Baid S**, Tolkoff-Rubin N, Farrell ML, Delmonico F, Williams WW, Hayden D, Ko D, Cosimi AB, Pascual M. Tacrolimus-associated posttransplant diabetes mellitus in renal transplant recipients: role of hepatitis C infection. *Transplant Proc* 2002; **34**: 1771-1773

57 **Yildiz A**, Tütüncü Y, Yazici H, Akkaya V, Kayacan SM, Sever MS, Carin M, Karşidağ K. Association between hepatitis C virus infection and development of posttransplantation diabetes mellitus in renal transplant recipients. *Transplantation* 2002; **74**: 1109-1113

58 **Finni PE**, Souza ER, Rioja S, Ventura S, Starling P, Almeida

JR, Ruzany F. Is hepatitis C a risk factor to posttransplant diabetes mellitus after renal transplantation in patients using tacrolimus? *Transplant Proc* 2004; **36**: 884-885

59 **Gourishankar S**, Jhangri GS, Tonelli M, Wales LH, Cockfield SM. Development of diabetes mellitus following kidney transplantation: a Canadian experience. *Am J Transplant* 2004; **4**: 1876-1882

60 **Martínez-Castelao A**, Hernández MD, Pascual J, Morales JM, Marcen R, Errasti P, Romero R, Oliver J, Jimeno L, Garcia Martinez J, Mendiluce A, Garcia Cosme P, Mazuecos A, Danz-Guajardo D, Alarcon A, Marrero D. Detection and treatment of post kidney transplant hyperglycemia: a Spanish multicenter cross-sectional study. *Transplant Proc* 2005; **37**: 3813-3816

61 **Sezer S**, Bilgic A, Uyar M, Arat Z, Ozdemir FN, Haberal M. Risk factors for development of posttransplant diabetes mellitus in renal transplant recipients. *Transplant Proc* 2006; **38**: 529-532

62 **Shah T**, Kasravi A, Huang E, Hayashi R, Young B, Cho YW, Bunnapradist S. Risk factors for development of new-onset diabetes mellitus after kidney transplantation. *Transplantation* 2006; **82**: 1673-1676

63 **Kamar N**, Mariat C, Delahousse M, Dantal J, Al Najjar A, Cassuto E, Lefrançois N, Cointault O, Touchard G, Villemain F, Di Giambattista F, Benhamou PY. Diabetes mellitus after kidney transplantation: a French multicentre observational study. *Nephrol Dial Transplant* 2007; **22**: 1986-1993

64 **Gentil MA**, Luna E, Rodriguez-Algarra G, Osuna A, González-Molina M, Mazuecos A, Cubero JJ, Del Castillo D. Incidence of diabetes mellitus requiring insulin treatment after renal transplantation in patients with hepatitis C. *Nephrol Dial Transplant* 2002; **17**: 887-891

65 **Sens YA**, Silva VD, Malafronte P, Souza JF, Miorin LA, Jabur P. Posttransplant diabetes mellitus in renal transplant patients with hepatitis C virus. *Transplant Proc* 2004; **36**: 886-888

66 **Baltar J**, Ortega T, Ortega F, Laures A, Rebollo P, Gomez E, Alvarez-Grande J. Posttransplantation diabetes mellitus: prevalence and risk factors. *Transplant Proc* 2005; **37**: 3817-3818

67 **Fabrizi F**, Messa P, Martin P, Takkouche B. Hepatitis C virus infection and post-transplant diabetes mellitus among renal transplant patients: a meta-analysis. *Int J Artif Organs* 2008; **31**: 675-682

68 **Bugianesi E**, McCullough AJ, Marchesini G. Insulin resistance: a metabolic pathway to chronic liver disease. *Hepatology* 2005; **42**: 987-1000

69 **Moucari R**, Asselah T, Cazals-Hatem D, Voitot H, Boyer N, Ripault MP, Sobesky R, Martinot-Peignoux M, Maylin S, Nicolas-Chanoine MH, Paradis V, Vidaud M, Valla D, Bedossa P, Marcellin P. Insulin resistance in chronic hepatitis C: association with genotypes 1 and 4, serum HCV RNA level, and liver fibrosis. *Gastroenterology* 2008; **134**: 416-423

70 **Harrison SA**. Correlation between insulin resistance and hepatitis C viral load. *Hepatology* 2006; **43**: 1168; author reply 1168-1169

71 **Hsu CS**, Liu CJ, Liu CH, Wang CC, Chen CL, Lai MY, Chen PJ, Kao JH, Chen DS. High hepatitis C viral load is associated with insulin resistance in patients with chronic hepatitis C. *Liver Int* 2008; **28**: 271-277

72 **Yoneda M**, Saito S, Ikeda T, Fujita K, Mawatari H, Kirikoshi H, Inamori M, Nozaki Y, Akiyama T, Takahashi H, Abe Y, Kubota K, Iwasaki T, Terauchi Y, Togo S, Nakajima A. Hepatitis C virus directly associates with insulin resistance independent of the visceral fat area in nonobese and nondiabetic patients. *J Viral Hepat* 2007; **14**: 600-607

73 **Anty R**, Gelsi E, Giudicelli J, Mariné-Barjoan E, Gual P, Benzaken S, Saint-Paul MC, Sadoul JL, Huet PM, Tran A. Glucose intolerance and hypoadiponectinemia are already present in lean patients with chronic hepatitis C infected with genotype non-3 viruses. *Eur J Gastroenterol Hepatol* 2007; **19**: 671-677

74 **Tanaka N**, Nagaya T, Komatsu M, Horiuchi A, Tsuruta G, Shirakawa H, Umemura T, Ichijo T, Matsumoto A, Yoshizawa K, Aoyama T, Kiyosawa K, Tanaka E. Insulin resistance and hepatitis C virus: a case-control study of non-obese, non-alcoholic and non-steatotic hepatitis virus carriers with persistently normal serum aminotransferase. *Liver Int* 2008; **28**: 1104-1111

75 **Sanyal AJ**, Chand N, Comar K, Mirshahi F. Hyperinsulinemia blocks the inhibition of hepatitis C virus (HCV) replication by interferon: a potential mechanism for failure of interferon therapy in subjects with HCV and nonalcoholic liver disease. *Hepatology* 2004; **40**: 179A

76 **Kapadia SB**, Chisari FV. Hepatitis C virus RNA replication is regulated by host geranylgeranylation and fatty acids. *Proc Natl Acad Sci USA* 2005; **102**: 2561-2566

77 **Browning JD**, Horton JD. Molecular mediators of hepatic steatosis and liver injury. *J Clin Invest* 2004; **114**: 147-152

78 **Kawaguchi T**, Ide T, Taniguchi E, Hirano E, Itou M, Sumie S, Nagao Y, Yanagimoto C, Hanada S, Koga H, Sata M. Clearance of HCV improves insulin resistance, beta-cell function, and hepatic expression of insulin receptor substrate 1 and 2. *Am J Gastroenterol* 2007; **102**: 570-576

79 **Chehadeh W**, Abdella N, Ben-Nakhi A, Al-Arouj M, Al-Nakib W. Risk factors for the development of diabetes mellitus in chronic hepatitis C virus genotype 4 infection. *J Gastroenterol Hepatol* 2009; **24**: 42-48

80 **Romero-Gómez M**, Fernández-Rodríguez CM, Andrade RJ, Diago M, Alonso S, Planas R, Solá R, Pons JA, Salmerón J, Barcena R, Perez R, Carmona I, Durán S. Effect of sustained virological response to treatment on the incidence of abnormal glucose values in chronic hepatitis C. *J Hepatol* 2008; **48**: 721-727

81 **Simó R**, Lecube A, Genescà J, Esteban JI, Hernández C. Sustained virological response correlates with reduction in the incidence of glucose abnormalities in patients with chronic hepatitis C virus infection. *Diabetes Care* 2006; **29**: 2462-2466

82 **Giordanino C**, Bugianesi E, Smedile A, Ciancio A, Abate ML, Olivero A, Pellicano R, Cassader M, Gambino R, Bo S, Ciccone G, Rizzetto M, Saracco G. Incidence of type 2 diabetes mellitus and glucose abnormalities in patients with chronic hepatitis C infection by response to treatment: results of a cohort study. *Am J Gastroenterol* 2008; **103**: 2481-2487

83 **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* 2003; **38**: 1384-1392

84 **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* 2004; **126**: 840-848

85 **Kawaguchi T**, Yoshida T, Harada M, Hisamoto T, Nagao Y, Ide T, Taniguchi E, Kumemura H, Hanada S, Maeyama M, Baba S, Koga H, Kumashiro R, Ueno T, Ogata H, Yoshimura A, Sata M. Hepatitis C virus down-regulates insulin receptor substrates 1 and 2 through up-regulation of suppressor of cytokine signaling 3. *Am J Pathol* 2004; **165**: 1499-1508

86 **Pazienza V**, Clément S, Pugnale P, Conzelman S, Foti M, Mangia A, Negro F. The hepatitis C virus core protein of genotypes 3a and 1b downregulates insulin receptor substrate 1 through genotype-specific mechanisms. *Hepatology* 2007; **45**: 1164-1171

87 **Bernsmeier C**, Duong FH, Christen V, Pugnale P, Negro F, Terracciano L, Heim MH. Virus-induced over-expression of protein phosphatase 2A inhibits insulin signalling in chronic

hepatitis C. *J Hepatol* 2008; **49**: 429-440
88 **Banerjee S**, Saito K, Ait-Goughoulte M, Meyer K, Ray RB, Ray R. Hepatitis C virus core protein upregulates serine phosphorylation of insulin receptor substrate-1 and impairs the downstream akt/protein kinase B signaling pathway for insulin resistance. *J Virol* 2008; **82**: 2606-2612
89 **Mitsuyoshi H**, Itoh Y, Sumida Y, Minami M, Yasui K, Nakashima T, Okanoue T. Evidence of oxidative stress as a cofactor in the development of insulin resistance in patients with chronic hepatitis C. *Hepatol Res* 2008; **38**: 348-353
90 **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* 2003; **98**: 2751-2756
91 **Knobler H**, Schattner A. TNF-{alpha}, chronic hepatitis C and diabetes: a novel triad. *QJM* 2005; **98**: 1-6
92 **Ratziu V**, Munteanu M, Charlotte F, Bonyhay L, Poynard T. Fibrogenic impact of high serum glucose in chronic hepatitis C. *J Hepatol* 2003; **39**: 1049-1055
93 **Hickman IJ**, Powell EE, Prins JB, Clouston AD, Ash S, Purdie DM, Jonsson JR. In overweight patients with chronic hepatitis C, circulating insulin is associated with hepatic fibrosis: implications for therapy. *J Hepatol* 2003; **39**: 1042-1048
94 **Muzzi A**, Leandro G, Rubbia-Brandt L, James R, Keiser O, Malinverni R, Dufour JF, Helbling B, Hadengue A, Gonvers JJ, Müllhaupt B, Cerny A, Mondelli MU, Negro F. Insulin resistance is associated with liver fibrosis in non-diabetic chronic hepatitis C patients. *J Hepatol* 2005; **42**: 41-46
95 **Bugianesi E**, Marchesini G, Gentilcore E, Cua IH, Vanni E, Rizzetto M, George J. Fibrosis in genotype 3 chronic hepatitis C and nonalcoholic fatty liver disease: Role of insulin resistance and hepatic steatosis. *Hepatology* 2006; **44**: 1648-1655
96 **Kita Y**, Mizukoshi E, Takamura T, Sakurai M, Takata Y, Arai K, Yamashita T, Nakamoto Y, Kaneko S. Impact of diabetes mellitus on prognosis of patients infected with hepatitis C virus. *Metabolism* 2007; **56**: 1682-1688
97 **Cua IH**, Hui JM, Kench JG, George J. Genotype-specific interactions of insulin resistance, steatosis, and fibrosis in chronic hepatitis C. *Hepatology* 2008; **48**: 723-731
98 **Cotler SJ**, Kallwitz E, TenCate V, Bhushan A, Berkes J, Benedetti E, Layden-Almer J, Layden TJ, Valyi-Nagy T, Guzman G. Diabetes and hepatic oxidative damage are associated with hepatitis C progression after liver transplantation. *Transplantation* 2007; **84**: 587-591
99 **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* 2004; **15**: 3166-3174
100 **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* 2001; **34**: 738-744
101 **Hora C**, Negro F, Leandro G, Oneta CM, Rubbia-Brandt L, Muellhaupt B, Helbling B, Malinverni R, Gonvers JJ, Dufour JF. Connective tissue growth factor, steatosis and fibrosis in patients with chronic hepatitis C. *Liver Int* 2008; **28**: 370-376
102 **Hickman IJ**, Clouston AD, Macdonald GA, Purdie DM, Prins JB, Ash S, Jonsson JR, Powell EE. Effect of weight reduction on liver histology and biochemistry in patients with chronic hepatitis C. *Gut* 2002; **51**: 89-94
103 **Cua IH**, Hui JM, Bandara P, Kench JG, Farrell GC, McCaughan GW, George J. Insulin resistance and liver injury in hepatitis C is not associated with virus-specific changes in adipocytokines. *Hepatology* 2007; **46**: 66-73
104 **Gwak GY**, Kim TH, Yu SJ, Yoon JH, Yong JJ, Park SC, Lee HS. Lack of association between serum leptin levels and hepatic steatosis, fibrosis or response to antiviral therapy in Korean chronic hepatitis C patients. *Hepatogastroenterology* 2007; **54**: 844-848
105 **Myers RP**, Messous D, Poynard T, Imbert-Bismut F. Association between leptin, metabolic factors and liver histology in patients with chronic hepatitis C. *Can J Gastroenterol* 2007; **21**: 289-294
106 **Lo Iacono O**, Venezia G, Petta S, Mineo C, De Lisi S, Di Marco V, Rodolico V, Amato M, Ferraro D, Giordano C, Almasio PL, Craxí A. The impact of insulin resistance, serum adipocytokines and visceral obesity on steatosis and fibrosis in patients with chronic hepatitis C. *Aliment Pharmacol Ther* 2007; **25**: 1181-1191
107 **Piche T**, Vandenbos F, Abakar-Mahamat A, Vanbiervliet G, Barjoan EM, Calle G, Giudicelli J, Ferrua B, Laffont C, Benzaken S, Tran A. The severity of liver fibrosis is associated with high leptin levels in chronic hepatitis C. *J Viral Hepat* 2004; **11**: 91-96
108 **Tsochatzis E**, Papatheodoridis GV, Hadziyannis E, Georgiou A, Kafiri G, Tiniakos DG, Manesis EK, Archimandritis AJ. Serum adipokine levels in chronic liver diseases: association of resistin levels with fibrosis severity. *Scand J Gastroenterol* 2008; **43**: 1128-1136
109 **Walsh MJ**, Vanags DM, Clouston AD, Richardson MM, Purdie DM, Jonsson JR, Powell EE. Steatosis and liver cell apoptosis in chronic hepatitis C: a mechanism for increased liver injury. *Hepatology* 2004; **39**: 1230-1238
110 **Seidel N**, Volkmann X, Länger F, Flemming P, Manns MP, Schulze-Osthoff K, Bantel H. The extent of liver steatosis in chronic hepatitis C virus infection is mirrored by caspase activity in serum. *Hepatology* 2005; **42**: 113-120
111 **Huang JF**, Yu ML, Dai CY, Hsieh MY, Lee LP, Lin ZY, Chen SC, Chang WY, Chuang WL. Pretreatment insulin sensitivity contributes to the treatment response to peginterferon plus ribavirin combination therapy for patients with chronic hepatitis C. *Hepatology* 2007; **46**: 349A
112 **Bortoletto G**, Realdon S, Dal Pero F, Gerotto M, Scribano L, Boninsegna S, Martines D, Alberti A. Insulin resistance (IR) defined by the homeostasis model of assessment insulin resistance (HOMA-IR) index has a direct effect on early viral kinetics during pegylated-interferon therapy for chronic hepatitis C. *Hepatology* 2007; **46**: 361A
113 **Nasta P**, Gatti F, Puoti M, Cologni G, Bergamaschi V, Borghi F, Matti A, Ricci A, Carosi G. Insulin resistance impairs rapid virologic response in HIV/hepatitis C virus coinfected patients on peginterferon-alfa-2a. *AIDS* 2008; **22**: 857-861
114 **Romero-Gómez M**, Del Mar Viloria M, Andrade RJ, Salmerón J, Diago M, Fernández-Rodríguez CM, Corpas R, Cruz M, Grande L, Vázquez L, Muñoz-De-Rueda P, López-Serrano P, Gila A, Gutiérrez ML, Pérez C, Ruiz-Extremera A, Suárez E, Castillo J. Insulin resistance impairs sustained response rate to peginterferon plus ribavirin in chronic hepatitis C patients. *Gastroenterology* 2005; **128**: 636-641
115 **D'Souza R**, Sabin CA, 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* 2005; **100**: 1509-1515
116 **Conjeevaram HS**, Kleiner DE, Everhart JE, Hoofnagle JH, Zacks S, Afdhal NH, Wahed AS. Race, insulin resistance and hepatic steatosis in chronic hepatitis C. *Hepatology* 2007; **45**: 80-87
117 **Persico M**, Capasso M, Persico E, Svelto M, Russo R, Spano D, Crocè L, La Mura V, Moschella F, Masutti F, Torella R, Tiribelli C, Iolascon A. Suppressor of cytokine signaling 3 (SOCS3) expression and hepatitis C virus-related chronic hepatitis: Insulin resistance and response to antiviral therapy. *Hepatology* 2007; **46**: 1009-1015
118 **Poustchi H**, Negro F, Hui J, Cua IH, Brandt LR, Kench JG, George J. Insulin resistance and response to therapy in

patients infected with chronic hepatitis C virus genotypes 2 and 3. *J Hepatol* 2008; **48**: 28-34

119 **Chu CJ**, Lee SD, Hung TH, Lin HC, Hwang SJ, Lee FY, Lu RH, Yu MI, Chang CY, Yang PL, Lee CY, Chang FY. Insulin resistance is a major determinant of sustained virological response in genotype 1 chronic hepatitis C patients receiving peginterferon alpha-2b plus ribavirin. *Aliment Pharmacol Ther* 2009; **29**: 46-54

120 **Bongiovanni M**, Ranieri R, Casana M, Tordato F, Cicconi P, Tincati C, Bini T, Monforte AA. Insulin resistance affects early virologic response in HIV-infected subjects treated for hepatitis C infection. *J Acquir Immune Defic Syndr* 2008; **47**: 258-259

121 **Walsh MJ**, Jonsson JR, Richardson MM, Lipka GM, Purdie DM, Clouston AD, Powell EE. Non-response to antiviral therapy is associated with obesity and increased hepatic expression of suppressor of cytokine signalling 3 (SOCS-3) in patients with chronic hepatitis C, viral genotype 1. *Gut* 2006; **55**: 529-535

122 **Gadina M**, Hilton D, Johnston JA, Morinobu A, Lighvani A, Zhou YJ, Visconti R, O'Shea JJ. Signaling by type I and II cytokine receptors: ten years after. *Curr Opin Immunol* 2001; **13**: 363-373

123 **Christen V**, Treves S, Duong FH, Heim MH. Activation of endoplasmic reticulum stress response by hepatitis viruses up-regulates protein phosphatase 2A. *Hepatology* 2007; **46**: 558-565

124 **Knowler WC**, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002; **346**: 393-403

125 **Orchard TJ**, Temprosa M, Goldberg R, Haffner S, Ratner R, Marcovina S, Fowler S. The effect of metformin and intensive lifestyle intervention on the metabolic syndrome: the Diabetes Prevention Program randomized trial. *Ann Intern Med* 2005; **142**: 611-619

126 **Overbeck K**, Genné D, Golay A, Negro F. Pioglitazone in chronic hepatitis C not responding to pegylated interferon-alpha and ribavirin. *J Hepatol* 2008; **49**: 295-298

127 **Elgouhari HM**, Cesario KB, Lopez R, Zein NN. Pioglitazone improves early virologic kinetic response to PEG IFN/RBV combination therapy in hepatitis C genotype 1 naïve pts. *Hepatology* 2008; **48**: 383A

128 **Conjeevaram H**, Burant CF, McKenna, Harsh D, Kang H, Das AK, Everett L, White D, Lok ASF. A randomized, double-blind, placebo-controlled study of PPAR-gamma agonist pioglitazone given in combination with peginterferon and ribavirin in patients with genotype-1 chronic hepatitis C. *Hepatology* 2008; **48**: 384A

129 **Romero-Gomez M**, Diago M, Andrade RJ, Calleja JL, Salmeron J, Fernandez-Rodriguez CM, Solà R, Herrerias JM, Garcia-Samaniego J, Moreno-Otero R, Olveira A, Núñez O, de la Mata M, Jorquera F, Morillas RM, Dalmau B, Martin-Vivaldi R, Arenas-Ruiz JI, Rodriguez E, Duran S, Giner P. Metformin with peginterferon alfa-2a and ribavirin in the treatment of naïve genotype 1 chronic hepatitis C patients with insulin resistance (TRIC-1): final results of a randomized and double-blinded trial. *Hepatology* 2008; **48**: 380A

130 **Shaw RJ**, Lamia KA, Vasquez D, Koo SH, Bardeesy N, Depinho RA, Montminy M, Cantley LC. The kinase LKB1 mediates glucose homeostasis in liver and therapeutic effects of metformin. *Science* 2005; **310**: 1642-1646

S- Editor Li LF **L- Editor** Kerr C **E- Editor** Zheng XM