



Insulin resistance and hepatitis C: an evolving story

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ABSTRACT

Insulin resistance and diabetes are inextricably linked to chronic hepatitis C. Our understanding of this relationship continues to improve. This review focuses on the molecular mechanisms relating insulin resistance to hepatitis C with a subsequent overview of the consequences of hepatitis C-associated insulin resistance and diabetes, as well as perspectives for future management.

INTRODUCTION

Hepatitis C remains a major health concern throughout the world. As the population exposed to hepatitis C ages, the morbidity related to this disease is also increasing. Insulin resistance (IR) and diabetes are becoming more prevalent as a result of rising obesity trends and sedentary lifestyle. Our understanding of the relationship between these two disease processes continues to grow. This review focuses on the biological function of insulin and the subsequent development of IR, specifically as it relates to hepatitis C. Molecular mechanisms for direct hepatitis C involvement in insulin signalling defects are discussed. Subsequently, the consequences of IR in the setting of chronic viral infection are detailed, to include fibrosis progression and decreased response to pegylated interferon (peg-IFN_α) and ribavirin (RBV) treatment. Improving IR via insulin-sensitising treatment and/or weight loss has been the goal of several recent clinical trials. The data surrounding these trials are summarised and perspectives for future management of hepatitis C and IR are provided.

BIOLOGICAL FUNCTION OF INSULIN

Insulin is the most potent physiological anabolic agent known, promoting the storage and synthesis of lipids, protein and carbohydrates, and inhibiting their breakdown and release into the circulation.¹ Insulin is produced by the pancreatic β -cells, mainly in response to postprandial hyperglycaemia. During fasting, insulin falls and this, along with increasing levels of glucagon, epinephrine and other counter regulatory hormones, stimulates glucose production and lipolysis.

The tissues that remove glucose from the circulation and impact glucose use the most are skeletal muscle (SM), liver and adipose tissue (figure 1). The liver plays a central role in the regulation of whole-body glucose, fatty acid and amino acid metabolism. It is the main source of endogenous glucose production and amino acid metabolism; it is a major site of fatty acid disposal (esterification

and oxidation); and it is the primary site of insulin degradation. SM plays a crucial role in maintaining systemic glucose metabolism, accounting for 85% of whole-body insulin-stimulated glucose uptake.² Insulin is also a critical regulator of most aspects of adipocyte biology.³ Insulin promotes lipogenesis through enhanced glucose transport, lipoprotein-derived fatty acid uptake, and fatty acid and triglyceride synthesis via transcriptional regulation, as well as by inhibiting lipolysis by repressing genes involved in fatty acid oxidation, which result in increased adipocyte triglyceride (TG) stores. The predominant transcription factors that mediate these changes include sterol regulatory element-binding protein-1c and adipocyte determination and differentiation-dependent factor 1.³

INSULIN RECEPTOR/SIGNALLING AND IR

The insulin receptor is a heterotetrameric bifunctional complex, consisting of two extracellular α subunits that bind insulin and two transmembrane β subunits with tyrosine kinase activity. Insulin binding to the α subunits activates the intrinsic kinase activity located in the β subunits and subsequently initiates a cascade of phosphorylation events that leads to different biological functions. Unlike other receptor tyrosine kinases, most functions of the insulin receptor require accessory molecules known as insulin receptor substrates (IRSs) (1–4) to engage multiple downstream signalling pathways.^{4–5} Insulin binding results in autophosphorylation of the receptor and tyrosine phosphorylation of intracellular IRS proteins, mainly IRS-1 and IRS-2. These actions are manifested via insulin's action on a complex network of intracellular pathways in hepatocytes, adipocytes and muscle cells upon binding to its cellular receptor. Two major cellular signalling pathways, phosphoinositide-3 kinase (PI3K)/Akt and the Ras/mitogen-activated protein kinase (MAPK) pathways, can be activated. Mammalian target of rapamycin (mTOR) is another signalling pathway that is present in at least two different complexes. Activation of the mTOR branch downstream of the PI3K/Akt pathway has emerged as the critical event in rendering IRS-1 and IRS-2 unresponsive to insulin/insulin-like growth factor-I (IGF-I), and in cell growth and proliferation.^{6–7}

These different cascades regulate diverse cellular processes, such as gene expression, protein synthesis and vesicle trafficking, which result in the regulation of glucose, lipid and protein metabolism, cell growth and differentiation (figure 2).^{1–8} One of the main results of these processes, is the final

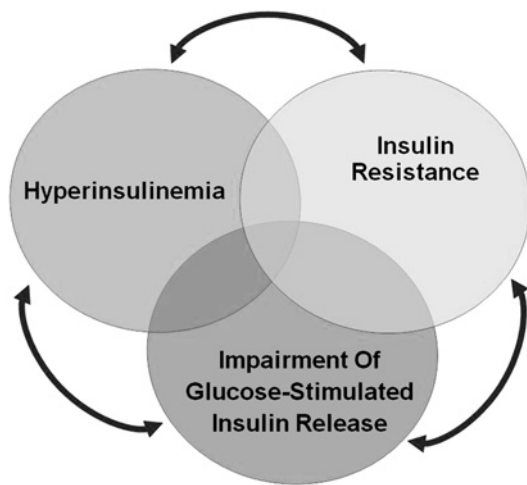


Figure 3 Venn diagram for dysregulated glucose metabolism. Hyperinsulinaemia, insulin resistance and impairment of glucose-stimulated insulin release are intertwined biologically. A single process could generate all three simultaneously.

synergistic interaction of both mechanisms results in impaired insulin signalling.

SITES OF IR

IR is typically manifested as both decreased insulin-mediated glucose uptake at the level of adipose and SM tissue (peripheral IR), and as an impaired suppression of hepatic glucose output (hepatic IR). Although IR may develop simultaneously in the liver and in the periphery (SM and adipose tissue), the degree of IR can be different. In fact, IRS-1 seems to have its major role in SM. The most likely mechanism of IR within the muscle cell is specific alterations in the insulin signal transduction pathway.²¹

In adipose tissue, IRS-1 and IRS-2 play different roles; IRS-1 promotes brown adipocyte differentiation and IRS-2 is primarily involved with white adipose tissue lipolysis.²² In hepatocytes, the IRS-1 and IRS-2 proteins function in a complementary fashion. Both are involved in the activation of PI3K, but IRS-1 has an important function in regulating gluconeogenesis, while IRS-2 is more closely involved in lipid metabolism.²³

HCV AND INSULIN RESISTANCE

Chronic hepatitis C (CHC) can be considered not only as viral disease but also as a special type of metabolic disease. CHC interacts with lipid metabolism leading to steatosis, impairs glucose metabolism leading to IR and T2DM, and is associated with an increased risk of carotid atherosclerosis.²⁴

The strong link between hepatitis C virus (HCV) infection and IR and T2DM was first reported by Allison *et al*²⁵ who observed that diabetes was significantly more prevalent in those with hepatitis C-related cirrhosis than those with cirrhosis resulting from conditions other than CHC. Others comparing the prevalence of T2DM in a population of patients with CHC with that of a comparator

group using a cross-sectional design have confirmed this association.^{26–33} Conversely, the prevalence of HCV infection in patients with diabetes is far higher than in the general population, ranging from 5% to 12%.^{34–43} The third National Health and Nutrition Examination Survey, which included 9841 subjects aged ≥ 20 years, showed that subjects with HCV are at threefold higher risk of developing T2DM.⁴⁴ A recent large meta-analysis has re-affirmed this association.⁴⁵

Further evidence for this association between HCV and IR and T2DM comes from a long-term longitudinal follow-up study assessing the incidence of diabetes in a large cohort of US subjects. Among those at high risk for T2DM, patients with CHC were 11 times more likely to develop T2DM than those without HCV infection (OR 11.58, 95% CI 1.39 to 96.6).⁴⁶ T2DM was also a more frequent complication in liver and kidney transplantation among HCV+ patients compared with HCV– patients.^{47–54} In a recent meta-analysis of 10 studies, the pooled RR for postkidney transplantation T2DM was 2.73 (95% CI 1.94 to 3.83).⁵⁵

The association between HCV infection and glucose abnormalities even at the prediabetes stages such as impaired glucose tolerance (IGT) or IR is also found.^{56–57} In 2003, Hui *et al* compared fasting serum insulin, C-peptide and HOMA (homeostatic model assessment)-IR levels between 121 patients with CHC without relevant hepatic fibrosis and 137 healthy volunteers matched by sex, body mass index (BMI) and waist-to-hip ratio. All three parameters were significantly higher in patients with CHC.⁵⁶ This finding was confirmed in a recent study of 600 consecutive patients (500 with CHC and 100 controls with chronic hepatitis B) where the prevalence of T2DM was 7.6%. Among the patients with CHC without diabetes ($n=462$), IR was present in 32.4%. IR was less frequent in chronic hepatitis B than in matched CHC cases (5% vs 35%, respectively, $p<0.001$).⁵⁸ Additionally, IR was associated with genotypes 1 and 4 and high serum HCV RNA levels.⁵⁸ A correlation between HCV RNA levels and HOMA score has been reported by others as well.^{59–60}

Lastly, data about amelioration of the HOMA score and decreased incidence of T2DM after completion of treatment in responder patients provide strong evidence for a causal relationship between HCV and glucose abnormalities. A study of 89 Japanese patients found that eradication of HCV led to improved HOMA scores and intrahepatic expression of IRS-1 and IRS-2.⁶¹ Similar results in HOMA scores were reported in a separate cohort of 181 genotype 4 patients.⁶² A longitudinal cohort study from Spain has assessed the incidence of glucose metabolism derangements after sustained virological response (SVR). Romero-Gómez *et al*⁶³ evaluated the effect of SVR on the incidence of IGT and T2DM in 1059 patients with CHC treated with Peg-IFN α 2a and RBV. They concluded that SVR reduces by half the incidence of T2DM and/or IGT during a post-treatment follow-up of 27 ± 17 months (range 9.3–67 months). Two more recent

and lengthy cohort studies yielded contradictory data. Giordanino *et al* in a cohort of 202 patients with a longer follow-up (8.0 years, range 5–16 years) failed to show a benefit in patients obtaining an SVR, even after adjustment for several baseline risk factors of T2DM.⁶⁴ In contrast, Arase *et al*, in a retrospective cohort study, followed 2842 HCV-positive patients for an average of 6.4 years and concluded that SVR causes a two-thirds reduction in the risk of T2DM development.⁶⁵

IR is present in 30–70% of individuals with CHC.^{56–58} Its presence can occur early in the course of HCV infection, independent of BMI, viral load and the severity of liver disease. HCV seems to increase the risk of incident T2DM in predisposed individuals. Recent clinical data suggest that IR is genotype dependent (1 and 4), related to HCV viral load and is improved in patients with HCV clearance following antiviral treatment. Taken together, these results suggest a direct link between HCV infection and IR that is independent of BMI and visceral adiposity, and that HCV infection itself may promote IR.

MOLECULAR MECHANISMS OF IR IN HCV

Development of IR and T2DM involves highly complex systemic mechanisms that have not yet been conclusively described. Numerous molecular pathways have been implicated. The interaction of various virus and host factors in inducing IR is the most accepted scenario (figure 4). We will discuss the potential molecular pathways by which HCV contributes to IR.

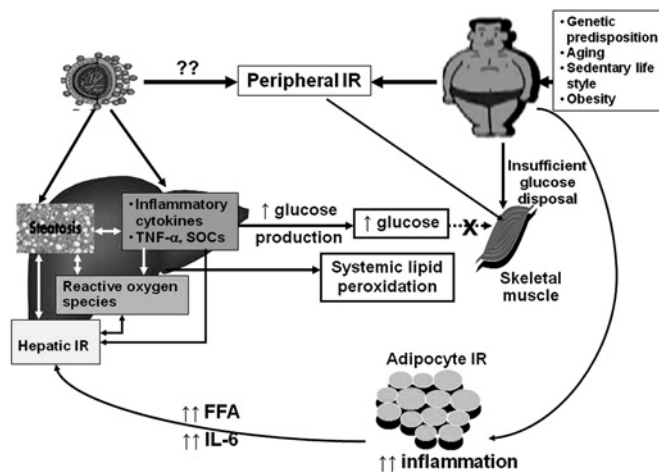


Figure 4 Molecular mechanisms of insulin resistance (IR) in hepatitis C virus (HCV) infection. The mechanisms are complex, with an interaction of various virus and host factors in inducing IR being the most accepted scenario. Host factors involve interplay between both environment and genetic predisposition, which interact with HCV infection in inducing IR. Hepatic IR in patients with chronic hepatitis C is associated with steatosis and enhanced intrahepatic expression of inflammatory cytokines and reactive oxygen species with possible interference with insulin signalling. Steatosis promotes an increase in intrahepatic and systemic lipid oxidation and endogenous glucose production. In the peripheral tissues (muscle and adipose tissue), host factors and possibly HCV hinder glucose disposal by skeletal muscles by decreasing glucose oxidation. Both host- and virus-induced specific changes of adipocytokines are associated with an increase in both hepatic and peripheral insulin resistance (see text for further explanations). FFA, free fatty acids, SOCS, suppressor of cytokine signalling; TNF, tumour necrosis factor.

Proinflammatory cytokines and adipokines

Both adipocytes and hepatocytes lie in close proximity to immune cells, including Kupffer cells, macrophages, lymphocytes and dendritic cells, and are thus subject to the impact of immune status. This close interaction can be of importance when inflammatory states are present, such as in metabolic syndrome.⁶⁶ Chronic inflammation is postulated to play a significant role in IR associated with HCV, due to increased levels of interleukin 1 (IL-1), transforming growth factor β (TGF β), tumour necrosis factor α (TNF α) (and its soluble receptor molecules sTNFR1 and sTNFR2), IL-6, IL-8, leptin and resistin, and reduced levels of adiponectin.⁶⁷

Expression of HCV core protein (genotype 1b) in transgenic mice induces hepatic IR.⁶⁸ When fed a high-fat diet, these mice develop frank diabetes and hepatic steatosis that is associated with elevated circulating levels of TNF α . The IR is reversed by administering antibodies against TNF α , although the mechanism of this effect has not been clearly elucidated.⁶⁸ Another study comparing proinflammatory cytokine expression in HCV+ liver tissues (chronic hepatitis, n=10) with HCV– normal liver tissues (n=6) found that intrahepatic expression of the cytokine IL-18 was significantly upregulated in CHC versus controls (p=0.02), with a concordant increase in IFN γ and TNF α expression (p=0.002 and 0.02, respectively).⁶⁹ Additionally, there was an increase in intrahepatic macrophage numbers with persistent HCV infection, which is also consistent with the chronic inflammatory state seen in CHC.⁶⁹

The role of TNF α -induced IR in CHC has been widely studied. TNF α has been shown to induce IR by impairing insulin signalling through serine phosphorylation of IRS-1 and IRS-2, thus down-regulating (GLUT2/GLUT4) gene expression,⁷⁰ preventing the uptake of glucose into hepatocytes and adipocytes and promoting a state of hyperinsulinaemia and hyperglycaemia.⁷¹

Although the hypothesis of chronic inflammation as an inducer of IR in CHC seems to be simple and acceptable, there are conflicting reports regarding the role of purely virus-induced inflammation in the development of IR in CHC. In an Italian study of 161 consecutive patients with CHC, serum TNF α levels were positively correlated with steatosis grades and HOMA-IR values, whereas serum levels of adiponectin were inversely correlated with steatosis grades, serum TNF α levels and HOMA-IR values.⁷² These results were independent of gender and HCV genotype. In contrast, a large Australian prospective study of 154 HCV-infected males without diabetes and 75 matched uninfected controls found higher serum levels of TNF α and IL-6 in HCV-infected patients than controls, but they did not correlate with IR. Serum levels of leptin and adiponectin were independently associated with IR (adiponectin inversely), but not with HCV infection itself. The authors concluded that virus-specific IR in CHC may be a cytokine-independent effect of the virus to modulate insulin sensitivity.⁷³

Direct effects of HCV in modulating insulin signalling

Significant attention is presently being drawn towards the way in which HCV can induce IR directly, through specific viral effects.⁷⁴ The HCV genome is composed of both structural (core, E1 and E2) and non-structural genes (NS2–NS5B), each of which has been implicated in IR development.

HCV core protein

Recent data suggest that HCV core protein reduces IRS-1 and IRS-2 protein levels and inhibits insulin signalling, although differing mechanisms have accounted for this suppression.^{75–76} It is not completely understood whether altered signalling results from changes in IRS expression, degradation or altered activity.^{68–75–79} At the molecular level, oxidative stress, downregulation of PPAR, increasing levels of the molecule suppressor of cytokine signalling (SOCS) and proteasome activator 28γ (PA28γ), and activation of the mTOR pathway are postulated mechanisms, all of which may occur in a genotype-specific manner.⁷⁹

During HCV replication, the core protein promotes an unfolded protein response that causes dysfunction of the endoplasmic reticulum (ER) and mitochondria by facilitating the uptake of calcium into the mitochondria and induces mitochondrial permeability transition.⁸⁰ Following calcium accumulation, there is a stimulation of electron transport, which increases the production of reactive oxygen species (ROS).^{80–81} Interestingly, clearance of HCV infection has been shown to improve IR and restore the hepatic expression of IRS-1 and IRS-2.⁶¹ It is possible that the core HCV protein stimulates increased levels of SOCS-3, which leads to ubiquitination and proteasomal degradation of IRS-1 and IRS-2.⁷⁵ Two clinical studies have also shown that the level of SOCS-3⁸² and polymorphisms in the SOCS-3 gene were predictive of response to IFN treatment.⁸³

Genotype-specific abnormalities in postreceptor insulin signalling that could help explain the clinical association of genotypes 1 and 4 with IR have not been clearly elucidated.⁵⁸ It is unclear if it is based on the known differences in treatment response between these groups or due to difference in the interactions between viral proteins and host signalling pathways.

There is recent evidence that while HCV core protein from both genotypes 3a and 1b reduced IRS-1 protein levels and inhibited insulin signalling, differing mechanisms accounted for this suppression. Specifically, genotype 3a core protein appears to cause IRS-1 degradation via the downregulation of PPARγ and upregulation of the SOCS-7 protein.⁷⁹ In contrast, genotype 1b core protein caused IRS-1 downregulation through a mechanism involving increased phosphorylation of IRS-1 at inhibitory serine residues (636/639), as well activation of the mTOR.⁷⁹

PA28γ is an inducer of late proteasome activity that may play a role in HCV-induced IR.¹⁸ Recent work combining mice transgenic for the HCV core

protein (HCVcpTg) with PA28γ (–/–) knockout mice has added to our understanding of IR induced by HCV by showing that the PA28γ-dependent pathway was required for HCV core protein-mediated suppression of IRS-1 tyrosine phosphorylation, suppression of IRS-2 expression and activation of the TNFα promoter.⁷⁷ PA28γ has also been shown to play a critical role in the development of steatosis and HCC.⁸⁴

Insulin regulates gene expression of key enzymes in glucose and lipid metabolism by modulating the activity of specific Forkhead box transcriptional regulators (FoxO1 and FoxA2) via the PI3K/Akt signalling pathway in the liver.⁸⁵ FoxO1 and FoxA2 may have a novel role in HCV-induced IR. In a recent study, HCV core protein, either alone or together with other viral proteins from the HCV genome, impaired insulin-induced FoxO1 translocation from the nucleus to the cytoplasm and subsequently significantly reduced accumulation of FoxA2 in the nucleus.⁸⁶

HCV NS5A

Nuclear factor-κB (NF-κB) and protein phosphatase 2A (PP2A) are two molecules that also may play a role in HCV-induced IR. HCV NS5A stimulates NF-κB-induced increase in the inflammatory cytokines TNFα, IL-6 and IL-8 by inducing mitochondrial ROS production and by binding to Toll-like receptor 4 (TLR-4) found on the plasma membranes of hepatocytes and B cells.^{87–89}

PP2A is upregulated either directly by NS5A⁹⁰ or due to increased ER stress.⁹¹ PP2A has been shown to mediate HCV-associated IR by dephosphorylating and thus inactivating Akt.⁹² Moreover PP2A has also been shown to inhibit IFN signalling, and this has been proposed as one of the potential links between IR and IFN resistance.⁹³ NS3-induced ER and oxidative stress may also activate NF-κB and increase the risk of inflammation, IR and HCC in a similar way to NS5A.⁹⁴

PPAR and HCV-induced IR

PPARs belong to the nuclear receptor superfamily and require heterodimerization with receptor X for retinoids (RXR) in order to function.^{95–96} The PPAR–RXR heterodimer, when bound to a ligand (including unsaturated fatty acids, eicosanoids, oxidised low-density lipoprotein and very low-density lipoprotein) changes conformation and binds to DNA at PPAR response elements, resulting in gene transcription.^{96–97}

There are three isotypes in mammals designated PPARα (NR1C1), PPARδ (NR1C2) and PPARγ (NR1C3).⁹⁸

PPARα/γ, together with their obligate partner RXR, are the three main nuclear receptors expressed in the liver and are involved in the control of lipid and glucose metabolism, inflammatory responses, and cellular differentiation and proliferation.

Expression of PPARα appears to be impaired with HCV infection.^{99–100} Expression of the PPARα gene in the liver was reduced by 86% compared

with controls, and the expression of its target gene, CPT1A, was coordinately reduced by 85%. De Gottardi *et al* showed that PPAR γ expression was significantly lower in genotype 3 compared with genotype 1 HCV infection. In this study, there was no significant relationship between PPAR mRNA levels and liver activity or fibrosis. In a follow-up study, treatment of genotype 3a core-expressing cells with the PPAR γ agonist rosiglitazone improved insulin signalling.¹⁰⁰ Adiponectin is another important cytokine that interacts with PPAR α to regulate hepatic TG content.¹⁰¹ Accumulation of hepatic TG is associated with loss of adiponectin receptors in the liver and, together with reduction in circulating adiponectin, contributes to systemic IR and various other metabolic anomalies.¹⁰² As adiponectin is upregulated by PPAR γ , it provides a connection between the two isotypes of PPAR and mechanisms for IR and steatosis in people with CHC. Future studies are required to define the role of adiponectin treatment clearly in humans.

Oxidative stress and IR

Oxidative stress has emerged as a key player in the development and the progression of many HCV-induced hepatic derangements, including IR and steatosis. HCV infection is characterised by increased markers of oxidative stress. Studies have indicated that HCV can directly induce oxidative stress intracellularly in hepatocytes.^{80 103–105} HCV core gene expression has been associated with increased ROS, decreased intracellular and/or mitochondrial glutathione content, and increased levels of oxidised thioredoxin and lipid peroxidation products.^{80 103–105} Contradictory data are available about the role of oxidative stress in HCV-induced IR.

A recent study found that in patients infected with HCV genotype non-3, BMI ($p=0.031$) and oxidative stress (measured as glutathione) ($p=0.037$) were independently associated with IR.¹⁰⁶ Conversely, Vidali *et al* showed that in CHC genotype non-3, oxidative stress (measured as antibodies to malondialdehyde–albumin adducts) is primarily correlated with hepatic steatosis and not with IR. The authors concluded that in genotype non-3 infection oxidative stress and IR contribute to steatosis, which in turn exacerbates both IR and oxidative stress and accelerates the progression of fibrosis.¹⁰⁷ It has been shown that oxidative stress serum markers tend to normalise in patients who achieve an SVR.¹⁰⁸

WHAT IS THE PRIMARY SITE OF IR IN CHC?

Recent trials have attempted to discriminate between the contribution of the HCV virus to ‘systemic’ and ‘hepatic’ IR and have shown that HCV infection is associated with both hepatic IR and peripheral (muscle) IR, but is predominantly peripheral.^{109 110} This observation is supported by decreased insulin-stimulated glucose disposal at high insulin dose clamp—that is, when endogenous glucose production is completely suppressed—whereas at low

dose insulin no significant difference was noticed in insulin-stimulated hepatic glucose output between CHC subjects and controls.¹⁰⁹ Free fatty acids tended to be higher in CHC versus controls basally, but was suppressed similarly to controls during low dose insulin. This suggests that IR is largely confined to SM and not adipose tissue.¹⁰⁹ Although these data are derived from a highly selected group of patients with CHC with no features of the metabolic syndrome and no histological evidence of cirrhosis, the possibility of the presence of previous skeletal muscle IR independent of HCV infection cannot be completely excluded. Previous data from patients with T2DM indicate that the initiation of IR is in the periphery, with hepatic steatosis following and exacerbating the degree of IR.¹¹¹ Supporting data are found in another trial that screened 400 young, healthy, lean subjects without diabetes and found that at least 12 (3%) of the screened subjects had IR.¹¹² These young lean insulin-resistant subjects had significant IR in SM due to decreased muscle glycogen synthesis that predated hepatic IR.

The reported improvement in glucose tolerance following liver transplantation in HCV-positive patients with diabetes is not always associated with complete regression of IR.¹¹³ In fact, transplanted patients still maintained the reduced muscle glucose uptake and the decreased non-oxidative glucose disposal observed before transplantation, indicating persistence of IR in peripheral tissues, particularly in the SM.¹¹³

The possible mechanisms of HCV-induced IR in SM have not been fully elucidated. However, the potential mechanisms include viral-induced adipocytokine release or HCV viral proteins directly interfering with muscle insulin signalling or inflammatory pathways. Despite the fact that one study found no evidence of viral replication in SM,¹¹⁴ further studies are needed to clarify this.

CONSEQUENCES OF HCV-ASSOCIATED IR/DIABETES

HCV-associated IR is involved in the development of various complications associated with HCV infection. Table 1 summarises the evidence for adverse outcomes associated with IR among patients with CHC.

Hepatic fibrosis

IR is closely associated with progression of hepatic fibrosis in patients with HCV infection.^{56 58 115–123} Also, the presence of IR is strongly associated with more rapid progression of fibrosis after liver¹⁴⁵ and kidney transplantation.¹⁴⁶ Hyperinsulinaemia and hyperglycaemia may promote fibrosis through the stimulation of hepatic stellate cells, thereby increasing the production of connective tissue growth factor and the accumulation of extracellular matrix.¹⁴⁷ Alternatively, IR-induced hepatic lipid accumulation may increase oxidative stress, resulting in progression of hepatic fibrosis.¹⁴⁸ In these cases, IR rather than steatosis seems to predict the stage of fibrosis and its progression over time.¹¹⁵

Table 1 Consequences of HCV-associated insulin resistance/diabetes

	No. of patients	Study design	% IR	HOMA-IR	Outcome measure	Result	Reference
Hepatic fibrosis	121	Retrospective case-control	NA	>2	Presence of advanced fibrosis	HCV-3 (OR 1.4, 95% CI 1.1 to 2; p=0.03) Non-HCV-3 (OR 1.2, 95% CI 1.1 to 1.4; p=0.007)	56
	528	Prospective	NA	NA	Presence of advanced fibrosis	OR 1.57, 95% CI 1.04 to 2.39 x (p=0.0063)	115
	221	Prospective	—	—	Presence of advanced fibrosis	HR 8.395, 95% CI (2.234 to 31.541)	116
	83	Prospective longitudinal	68%	—	Fibrosis progression	IR (OR 2.692, 95% CI 1.463 to 4.954). Diabetic vs non-diabetic with IR	117
	68	Prospective, cross-sectional	38% 14% (diabetic)	HOMA-IR >2.7	Presence of advanced fibrosis	60 vs 30%, p=0.006	118
	201 HCV-1	Prospective	x	x	Presence of advanced fibrosis	HCV-1 (OR 3.22; p=0.02) HCV-3 (OR 3.17; p=0.04).	119
	346 HCV-1 and HCV-3	Prospective study	46%	HOMA-IR >3	Presence of severe fibrosis	OR 3.864, 95% CI 1.859 to 8.034; p<0.001	120
	226 HCV-4	Prospective study	32.4%	HOMA-IR >2 HOMA-IR >3	Presence of severe fibrosis Association between IR and liver fibrosis stage	OR 2.44, 95% CI 1.15 to 5 OR 1.803, 95% CI 1.155 to 2.815; p=0.009	121 122
	170	Prospective study	—	Mean HOMA 2.91	Fibrosis progression	One unit increase of HOMA was associated with increased fibrosis score 0.87% (95% CI 0.60% to 1.13%; p=0.01)	58
	500	Prospective study	—	—	—	—	123
Virological response	59	Pilot open label study	—	—	—	—	124
	131 (HCV-4)	Prospective study	—	HOMA >2	RVR, SVR	RVR (OR 0.12, 95% CI 72.2 to 194.76; p=0.002) SVR 89% vs 41% (p=0.0001)	125
	47 (HIV/HCV co-infection)	Prospective study	—	HOMA >3	RVR	27 vs 73% (p=0.008)	126
	90 (HCV-1)	Retrospective	—	HOMA >2	RVR, SVR	SVR 49% vs 39% (NS) RVR (OR 0.14, 95% CI 0.03 to 065; p=0.013)	127
	131 HCV-1	Prospective	—	HOMA >2	SVR	60% vs 32% (p=0.004)	128
	399 HCV-1	Multicentre prospective	—	HOMA >2	SVR	49% vs 36% (p=0.001)	129
	330 HCV-1 and HCV-2	Open label retrospective	29.1%	HOMA >2.5	SVR	82.1% vs 68.8% (p=0.008)	130
	51 HCV-1	Retrospective	—	HOMA >2	SVR	65% vs 24% (p<0.001)	131
	133 HCV-1	Retrospective	—	HOMA >2	SVR	61% vs 42.4% (p=0.001)	132
	82 HCV-2 and HCV-3	Retrospective	—	HOMA >2	SVR	94 vs 65% (p<0.001)	133
Hepatocellular carcinoma	68	Prospective longitudinal	68%	—	Hepatoma-free survival	10 years: 92.5% vs 100% 20 years: 66.4% vs 95.5% 30 years: 40.9% vs 81.6%	134
	23820	Prospective longitudinal	1.5%	—	Incidence of HCC	RR of 60.3 (95% CI 23.6 to 153.6)	135
	541	Retrospective	16%	—	Incidence of HCC	13% vs 5.9% 11.4% (95% CI 3.0 to 19.8) vs 5.0% (95% CI 2.2 to 7.8); p=0.013	136
	Patients=2061 controls=6183	Population-based case-control study	47%	—	—	OR 36.88, 95% CI 2.64 to 3.40; p=0.0001	137
	Patients=823 controls=3459	Case-control study	30.5%	—	—	1.57 (95% CI 1.08 to 2.28; p=0.0176)	138
	279	Prospective longitudinal	—	—	Incidence of HCC	—	139
	5929	Retrospective	9.2%	—	Incidence of HCC	—	140

Table 1 continued

No. of patients	Study design	% IR	HOMA-IR	Outcome measure	Result	Reference
197	Retrospective	11.7%		Incidence of HCC	HR 4.627, 95% CI 1.677 to 12.766	139
104	Prospective study	26%		Prediction of the presence of OV's	OR 1.296, 95% CI 1.018 to 1.649; p=0.03	140
39	Retrospective	64% (PTDM)		Mortality	56% vs 14%, p=0.01	141
95	Retrospective	50% metabolic syndrome		Fibrosis progression in recurrent HCV after OLT.	OR=6.3; p=0.017.	142
163	Retrospective			Fibrosis progression	HR 2.68; p=0.039	143
435	Retrospective	10.5% (PTDM)		Complications	48% vs 24%, p=0.005	144
				Cardiac	28% vs 5%, p=0.001	
				Major infections	22% vs 9%, p=0.05	
				Neurological	22 vs 6%, p=0.009	
				Neuropsychiatric	50 vs 30%, p=0.03	
				Acute rejection	Not difference	
				Survival		
16	Prospective cohort study	16% diabetic (23% IR)	(HOMA-IR >2.5)	Fibrosis progression	HR 2.07, 95% CI 1.10 to 3.91	145

HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HOMA, homeostatic model assessment; IR, insulin resistance; NA, not available; OLT, orthotopic liver transplantation; OV's, oesophageal varices; PTDM, post-transplant diabetes mellitus; RVR, rapid virological response; SVR, sustained virological response.

Response to antiviral treatment

Increasing levels of IR are associated with reduced rates of rapid virological response (RVR)^{124–126} as well as SVR in patients with HCV genotype 1, 2, 3 and 4 infections treated with a combination of Peg-IFN α and RBV.^{127–132} However, the mechanisms of IR-induced IFN resistance are not completely understood.

Intracellular factors dysregulated by HCV and responsible for the insulin-resistant phenotype may have additional effects as they are also involved in regulating IFN α signalling. These factors include some members of the SOCS family^{75 79 82 83 149} and the PP2A.⁹² IR is known to increase hepatic lipid synthesis.¹⁵⁰ Since the lipid droplet is an important organelle for HCV replication,¹⁵¹ accumulation of hepatic lipid droplets may increase HCV replication and result in poor responses to antiviral treatment.

Hepatocellular carcinoma (HCC)

IR has been recognised as an independent risk factor for the development of HCC.^{118 133–139} Potential pathogenic mechanisms include a direct mitogenic effect of insulin¹⁵² as well as oxidative stress and resultant steatosis that may also contribute to the development of HCC.^{153 154}

Oesophageal varices (OV's)

IR is emerging as a risk factor for OV's in patient with cirrhosis with HCV infection.¹⁴⁰ The pathogenic mechanism is not completely understood. IR may be associated with OV's via progression of liver fibrosis.¹¹⁵ Insulin modulates the endothelial synthesis of nitric oxide and endothelin¹⁵⁵ to induce the production of TNF α and connective growth factor, and to stimulate hepatic stellate cells.¹⁴⁷ Therefore, insulin could contribute to the pathogenesis of portal hypertension by interfering with both mechanical and dynamic mechanisms with collagen deposition, vasoconstriction and regulation of sinusoidal structure.¹⁴⁰

Liver transplant outcome

Patients with T2DM or even IR have higher post-transplantation complication rates (either liver or non-liver related) than those without glucose metabolic disarrangement.^{141–145} Interestingly, the incidence of post-transplant diabetes is higher in patients with liver diseases due to CHC rather than other causes.^{47–49} Further data are needed to clarify the relationship between IR and post-transplant complications.

PERSPECTIVES FOR MANAGEMENT

In view of the suboptimal response to the current antiviral treatments, it is imperative that thought is given to improving these potentially modifiable risk factors, especially IR and T2DM which are associated with adverse outcomes. Although increasing insulin sensitivity may be a rationale option in patients with CHC, especially those with metabolic syndrome, the ideal therapeutic modality for the prevention and management of IR and T2DM in the setting of HCV has not yet been established.

Box 1 Major facts about insulin resistance in the setting of HCV

- ▶ HCV is associated with insulin resistance and diabetes.²⁵
- ▶ The pathogenesis of insulin resistance represents a complex interplay between host and viral factors.
- ▶ Insulin resistance is linked to fibrosis progression.^{56 58 115–132}
- ▶ Insulin resistance is associated with a decreased early and sustained response to current antiviral therapy.^{124–132}

Different approaches have been proposed which include both pharmacological and lifestyle interventions. However, this is rather empirical, as the mechanism by which IR leads to potential IFN resistance are not completely elucidated.

The use of insulin-sensitising agents to enhance the antiviral treatment response of Peg-IFN and RBV has been postulated to be of benefit. Potential treatments studied to date include the thiazolidinedione, pioglitazone (PIO)—a specific PPAR γ agonist—and the biguanide, metformin, whose mechanism of action is specifically directed against the hepatic AMP-activated protein kinase.¹⁵⁶

The primary data on the use of PIO are from a prospective, multicentre study aimed at investigating the efficacy and safety of a 15 mg daily dose added to once-weekly Peg-IFN α 2/RBV combination therapy in retreatment of patients with CHC who were previously non-responders to a Peg-IFN α /RBV combination. All patients had a baseline HOMA >2.¹⁵⁷ The study was prematurely terminated as none of the first five patients enrolled in the trial had a sufficient virological response after 12 week. However, the authors surmise that their approach may have been inadequate in view of the suboptimal dose (15 mg four times a day).¹⁵⁸

Emerging data from several recent studies using PIO in combination with Peg-IFN α /RBV have yielded conflicting results.^{159–162} Elgouhari *et al* studied PIO 30 mg/day given for 4 weeks as monotherapy and then added Peg-IFN and RBV to treatment-naïve patients with CHC without diabetes. The authors showed that the triple regimen containing PIO increased the rate of virological response significantly after 4 weeks of treatment

compared with Peg-IFN and RBV alone. Long-term data are keenly awaited.¹⁵⁹ A randomised placebo-controlled study performed in the USA with PIO 30 mg/day plus Peg-IFN and RBV (ie, without preceding administration as monotherapy) clearly improved IR and steatosis, and increased the on-treatment virological response. However, SVR was not improved.¹⁶⁰ A subsequent trial with PIO 30 mg/day plus Peg-IFN and RBV was conducted conclusively in patients infected with HCV genotype 4 and resulted in higher rates of RVR and SVR with improvement in all parameters of IR.¹⁶¹

In contrast to these findings, interim 12 week analysis of a large, randomised, double-blind, placebo-controlled study of CHC genotype 1 patients with IR using PIO monotherapy for 16 weeks (30 mg/day \times 8 weeks then 45 mg/day \times 8 weeks) prior to the 48 week antiviral treatment with Peg-IFN and RBV found no improvement in RVR or early virological response despite improvement in adiponectin and several glycaemic variables including plasma glucose and insulin levels, and HOMA score.¹⁶²

Metformin has also been studied as potential adjuvant therapy for patients with IR, with mixed results. The TRIC-1 study,¹⁶³ which involved CHC genotype 1 patients with IR who were treated with metformin plus standard of care (SOC) reduced IR significantly but afforded only a marginal, non-significant gain in the SVR rate, despite an increased RVR after 4 weeks of triple therapy. In a subset analysis, women who received metformin doubled the SVR rates compared with the placebo group (57% vs 28%, $p=0.03$).¹⁶³

Ultimately, the use of insulin sensitisers in triple therapy raises many questions. Insulin sensitisers alone do not seem to affect viral load. While all studies to date utilising triple therapy with an insulin sensitiser and Peg-IFN and RBV have demonstrated improvement in IR, a variable virological response has been seen. This varying response suggests that there are probably many variables, including both host and viral factors, that alter responses to antiviral therapy even when insulin sensitivity is improved. Further study is needed to clarify the role of genotype, the degree of insulin sensitivity improvement, gender and genetics (such as the IL28 β mutation) on viral kinetics. Although the relationships between early viral kinetics during antiviral treatment in patients with CHC and IR are not completely understood, recent data support that increasing levels of IR are associated with reduced rates of the RVR.^{124 126} Similar data were recently published by Nasta *et al*¹²⁵ in HIV/HCV-co-infected patients. Moreover, in a recent study, hyperinsulinaemia reduced the 24 h virological response to Peg-IFN treatment in patients with CHC and IR.¹⁶⁴

As an alternative to pharmacological improvement of IR, assessment of the effect of a dietary and/or lifestyle changes on IR in patients with CHC, with its impact on hindering the progression of liver fibrosis and enhancing response to antiviral treatment, is interesting and worthy of further

Box 2 Summary

- ▶ Insulin resistance in setting of HCV is still an evolving story.
- ▶ Our understanding of the pathogenesis of HCV-induced insulin resistance and its deleterious effect are greatly improved.
- ▶ Direct effects of HCV in modulating insulin signalling via core protein and NS5A are better understood.^{75 76 87–89}
- ▶ Insulin-sensitising agents including the thiazolidinediones and metformin have a variable response on viral kinetics and SVR.
 - Studies are ongoing to further address the utility of insulin sensitising agents in improving SVR or mitigating disease progression.^{159–163}
- ▶ Our improved understanding of HCV-induced insulin resistance may allow for development of better strategies to eradicate the virus or prevent disease progression in the future.

evaluation. A 3 month study that encompassed body weight reduction and increased physical activity was associated with improvement histology and fasting insulin.^{165 166} Virological response was not assessed.

In another small pilot trial, 15 patients were placed on a strict low-calorie diet for 3 months to achieve a 10% reduction in BMI before starting treatment, whereas 17 were on a free diet for the same period. All patients were offered standard combined antiviral therapy with Peg-IFN and RBV. The use of a low-calorie diet was associated with an improved virological response (60% vs 17.6%; $p=0.035$), although it is unclear if this represent and end of treatment response or SVR. Improvement in virological response was associated with a reduction in HOMA.¹⁶⁷

Ultimately, there are no current clinical guidelines advocating the use of antidiabetic agents for patients with CHC and IR or diabetes mellitus. While the potential exists for improved outcomes to treatment among the various CHC genotypes, much is yet to be learned in reference to improving IR and its effect on virological response.

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REFERENCES

1. **Saltiel AR**, Kahn CR. Insulin signaling and the regulation of glucose and lipid metabolism. *Nature* 2001;**414**:799–806.
2. **DeFronzo RA**, Jacot E, Jequier E, *et al.* The effect of insulin on the disposal of intravenous glucose. Results from indirect calorimetry and hepatic and femoral venous catheterization. *Diabetes* 1981;**30**:1000–7.
3. **Shimano H**. Sterol regulatory element-binding proteins (SREBPs): transcriptional regulators of lipid synthetic genes. *Prog Lipid Res* 2001;**40**:439–52.
4. **White MF**. Insulin signaling in health and disease. *Science* 2003;**302**:1710–11.
5. **Withers DJ**. Insulin receptor substrate proteins and neuroendocrine function. *Biochem Soc Trans* 2001;**29**:525–9.
6. **Sesti G**. Pathophysiology of insulin resistance. *Best Pract Res Clin Endocrinol Metab* 2006;**20**:665–79.
7. **Wang X**, Proud CG. The mTOR pathway in the control of protein synthesis. *Physiology (Bethesda)* 2006;**21**:362–9.
8. **Schulinkamp RJ**, Pagano TC, Hung D, *et al.* Insulin receptors and insulin action in the brain: review and clinical implications. *Neurosci Biobehav Rev* 2000;**24**:855–72.
9. **Pessin JE**, Frattali AL. Molecular dynamics of insulin/IGF-I receptor transmembrane signaling. *Mol Reprod Dev* 1993;**35**:339–4; discussion 344–35.
10. **Su WW**, Lee KT, Yeh YT, *et al.* Association of circulating insulin-like growth factor 1 with hepatocellular carcinoma: one cross-sectional correlation study. *J Clin Lab Anal* 2010;**24**:195–200.
11. **Laron Z**. The GH-IGF1 axis and longevity. The paradigm of IGF1 deficiency. *Hormones (Athens)* 2008;**7**:24–7.
12. **Yeni-Komshian H**, Carantoni M, Abbasi F, *et al.* Relationship between several surrogate estimates of insulin resistance and quantification of insulin mediated glucose disposal in 490 healthy, nondiabetic volunteers. *Diabetes Care* 2000;**23**:171–5.
13. **Kahn CR**. Insulin resistance, insulin insensitivity, and insulin unresponsiveness: a necessary distinction. *Metabolism* 1978;**27**:1893–902.
14. **Laakso M**. Gene variants, insulin resistance and dyslipidemia. *Curr Opin Lipidol* 2004;**15**:115–20.
15. **Frittitta L**, Barrata R, Spampinato D. The Q121K PC-1 variant and obesity have additive and independent effects in causing insulin resistance. *J Clin Endocrinol Metab* 2001;**86**:5888–91.
16. **Baroni MG**, Arca M, Sentinelli F. The G972R variant of the insulin receptor substrate-1 (IRS-1) gene, body fat distribution and insulin resistance. *Diabetologia* 2001;**44**:367–72.
17. **Almind K**, Inoue G, Pedersen O, *et al.* A common aminoacid polymorphism in insulin receptor substrate-1 causes impaired insulin signalling. Evidence from transfection studies. *J Clin Invest* 1996;**97**:2569–75.
18. **Gurnell M**, Savage DB, Chatterjee VK, *et al.* The metabolic syndrome: peroxisome proliferator-activated receptor gamma and its therapeutic modulation. *J Clin Endocrinol Metab* 2003;**88**:2412–21.
19. **Deeb SS**, Fajas L, Nemoto M, *et al.* A Pro121Ala substitution in PPAR-gamma 2 associated with decreased receptor activity, lower body mass index and improved insulin sensitivity. *Nat Genet* 1998;**20**:284–7.
20. **Kadowaki T**, Hara K, Yamauchi T, *et al.* Molecular mechanisms of insulin resistance in obesity. *Exp Biol Med* 2003;**228**:1111–17.
21. **Sykiotis GP**, Papavassiliou AG. Serine phosphorylation of insulin receptor substrate-1: a novel target for the reversal of insulin resistance. *Mol Endocrinol* 2001;**15**:1864–9.
22. **Virkamäki A**, Ueki K, Kahn CR. Protein-protein interaction in insulin signaling and the molecular mechanisms of insulin resistance. *J Clin Invest* 1999;**103**:931–43.
23. **Taniguchi CM**, Ueki K, Kahn R. Complementary roles of IRS-1 and IRS-2 in the hepatic regulation of metabolism. *J Clin Invest* 2005;**115**:718–27.
24. **Ishizaka N**, Ishizaka Y, Takahashi E, *et al.* Association between hepatitis C virus seropositivity, carotid-artery plaque, and intima-media thickening. *Lancet* 2002;**359**:133–5.
25. **Allison ME**, Wrehgitt T, Palmer CR, *et al.* Evidence for a link between hepatitis C virus infection and diabetes mellitus in a cirrhotic population. *J Hepatol* 1994;**21**:1135–9.
26. **Mason AL**, Lau JY, Hoang N, *et al.* Association of diabetes mellitus and chronic hepatitis C virus infection. *Hepatology* 1999;**29**:328–33.
27. **Grimbert S**, Valensi P, Levy-Marchal C, *et al.* High prevalence of diabetes mellitus in patients with chronic hepatitis C. A case-control study. *Gastroenterol Clin Biol* 1996;**20**:544–8.
28. **Caronia S**, Taylor K, Pagliaro L, *et al.* Further evidence for an association between non-insulin-dependent diabetes mellitus and chronic hepatitis C virus infection. *Hepatology* 1999;**30**:1059–63.
29. **Zein NN**, Abdulkarim AS, Wiesner RH, *et al.* Prevalence of diabetes mellitus in patients with end stage liver cirrhosis due to hepatitis C, alcohol, or cholestatic disease. *J Hepatol* 2000;**32**:209–17.
30. **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**:1318–23.
31. **Lecube A**, Hernández C, Genesca J, *et al.* High prevalence of glucose abnormalities in patients with hepatitis C virus infection: a multivariate analysis considering the liver injury. *Diabetes Care* 2004;**27**:1171–5.
32. **Huang JF**, Dai CY, Hwang SJ, *et al.* 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**:1237–43.
33. **Imazeki F**, Yokosuka O, Fukai K, *et al.* 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**:355–62.
34. **ray H**, Wrehgitt T, Stratton IM, *et al.* High prevalence of hepatitis C infection in Afro-Caribbean patients with type 2 diabetes and abnormal liver function tests. *Diabet Med* 1995;**12**:244–9.
35. **Simo R**, Herna'ndez C, Genesca J, *et al.* High prevalence of hepatitis C virus infection in diabetic patients. *Diabetes Care* 1996;**19**:998–1000.
36. **Sotiropoulos A**, Peppas TA, Skliros E, *et al.* Low prevalence of hepatitis C virus infection in Greek diabetic patients. *Diabet Med* 1999;**16**:250–2.
37. **Sangiorgio L**, Attardo T, Gangemi R, *et al.* Increased frequency of HCV and HBV infection in type 2 diabetic patients. *Diabetes Res Clin Pract* 2000;**48**:147–51.
38. **Picerno I**, Di Pietro A, Spataro P, *et al.* Is diabetes mellitus a risk factor for HCV infection? *Ann Ig* 2002;**14**:473–7.
39. **Okan V**, Araz M, Aktaran S, *et al.* Increased frequency of HCV but not HBV infection in type 2 diabetic patients in Turkey. *Int J Clin Pract* 2002;**56**:175–7.
40. **Fukui M**, Kitagawa Y, Nakamura N, *et al.* Hepatitis C virus and atherosclerosis in patients with type 2 diabetes. *JAMA* 2003;**289**:1245–6.

41. **Balogun WO**, Adeleye JO, Akinlade KS, *et al.* Low prevalence of hepatitis-C viral seropositivity among patients with type-2 diabetes mellitus in a tertiary hospital. *J Natl Med Assoc* 2006;**98**:1805–8.
42. **Chen HF**, Li CY, Chen P, *et al.* Seroprevalence of hepatitis B and C in type 2 diabetic patients. *J Chin Med Assoc* 2006;**69**:146–52.
43. **Gulcan A**, Gulcan E, Tokar A, *et al.* Evaluation of risk factors and seroprevalence of hepatitis B and C in diabetic patients in Kutahya, Turkey. *J Investig Med* 2008;**56**:858–63.
44. **Mehta SH**, Brancati FL, Sulkowski MS, *et al.* Prevalence of type 2 diabetes mellitus among persons with hepatitis C virus infection in the United States. *Ann Intern Med* 2000;**133**:592–9.
45. **White DL**, Ratziu V, El-Serag HB. Hepatitis C infection and risk of diabetes: a systematic review and meta-analysis. *J Hepatol* 2008;**49**:831–44.
46. **Mehta SH**, Brancati FL, Strathdee SA, *et al.* Hepatitis C virus infection and incident type 2 diabetes. *Hepatology* 2003;**38**:50–6.
47. **Bigam DL**, Pennington JJ, Carpentier A, *et al.* Hepatitis C-related cirrhosis: a predictor of diabetes after liver transplantation. *Hepatology* 2000;**32**:87–90.
48. **Ma Y**, Yan WW. Chronic hepatitis C virus infection and post liver transplantation diabetes mellitus. *World J Gastroenterol* 2005;**11**:6085–9.
49. **Delgado-Borrego A**, Casson D, Schoenfeld D, *et al.* Hepatitis C virus is independently associated with increased insulin resistance after liver transplantation. *Transplantation* 2004;**77**:703–10.
50. **Saliba F**, Lakehal M, Pageaux GP, *et al.* Risk factors for new-onset diabetes mellitus following liver transplantation and impact of hepatitis C infection: an observational multicenter study. *Liver Transpl* 2007;**13**:136–44.
51. **Delgado-Borrego A**, Liu Y-S, Jordan SH, *et al.* 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. **Finni PE**, Souza ER, Rioja S, *et al.* Is hepatitis C a risk factor to post transplant diabetes mellitus after renal transplantation in patients using tacrolimus? *Transplant Proc* 2004;**36**:884–5.
53. **Shah T**, Kasravi A, Huang E, *et al.* Risk factors for development of new-onset diabetes mellitus after kidney transplantation. *Transplantation* 2006;**82**:1673–6.
54. **Kamar N**, Mariat C, Delahousse M, *et al.* Diabetes mellitus after kidney transplantation: a French multicentre observational study. *Nephrol Dial Transplant* 2007;**22**:1986–93.
55. **Fabrizi F**, Messa P, Martin P, *et al.* Hepatitis C virus infection and post-transplant diabetes mellitus among renal transplant patients: a meta-analysis. *Int J Artif Organs* 2008;**31**:675–82.
56. **Hui JM**, Sud A, Farrell GC, *et al.* Insulin resistance is associated with chronic hepatitis C virus infection and fibrosis progression [corrected]. *Gastroenterology* 2003;**125**:1695–704.
57. **Yoneda M**, Saito S, Ikeda T, *et al.* Hepatitis C virus directly associates with insulin resistance independent of the visceral fat area in nonobese and nondiabetic patients. *J Viral Hepat* 2007;**14**:600–7.
58. **Moucarri R**, Asselah T, Cazals-Hatem D, *et al.* Insulin resistance in chronic hepatitis C: association with genotypes 1 and 4, serum HCV RNA level, and liver fibrosis. *Gastroenterology* 2008;**134**:416–23.
59. **Harrison SA**. Correlation between insulin resistance and hepatitis C viral load. *Hepatology* 2006;**43**:1168; author reply 1168–1169.
60. **Hsu CS**, Liu CJ, Liu CH, *et al.* High hepatitis C viral load is associated with insulin resistance in patients with chronic hepatitis C. *Liver Int* 2008;**28**:271–7.
61. **Kawaguchi T**, Ide T, Taniguchi E, *et al.* Clearance of HCV improves insulin resistance, beta-cell function, and hepatic expression of insulin receptor substrate 1 and 2. *Am J Gastroenterol* 2007;**102**:570–6.
62. **Chehadeh W**, Abdella N, Ben-Nakhi A, *et al.* Risk factors for the development of diabetes mellitus in chronic hepatitis C virus genotype 4 infection. *J Gastroenterol Hepatol* 2009;**24**:42–8.
63. **Romero-Gómez M**, Fernández-Rodríguez CM, Andrade RJ, *et al.* Effect of sustained virological response to treatment on the incidence of abnormal glucose values in chronic hepatitis C. *J Hepatol* 2008;**48**:721–7.
64. **Giordanino C**, Bugianesi E, Smedile A, *et al.* 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**:2481–7.
65. **Arase Y**, Suzuki F, Suzuki Y, *et al.* Sustained virological response reduces incidence of onset of type 2 diabetes in chronic hepatitis C. *Hepatology* 2009;**49**:739–44.
66. **Hotamisligil GS**. Inflammation and metabolic disorders. *Nature* 2006;**444**:860–7.
67. **Sheikh MY**, Choi J, Qadri I, *et al.* Hepatitis C virus infection: molecular pathways to metabolic syndrome. *Hepatology* 2008;**47**:2127–33.
68. **Shintani Y**, Fujie H, Miyoshi H, *et al.* Hepatitis C virus infection and diabetes: direct involvement of the virus in the development of insulin resistance. *Gastroenterology* 2004;**126**:840–8.
69. **McGuinness PH**, Painter D, Davies S, *et al.* Increases in intrahepatic CD68 positive cells, MAC387 positive cells, and proinflammatory cytokines (particularly interleukin 18) in chronic hepatitis C infection. *Gut* 2000;**46**:260–9.
70. **Im SS**, Kwon SK, Kim TH, *et al.* Regulation of glucose transporter type 4-isoform-gene expression in muscle and adipocytes. *IUBMB Life* 2007;**59**:134–45.
71. **Ohmura E**, Hosaka D, Yazawa M, *et al.* Association of free fatty acids (FFA) and tumor necrosis factor-alpha (TNF-alpha) and insulin-resistant metabolic disorder. *Horm Metab Res* 2007;**39**:212–17.
72. **Durante-Mangoni E**, Zampino R, Marrone A, *et al.* Hepatic steatosis and insulin resistance are associated with serum imbalance of adiponectin/tumour necrosis factor-alpha in chronic hepatitis C patients. *Aliment Pharmacol Ther* 2006;**24**:1349–57.
73. **Cua IH**, Hui JM, Bandara P, *et al.* Insulin resistance and liver injury in hepatitis C is not associated with virus-specific changes in adipocytokines. *Hepatology* 2007;**46**:66–73.
74. **Alaei M**, Negro F. Hepatitis C virus and glucose and lipid metabolism. *Diabetes Metab* 2008;**34**:692–700.
75. **Kawaguchi T**, Yoshida T, Harada M, *et al.* Hepatitis C virus down-regulates insulin receptor substrates 1 and 2 through up-regulation of suppressor of cytokine signaling 3. *Am J Pathol* 2004;**165**:1499–508.
76. **Aytug S**, Reich D, Sapiro LE, *et al.* Impaired IRS-1/PI3-kinase signaling in patients with HCV: a mechanism for increased prevalence of type 2 diabetes. *Hepatology* 2003;**38**:1384–92.
77. **Miyamoto H**, Moriishi K, Moriya K, *et al.* Involvement of the PA28gamma-dependent pathway in insulin resistance induced by hepatitis C virus core protein. *J Virol* 2007;**81**:1727–35.
78. **Banerjee S**, Saito K, Ait-Goughoulte M, *et al.* 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**:2606–12.
79. **Pazienza V**, Clément S, Pugnale P, *et al.* The hepatitis C virus core protein of genotypes 3a and 1b downregulates insulin receptor substrate 1 through genotype-specific mechanisms. *Hepatology* 2007;**45**:1164–71.
80. **Korenaga M**, Wang T, Li Y, *et al.* Hepatitis C virus core protein inhibits mitochondrial electron transport and increases ROS production. *J Biol Chem* 2005;**280**:37481–8.
81. **Machida K**, Cheng KT, Lai CK, *et al.* Hepatitis C virus triggers mitochondrial permeability transition with production of reactive oxygen species, leading to DNA damage and STAT3 activation. *J Virol* 2006;**80**:7199–207.
82. **Persico M**, Capasso M, Persico E, *et al.* Suppressor of cytokine signaling 3 (SOCS3) expression and hepatitis C virus-related chronic hepatitis: insulin resistance and response to antiviral therapy. *Hepatology* 2007;**46**:1009–15.
83. **Persico M**, Capasso M, Russo R, *et al.* Elevated expression and polymorphisms of SOCS3 influence patient response to antiviral therapy in chronic hepatitis C. *Gut* 2008;**57**:507–15.
84. **Moriishi K**, Mochizuki R, Moriya K, *et al.* Critical role of PA28gamma in hepatitis C virus-associated steatogenesis and hepatocarcinogenesis. *Proc Natl Acad Sci USA* 2007;**104**:1661–6.
85. **Higuchi S**, Kubota M, Iguchi K, *et al.* Transcriptional regulation of aquaporin 3 by insulin. *J Cell Biochem* 2007;**102**:1051–8.
86. **Banerjee A**, Meyer K, Mazumdar B, *et al.* Hepatitis C virus differentially modulates activation of forkhead transcription factors and insulin-induced metabolic gene expression. *J Virol* 2010;**84**:5936–46.
87. **Tardif KD**, Mori K, Siddiqui A. Hepatitis C virus subgenomic replicons induce endoplasmic reticulum stress activating an intracellular signaling pathway. *J Virol* 2002;**76**:7453–9.
88. **Riordan SM**, Skinner NA, Kurtovic J, *et al.* Toll-like receptor expression in chronic hepatitis C: correlation with pro-inflammatory cytokine levels and liver injury. *Inflamm Res* 2006;**55**:279–85.

89. **Gong G**, Waris G, Tanveer R, *et al*. Human hepatitis C virus NS5A protein alters intracellular calcium levels, induces oxidative stress, and activates STAT-3 and NF-kappa B. *Proc Natl Acad Sci USA* 2001;**98**:9599–604.
90. **Georgopoulou U**, Tsitoura P, Kalamvoki M, *et al*. The protein phosphatase 2A represents a novel cellular target for hepatitis C virus NS5A protein. *Biochimie* 2006;**88**:651–62.
91. **Christen V**, Treves S, Duong FH, *et al*. Activation of endoplasmic reticulum stress response by hepatitis viruses up-regulates protein phosphatase 2A. *Hepatology* 2007;**46**:558–65.
92. **Bernsmeier C**, Duong FH, Christen V, *et al*. Virus-induced over-expression of protein phosphatase 2A inhibits insulin signalling in chronic hepatitis C. *J Hepatol* 2008;**49**:429–40.
93. **Duong FH**, Filipowicz M, Tripodi M, *et al*. Hepatitis C virus inhibits interferon signaling through up-regulation of protein phosphatase 2A. *Gastroenterology* 2004;**126**:263–27.
94. **Bureau C**, Bernad J, Chaouche N, *et al*. Nonstructural 3 protein of hepatitis C virus triggers an oxidative burst in human monocytes via activation of NADPH oxidase. *J Biol Chem* 2001;**276**:23077–83.
95. **Desvergne B**, Wahli W. Peroxisome proliferator-activated receptors: nuclear control of metabolism. *Endocr Rev* 1999;**20**:649–88.
96. **Bardot O**, Aldridge TC, Latruffe N, *et al*. PPAR-RXR heterodimer activates a peroxisome proliferator response element upstream of the bifunctional enzyme gene. *Biochem Biophys Res Commun* 1993;**192**:37–45.
97. **Gearing KL**, Gottlicher M, Teboul M, *et al*. Interaction of the peroxisome-proliferator-activated receptor and retinoid X receptor. *Proc Natl Acad Sci USA* 1993;**90**:1440–4.
98. **Nuclear Receptors Nomenclature Committee**. A unified nomenclature system for the nuclear receptor superfamily. *Cell* 1999;**97**:161–3.
99. **Dharancy S**, Malapel M, Perlemuter G, *et al*. Impaired expression of the peroxisome proliferator-activated receptor alpha during hepatitis C virus infection. *Gastroenterology* 2005;**128**:334–42.
100. **de Gottardi A**, Paziienza V, Pugnale P, *et al*. Peroxisome proliferator-activated receptor-alpha and-gamma mRNA levels are reduced in chronic hepatitis C with steatosis and genotype 3 infection. *Aliment Pharmacol Ther* 2006;**23**:107–14.
101. **Tanaka N**, Moriya K, Kiyosawa K, *et al*. PPAR alpha activation is essential for HCV core protein-induced hepatic steatosis and hepatocellular carcinoma in mice. *J Clin Invest* 2008;**118**:683–94.
102. **Haluzik M**, Parizkova J, Haluzik MM. Adiponectin and its role in the obesity-induced insulin resistance and related complications. *Physiol Res* 2004;**53**:123–29.
103. **Abdalla MY**, Ahmad IM, Spitz DR, *et al*. Hepatitis C virus-core and non structural proteins lead to different effects on cellular antioxidant defenses. *J Med Virol* 2005;**76**:489–7.
104. **Moriya K**, Nakagawa K, Santa T, *et al*. Oxidative stress in the absence of inflammation in a mouse model for hepatitis C virus-associated hepatocarcinogenesis. *Cancer Res* 2001;**61**:4365–70.
105. **Okuda M**, Li K, Beard MR, *et al*. Mitochondrial injury, oxidative stress, and antioxidant gene expression are induced by hepatitis C virus core protein. *Gastroenterology* 2002;**122**:366–75.
106. **Oliveira AC**, Parise ER, Catarino RM, *et al*. Insulin resistance and not steatosis is associated with modifications in oxidative stress markers in chronic hepatitis C, non-3 genotype. *Free Radic Res* 2009;**43**:1187–94.
107. **Vidali M**, Tripodi MF, Ivaldi A, *et al*. Interplay between oxidative stress and hepatic steatosis in the progression of chronic hepatitis C. *J Hepatol* 2008;**48**:399–406.
108. **Levent G**, Ali A, Ahmet A, *et al*. Oxidative stress and antioxidant defense in patients with chronic hepatitis C patients before and after pegylated interferon alpha-2b plus ribavirin therapy. *J Transl Med* 2006;**4**:25.
109. **Milner KL**, van der Poorten D, Trenell M, *et al*. Chronic hepatitis C is associated with peripheral rather than hepatic insulin resistance. *Gastroenterology* 2010;**138**:932–41.e1-3.
110. **Vanni E**, Abate ML, Gentilcore E, *et al*. Sites and mechanisms of insulin resistance in nonobese, nondiabetic patients with chronic hepatitis C. *Hepatology* 2009;**50**:697–706.
111. **Tiikkainen M**, Häkkinen AM, Korsheninnikova E, *et al*. Effects of rosiglitazone and metformin on liver fat content, hepatic insulin resistance, insulin clearance, and gene expression in adipose tissue in patients with type 2 diabetes. *Diabetes* 2004;**53**:2169–76.
112. **Petersen KF**, Dufour S, Savage DB, *et al*. The role of skeletal muscle insulin resistance in the pathogenesis of the metabolic syndrome. *Proc Natl Acad Sci USA* 2007;**104**:12587–94.
113. **Tietge UJ**, Selberg O, Kreter A, *et al*. Alterations in glucose metabolism associated with liver cirrhosis persist in the clinically stable long-term course after liver transplantation. *Liver Transpl* 2004;**10**:1030–40.
114. **Laskus T**, Radkowski M, Wang LF, *et al*. 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* 1998;**28**:1398–401.
115. **Hsu CS**, Liu CH, Liu CJ, *et al*. Association of metabolic profiles with hepatic fibrosis in chronic hepatitis C patients with genotype 1 or 2 infection. *J Gastroenterol Hepatol* 2010;**25**:970–7.
116. **Muzzi A**, Leandro G, Rubbia-Brandt L, *et al*. Insulin resistance is associated with liver fibrosis in non-diabetic chronic hepatitis C patients. *J Hepatol* 2005;**42**:41–6.
117. **Taura N**, Ichikawa T, Hamasaki K, *et al*. Association between liver fibrosis and insulin sensitivity in chronic hepatitis C patients. *Am J Gastroenterol* 2006;**101**:2752–9.
118. **Kita Y**, Mizukoshi E, Takamura T, *et al*. Impact of diabetes mellitus on prognosis of patients infected with hepatitis C virus. *Metabolism* 2007;**56**:1682–8.
119. **Petta S**, Camma C, Di Marco V, *et al*. Insulin resistance and diabetes increase fibrosis in the liver of patients with genotype 1 HCV infection. *Am J Gastroenterol* 2008;**103**:1136–44.
120. **Cua IH**, Hui JM, Kench JG, *et al*. Genotype-specific interactions of insulin resistance, steatosis, and fibrosis in chronic hepatitis C. *Hepatology* 2008;**48**:723–31.
121. **Moucari R**, Ripault MP, Martinot-Peignoux M, *et al*. Insulin resistance and geographical origin: major predictors of liver fibrosis and response to peginterferon and ribavirin in HCV-4. *Gut* 2009;**58**:1662–9.
122. **Halfon P**, Pénaranda G, Carrat F, *et al*. Influence of insulin resistance on hepatic fibrosis and steatosis in hepatitis C virus (HCV) mono-infected compared with HIV-HCV co-infected patients. *Aliment Pharmacol Ther* 2009;**30**:61–70.
123. **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**:1509–15.
124. **Khattab M**, Eslam M, Sharwa MA, *et al*. Insulin resistance predicts rapid virologic response to peginterferon/ribavirin combination therapy in hepatitis C genotype 4 patients. *Am J Gastroenterol*. 2010;**105**:1970–7.
125. **Nasta P**, Gatti F, Puoti M, *et al*. Insulin resistance impairs rapid virologic response in HIV/hepatitis C virus coinfecting patients on peginterferon-alfa-2a. *AIDS* 2008;**22**:857–61.
126. **Grasso A**, Malfatti F, De Leo P, *et al*. Insulin resistance predicts rapid virological response in non-diabetic, non-cirrhotic genotype 1 HCV patients treated with peginterferon alpha-2b plus ribavirin. *J Hepatol* 2009;**51**:984–90.
127. **Romero-Gómez M**, Del Mar Vilorio M, Andrade RJ, *et al*. Insulin resistance impairs sustained response rate to peginterferon plus ribavirin in chronic hepatitis C patients. *Gastroenterology* 2005;**128**:636–41.
128. **Conjeevaram HS**, Kleiner DE, Everhart JE, *et al*. Race, insulin resistance and hepatic steatosis in chronic hepatitis C. *Hepatology* 2007;**45**:80–7.
129. **Dai CY**, Huang JF, Hsieh MY, *et al*. Insulin resistance predicts response to peginterferon-alpha/ribavirin combination therapy in chronic hepatitis C patients. *J Hepatol* 2009;**50**:712–18.
130. **Mizuta T**, Kawaguchi Y, Eguchi Y, *et al*. Whole-body insulin sensitivity index is a highly specific predictive marker for virological response to peginterferon plus ribavirin therapy in chronic hepatitis C patients with genotype 1b and high viral load. *Dig Dis Sci* 2010;**55**:183–9.
131. **Chu CJ**, Lee SD, Hung TH, *et al*. 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.
132. **Poustchi H**, Negro F, Hui J, *et al*. Insulin resistance and response to therapy in patients infected with chronic hepatitis C virus genotypes 2 and 3. *J Hepatol* 2008;**48**:28–34.
133. **Chen CL**, Yang HI, Yang WS, *et al*. Metabolic factors and risk of hepatocellular carcinoma by chronic hepatitis B/C infection: a follow-up study in Taiwan. *Gastroenterology* 2008;**135**:111–21.
134. **Veldt BJ**, Chen W, Heathcote EJ, *et al*. Increased risk of hepatocellular carcinoma among patients with hepatitis C cirrhosis and diabetes mellitus. *Hepatology* 2008;**47**:1856–62.
135. **Davila JA**, Morgan RO, Shaib Y, *et al*. Diabetes increases the risk of hepatocellular carcinoma in the United States: a population based case control study. *Gut* 2005;**54**:533–9.

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* 2001;**96**:2462-7.
137. **Tazawa J**, Maeda M, Nakagawa M, *et al*. Diabetes mellitus may be associated with hepatocarcinogenesis in patients with chronic hepatitis C. *Dig Dis Sci* 2002;**47**:710-15.
138. **Wang CS**, Yao WJ, Chang TT, *et al*. The impact of type 2 diabetes on the development of hepatocellular carcinoma in different viral hepatitis statuses. *Cancer Epidemiol Biomarkers Prev* 2009;**18**:2054-60.
139. **Konishi I**, Hiasa Y, Shigematsu S, *et al*. Diabetes pattern on the 75 g oral glucose tolerance test is a risk factor for hepatocellular carcinoma in patients with hepatitis C virus. *Liver Int* 2009;**29**:1194-201.
140. **Cammà C**, Petta S, Di Marco V, *et al*. Insulin resistance is a risk factor for esophageal varices in hepatitis C virus cirrhosis. *Hepatology* 2009;**49**:195-203.
141. **Baid S**, Cosimi AB, Farrell ML, *et al*. Post transplant diabetes mellitus in liver transplant recipients: risk factors, temporal relationship with hepatitis C virus allograft hepatitis, and impact on mortality. *Transplantation* 2001;**72**:1066-72.
142. **Hanouneh IA**, Feldstein AE, McCullough AJ, *et al*. The significance of metabolic syndrome in the setting of recurrent hepatitis C after liver transplantation. *Liver Transpl* 2008;**14**:1287-93.
143. **Foxton MR**, Quaglia A, Muiresan P, *et al*. The impact of diabetes mellitus on fibrosis progression in patients transplanted for hepatitis C. *Am J Transplant* 2006;**6**:1922-9.
144. **John PR**, Thuluvath PJ. Outcome of patients with new-onset diabetes mellitus after liver transplantation compared with those without diabetes mellitus. *Liver Transpl* 2002;**8**:708-13.
145. **Veldt BJ**, Poterucha JJ, Watt KD, *et al*. Insulin resistance, serum adipokines and risk of fibrosis progression in patients transplanted for hepatitis C. *Am J Transplant* 2009;**9**:1406-13.
146. **Abbott KC**, Lentine KL, Bucci JR, *et al*. Impact of diabetes and hepatitis after kidney transplantation on patients who are affected by hepatitis C virus. *J Am Soc Nephrol* 2004;**15**:3166-74.
147. **Ratziu V**, Munteanu M, Charlotte F, *et al*. Fibrogenic impact of high serum glucose in chronic hepatitis C. *J Hepatol* 2003;**39**:1049-55.
148. **Negro F**, Sanyal AJ. Hepatitis C virus, steatosis and lipid abnormalities: clinical and pathogenic data. *Liver Int* 2009;**29** (Suppl 2):26-37.
149. **Walsh MJ**, Jonsson JR, Richardson MM, *et al*. 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. *Gut* 2006;**55**:529-35.
150. **Shimomura I**, Matsuda M, Hammer RE, *et al*. Decreased IRS-2 and increased SREBP-1c lead to mixed insulin resistance and sensitivity in livers of lipodystrophic and ob/ob mice. *Mol Cell* 2000;**6**:77-86.
151. **Miyanari Y**, Atsuzawa K, Usuda N, *et al*. The lipid droplet is an important organelle for hepatitis C virus production. *Nat Cell Biol* 2007;**9**:1089-97.
152. **Kawaguchi T**, Taniguchi E, Morita Y, *et al*. Association of exogenous insulin or sulphonylurea treatment with an increased incidence of hepatoma in patients with hepatitis C virus infection. *Liver Int* 2010;**30**:479-86.
153. **Choi J**, Ou JH. Mechanisms of liver injury. III. Oxidative stress in the pathogenesis of hepatitis C virus. *Am J Physiol Gastrointest Liver Physiol* 2006;**290**:G847-51.
154. **El-Serag HB**. Epidemiology of hepatocellular carcinoma in USA. *Hepatol Res* 2007;**37**(Suppl 2):S88-94.
155. **Iwakiri Y**, Groszmann RJ. Vascular endothelial dysfunction in cirrhosis. *J Hepatol* 2007;**46**:927-34.
156. **Shaw RJ**, Lamia KA, Vasquez D, *et al*. The kinase LKB1 mediates glucose homeostasis in liver and therapeutic effects of metformin. *Science* 2005;**310**:1642-6.
157. **Overbeck K**, Genné D, Golay A, *et al*. Pioglitazone in chronic hepatitis C not responding to pegylated interferon alpha and ribavirin. *J Hepatol* 2008;**49**:295-8.
158. **Negro F**. Correction of insulin resistance in chronic hepatitis C patients not responding to the standard of care: more questions than answers. *J Hepatol* 2009;**50**:1271-2.
159. **Elgouhari HM**, Cesario KB, Lopez R, *et al*. Pioglitazone improves early virologic kinetic response to PEG IFN/RBV combination therapy in hepatitis C genotype 1 naïve patients. *Hepatology* 2008;**48**:383A.
160. **Conjeevaram H**, Burant CF, McKenna, *et al*. 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.
161. **Khattab M**, Emad M, Abdelaleem A, *et al*. Pioglitazone improves virological response to peginterferon alpha-2b/ribavirin combination therapy in hepatitis C genotype 4 patients with insulin resistance. *Liver Int* 2010;**30**:447-54.
162. **Harrison S**, Hamzeh FM, Lentz E, *et al*. Virologic and metabolic responses in chronic hepatitis C (CHC) patients with insulin resistance (IR) treated with pioglitazone and peginterferon alpha-2 A plus ribavirin. *Abstract presented in EASL Apr 15 2010*.
163. **Romero-Gómez M**, Diago M, Andrade RJ, *et al*. Treatment of insulin resistance with metformin in naïve genotype 1 chronic hepatitis C patients receiving peginterferon alfa-2a plus ribavirin. *Hepatology* 2009;**50**:1702-8.
164. **Bortoletto G**, Scribano L, Realdon S, *et al*. Hyperinsulinaemia reduces the 24-h virological response to PEG-interferon therapy in patients with chronic hepatitis C and insulin resistance. *J Viral Hepat* 2010;**17**:475-80.
165. **Hickman IJ**, Clouston AD, Macdonald GA, *et al*. Effect of weight reduction on liver histology and biochemistry in patients with chronic hepatitis C. *Gut* 2002;**51**:89-94.
166. **Hickman IJ**, Jonsson JR, Prins JB, *et al*. Modest weight loss and physical activity in overweight patients with chronic liver disease results in sustained improvements in alanine aminotransferase, fasting insulin, and quality of life. *Gut* 2004;**53**:413-19.
167. **Tarantino G**, Conca P, Ariello M, *et al*. Does a lower insulin resistance affect antiviral therapy response in patients suffering from HCV related chronic hepatitis? *Gut* 2006;**55**:585.