Introduction

Chronic hepatitis C virus (HCV) infection is a systemic disease leading to hepatic and extra-hepatic manifestations. A potential synergism exists between HCV infection and diabetes and this is attributed to multi-level and multi-faceted interactions between HCV and glucose metabolism. Allison et al. first reported an increased prevalence of diabetes mellitus in patients with HCV-associated liver cirrhosis but the categorisation of diabetes was not possible initially due to lack of genetic and immunological data.

The association between HCV and diabetes was initially perceived to be a non-specific consequence of liver inflammation but several mechanisms have now been cited. HCV infections can trigger autoimmune reactions against pancreatic β cells in genetically susceptible subjects leading to direct destruction of β cells thereby causing type 1 diabetes. Conversely, a complex interaction between insulin resistance (IR), hepatic steatosis and inflammatory cytokines have been implicated for the development of type 2 diabetes in HCV infected individuals. HCV causes alteration in hepatic carbohydrate and lipid metabolism and has also been linked with modifications of molecular mechanisms like oxidative stress, mitochondrial function, signalling in the insulin receptor substrate-1 pathway and influences on the activities of pro-inflammatory cytokines and adipokines. This creates an environment for metabolic syndrome leading to altered glucose homeostasis resulting in impaired glucose tolerance and type 2 diabetes.

HCV infection is the most common indication for liver transplantation. Patients may either have pre-existing diabetes mellitus (PDM) or may develop new-onset diabetes after transplant (NODAT). In the first year post-transplant, diabetes is most likely due to intense immunosuppression which potentiates the dysglycaemic effects of HCV by enhancing viral replication. This potentially resolves after the immunosuppressive regimen is stabilised but long-term diabetes (pre-existing and NODAT) may persist, leading to advanced hepatic fibrosis and graft failure.

The magnitude of the problem

Chronic hepatitis C has a global prevalence of 2–3%; approximately 150–200 million people are thought to be currently infected worldwide and an additional 3–4 million are infected each year. It is the most common cause of liver cirrhosis and liver cancer, and it remains the primary cause for liver transplantation in the western countries. Chronic HCV infection is believed to be a multi-faceted systemic disease which not only influences the hepatic environment causing inflammation, steatosis and fibrosis but also alters the metabolism of glucose and lipids, leading to metabolic sequelae such as insulin resistance, diabetes and dyslipidaemia. HCV has been identified as an independent risk factor for the development of diabetes in predisposed individuals (with family history and visceral obesity) and it is more prevalent with certain HCV genotypes. Moreover, it can also induce direct destruction of pancreatic β cells and trigger autoimmune reactions by molecular mimicry in the pancreas, leading to auto-immune diabetes. Its immunological effects can also lead to the development of diabetes in patients who had undergone liver transplantation for HCV infection which is further made worse by intense immunosuppression used in such settings.

This article provides an overview of the intriguing relationship between HCV infection and diabetes, the two major public health challenges which lead to widespread health and financial burden worldwide. Copyright © 2016 John Wiley & Sons.
hepatic transplantation; it is estimated that 80% of patients with cirrhosis show glucose intolerance and 10–20% of them have diabetes mellitus.\(^9\) After the initial association was described in 1994\(^1\) several epidemiological studies on the seroprevalence of HCV have shown higher prevalences in diabetic patients than in controls, and further analyses have also shown a higher prevalence of diabetes in patients who are sero-positive for HCV than in controls without HCV infection.\(^3\)

In a large and population-based study conducted by the National Health and Nutrition Examination Survey (NHANES-III), it was shown that people who were anti-HCV positive and aged \(\geq 40\) 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 type 2 diabetes compared to anti-HCV negative individuals.\(^10\) In the US, a community-based study echoed similar opinion suggesting people with a high risk of developing type 2 diabetes based on age and BMI were those patients with HCV and it was 11 times higher than in patients who do not have the infection (relative hazard 11.58; 95% CI 1.39–96.6).\(^11\)

In the UK, a higher HCV antibody titre was found in patients recruited for UKPDGS and 16% had abnormal liver function tests (LFTs).\(^12\) Recent meta-analyses have also established a similar association, depicting a higher risk of diabetes in HCV infected cases when compared to hepatitis B virus (HBV) infected controls, and established that such an association becomes stronger over the course of time.\(^13,14\)

In an earlier retrospective study in patients who had liver transplantation (LT) for HCV-induced cirrhosis, at least 50% developed type 2 diabetes in comparison to 9% of patients with liver disease unrelated to HCV infection.\(^1\) A Canadian study of 278 patients who had LT for multiple reasons showed that HCV-related cirrhosis was an independent risk factor for type 2 diabetes in one year after transplantation (\(p=0.002\)).\(^15\) A very similar picture was obtained from Harvard showing that post-transplant diabetes mellitus (PTDM) was higher in HCV positive than in HCV negative (64% vs 28%, \(p=0.0001\)) liver transplant patients\(^16\) and PTDM was an independent risk factor for mortality (HR 3.67; \(p<0.0001\)), confirming that the development of diabetes is a major comorbidity in these patients which may increase the risk of graft failure or rejection as well.

**Pathophysiology**

**HCV infection and type 1 diabetes**

The hallmark of type 1 diabetes is an auto-immune process which selectively destroys pancreatic \(\beta\) cells through interaction of genetic susceptibility and environmental agents. Several viruses, such as rubella virus, Coxsackie B virus, echo virus and human cytomegalovirus, have been implicated in the pathogenesis of type 1 diabetes.\(^17-19\) Similarly, an association of acute HCV infection and auto-immune diabetes has been postulated to be either due to a direct cytolytic effect on the pancreatic \(\beta\) cells or involvement of a process of molecular mimicry which serves as a trigger for HCV related auto-immunity.\(^20\) Glutamic acid decarboxylase (GAD) 65 shares structural similarity with several antigenic portions of the HCV polyprotein which promotes \(\beta\) cell auto-immunity by the multiple hit mechanism of molecular mimicry involving a lot of pro-inflammatory cytokines like tumour necrosis factor (TNF-\(\alpha\), interleukin (IL-)-1\(\beta\) and IL-8.\(^21\)

Interferon (IFN-\(\alpha\)) forms a main-stay of treatment for chronic HCV infection and is usually combined with ribavirin and protease inhibitors. Epidemiological data suggest that the incidence of type 1 diabetes in IFN-\(\alpha\) treated HCV patients is 10–18-fold higher than in the general population.\(^22\)

IFN-\(\alpha\) has antiviral, anti-proliferative and immunomodulatory activities. It either induces or accelerates the dysglycaemic process by increasing human leucocyte antigen (HLA) class I antigen expression and natural killer (NK) and T cell activities which brings an enhanced Th1 immune reaction. This reaction leads to the auto-immune process by activation of CD4+ lymphocytes that secrete IL-2, CD8+ and cytotoxic cells causing \(\beta\) cell apoptosis.\(^8\) An Italian study\(^23\) demonstrated the development of diabetes in 10 out of 11 241 (0.08%) of their alpha interferon treated patients with similar results from a Japanese study which showed development of diabetes in five out of 667 patients with an incidence of 0.7%.\(^24\) Larger studies have demonstrated that the prevalence of at least one marker of pancreatic auto-immunity (GAD or islet cell antibodies) rises after interferon treatment which goes on to show that pancreatic auto-immunity can increase after alpha interferon treatment and some of them go on to develop type 1 diabetes.\(^25\)

**HCV infection and type 2 diabetes**

Patients infected with HCV have more glucose intolerance than the general population and up to one-third of patients with chronic HCV infection induced liver disease develop type 2 diabetes mellitus.\(^26\) It is proposed that HCV usually has a permissive role in the development of abnormal glucose metabolism and works in concert with other determinants. The key factors which interact to produce hyperglycaemia are the development of an inflammatory environment, hepatic steatosis and insulin resistance induced by HCV. Several authors\(^27,28\) have supported this concept that IR and subsequent hyperinsulinaemia are integral and the most critical component leading to hepatic fat accumulation and progression of fibrosis – which eventually leads to a constellation of problems relating to metabolic syndrome that includes type 2 diabetes, obesity, hypertension and hyperlipidaemia; however, counterarguments have been also proposed by other authors.\(^29-31\)

What, then, causes IR and hyperinsulinaemia in HCV infected individuals? The earliest explanation was in favour of impaired hepatic insulin extraction and reduced hepatic clearance due to co-existing advanced liver disease.\(^32\)

Secondly, HCV induces hypersecretion of insulin resistant pro-inflammatory cytokines such as IL-6 and TNF-\(\alpha\). These, along with host derived IFN-\(\gamma\), modulate the function of monocytes and macrophages leading to chronic inflammation.\(^33\) In addition, the TNF-\(\alpha\) also has a lipolysis-stimulating effect leading to increased
serum levels of free fatty acids which reduces insulin sensitivity. HCV core protein up-regulates suppressors of cytokine signalling 3 proteins (SOCS3) which causes ubiquitination and down-regulation of insulin receptor substrate-1 (IRS-1) and IRS-2 accelerating their degradation. The HCV core protein also blocks the tyrosine phosphorylation of IRS-1 and threonine phosphorylation of Akt, a downstream molecule in the insulin signalling pathway. Impaired activation of Akt leads to down-regulation of glucose transporter-4 (GLUT 4) and GLUT 2 resulting in reduced glucose uptake. Moreover, impaired activity of Akt molecule also results in increased expression of gluconeogenic genes namely glucose 6 phosphatase (G6P) and phosphoenolpyruvate carboxykinase-2 (PCK2), resulting in increased glucose production. (Figure 1.)

The third proposed mechanism suggests that HCV core protein, alone or in combination with other viral proteins, causes an imbalance between positive tyrosine phosphorylation and negative serine phosphorylation of IRS-1 which contributes to defective activation of phosphoinositide 3 kinase (PI3K) and its impaired association with IRS-1 which contributes to IR.

Finally, HCV genotype 2a can also down-regulate TSC1/TSC2 (hamartin–tuberin complex) leading to activation of mammalian target of the rapamycin complex (mTOR) and S6 kinase 1 (S6K1) pathway which in turn promotes IRS-1 degradation by accelerated serine phosphorylation. Several studies have supported development of IR in patients with chronic HCV both in the normoglycaemic population and in those with diabetes. They have shown that a higher viral load is usually associated with higher levels of insulin, C-peptide and high Homeostasis Model Assessment-IR (HOMA-IR) scores.
which are all used as markers of impaired insulin sensitivity and hyperinsulinaemia.\textsuperscript{39-41}

Contradictory to these arguments some authors believe that the association between HCV infection and type 2 diabetes is over-hyped and lacks depth of explanation. They propose that these multiple potential mechanisms for HCV induced IR does not have much clinical relevance when it concerns community-based populations. They argue that the majority of these studies have ignored that advanced liver disease and its severity is a confounding factor and contributes itself in the development of IR which leads to selection bias. Secondly, obesity, age, ethnicity and people who already have pre-diabetes have deeply disturbed insulin signaling pathways and a pre-existing pro-inflammatory state which cannot be further disturbed by the potential mechanisms proposed for HCV induced hepatic IR. Hence, for them type 2 diabetes lacks causal association with HCV and may be considered as an innocent bystander which is begging to break away.\textsuperscript{29-31}

HCV genotypes and diabetes

HCV exhibits genetic diversity and is characterised by regional variation in genotype prevalence that may influence hepatic and extra-hepatic manifestations in chronic HCV infection. HCV genotype 1 is most prevalent worldwide (46.2\% of all HCV cases) followed with genotype 3 (30.1\%).\textsuperscript{42} Genotypes 2, 4 and 6 account for genotype prevalence that may influence activation of the mTOR pathway.\textsuperscript{43} These two genotypes are also believed to be potent activators of fatty acid synthetase accounting for a higher level of \textit{de novo} synthesis of lipids and an increased incidence of liver steatosis.\textsuperscript{47} A prospective study of almost 500 patients with chronic HCV infected patients compared to chronic hepatitis B patients, on a multivariate analysis found that there is a significant correlation between genotype 1 or 4 infection and IR, both in the presence and absence of diabetes mellitus.\textsuperscript{46} A high prevalence of diabetes has been observed with genotype 4 in Kuwaiti patients with low median age and less obesity,\textsuperscript{48} whereas the corresponding figures for patients from France were less suggesting that the diabetogenesis inflicted by different HCV genotypes may vary according to ethnicity, age and body phenotype.

However, all studies do not support the genotype-specific involvement and manifestations. Kawaguchi \textit{et al.}\textsuperscript{35} found no association between fasting insulin levels and HCV genotypes and, similarly, Huang \textit{et al.}\textsuperscript{50} in their study showed that neither genotype 1 nor genotype 2 was significantly associated with type 2 diabetes.

\textbf{Hepatitis C and diabetes in post-transplant patients}

The development of diabetes is common after solid organ transplantation and it remains one of the major challenges in reducing premature deaths in post-transplant patients. Post-transplant diabetes can be divided into two categories: those who had PDM and those who developed NODAT. Both these categories of patients are at a significantly greater risk of developing HCV related fibrosis compared to those without diabetes, as shown in a study from the United States where 20\% of adult liver transplant recipients had PDM and 29\% developed NODAT and were at a greater risk of developing at least stage 2 fibrosis.\textsuperscript{5} The incidence of NODAT in patients ranges from 9-63.3\% and widespread variations remain in reporting, largely because different studies have used different diagnostic criteria and post-transplantation blood glucose screening has been patchy.\textsuperscript{51,52} Moreover, variations in incidence estimates may also result from differences in follow-up time, whether or not the condition is transient or persistent.\textsuperscript{52,53}

Several preliminary reports have noted that the prevalence of PTDM varies between 40-60\% in HCV infected orthotopic liver transplantation (OLT) patients which is higher than recipients who receive a transplant for other terminal liver diseases.\textsuperscript{34} This was further confirmed in a recent meta-analysis which shows a 2.68-fold increased risk of NODAT in HCV infection when compared to HCV negative recipients.\textsuperscript{34} Multiple risk factors have been linked to the causation of NODAT – including HCV infection, advanced age, race, ethnic origin, family history, raised BMI, acute rejection and use of immunosuppressive agents – but controversy still remains.\textsuperscript{55} The potential mechanisms involved are abnormal glucose metabolism, IR secondary to chronic liver dysfunction, immune-mediated or direct destruction of the islets cells by HCV, secondary haemochromatosis, and the widespread use of immunosuppressants.\textsuperscript{16}

The diabetogenic effects of agents such as cyclosporine, tacrolimus and corticosteroids are well established although the individual effects may be quite variable.\textsuperscript{36,57} A recent review of 16 studies of post-transplantation new-onset diabetes reported a mean incidence of 18.2\% in liver transplant recipients on a tacrolimus-based regimen when compared to 7.7\% on a cyclosporine regimen, while other studies have found that the risk with tacrolimus is five time higher.\textsuperscript{58} Bigam \textit{et al.}, in their cohort of HCV positive OLT patients, found that HCV and use of methylprednisolone were independent risk factors for the development of PTDM.\textsuperscript{55}

The clinical impact of PTDM can be quite variable as patients may be completely asymptomatic or may have more infections, poor quality of life, impaired or failure of graft survival, or significant cardiovascular disease related morbidity and mortality. In a recent study, PDM was associated with a modest increase in liver graft failure risk (HR 1.31; p<0.001) and a major cause of all-cause (1.37;
patients reduces IR and the onset of the incidence of abnormal glucose value, hence the clearance of HCV reduces the onset of diabetes.\textsuperscript{64,65} However, IFN itself may cause hyperglycaemia and type 1 diabetes by initiating a severe auto-immune process against pancreatic β cells in genetically predisposed individuals. The most potential reason for this would be similar to the naturally occurring IFN-α which may be either directly cytotoxic to β cells or may bring about apoptosis by activating the oligoadenylate synthetase ribonuclease L and protein kinase R pathway.\textsuperscript{66} The typical presentation is fulminant, however, the time period to the development of IFN induced type 1 diabetes is shorter in patients who receive Peg-IFN when compared to non-Peg IFN in combination with ribavirin, suggesting that the longer duration of action of Peg-IFN and the deviation to Th1-type immune response by ribavirin may significantly increase the risk.

There has been a paradigm shift in the management of chronic HCV infection in recent years. Newer direct antiviral agents (DAAs) are focused on HCV NS3/4A protein (protease), NS5B protein (polymerase) and NS5A (non-structural) protein, which play an important role in viral replication and assembly.\textsuperscript{67} The first generation NS3/4A protease inhibitors (boceprevir and telaprevir) can achieve cure rates of 45–70% when combined with Peg-IFN and ribavirin, whereas the second generation (sofosbuvir and simeprevir) increases the cure rates up to 90% without the need of interferon and are effective against all HCV genotypes.\textsuperscript{68} The non-structural NS5A protein exhibits pleiotropic actions and play an important role in HCV replication, assembly and complex interactions with cellular functions which are necessary for HCV survival in the host. NS5A inhibitors such as daclatasvir and ledipasvir interfere with the phosphorylation-hyperphosphorylation process needed for viral replication and have been studied in triple (with Peg-IFN and ribavirin) and in quadruple (Peg-IFN, ribavirin and protease inhibitors) combination regimens and produce significant HCV RNA clearance, helping to achieve SVR of 67–75% within 12–24 weeks.\textsuperscript{69}

Although the field of DAAs for chronic HCV treatment has exploded, very little is known about the metabolic effects of these newer classes of drugs; however, the results are promising. The realistic possibility of moving to IFN-free therapies can offer avoidance of auto-immune mediated hyperglycaemic effects. Moreover, they offer a shorter, simpler and well-tolerated treatment regimen, helping to attain a greater SVR which will reduce the development of IR. A recent retrospective analysis evaluated glycaemic control modifications and has shown reduction in fasting glucose (67%) and HbA1c (mean value reduction of -1.95%) in patients with type 2 diabetes and chronic HCV treated with DAAs only.\textsuperscript{69} Interestingly, 23% of patients needed reduction in the dose of their oral hypoglycaemic agents. More studies are needed to evaluate the actual impact of these agents on diabetes and other metabolic sequelae in chronic HCV.\textsuperscript{69}

### Perspectives of treatment in HCV and diabetes

The association between HCV infection and diabetes is real and appears to be causally linked, at least in predisposed individuals (older and overweight). This needs implementation of preventive measures which should be directed towards lifestyle changes that can reduce the risk of HCV infection and/or diabetes development. Identification of patients who are at risk for developing diabetes in the setting of HCV infection is paramount as it can reduce progression of liver disturbance.

### Antiviral treatment

Therapeutically, the primary treatments used for chronic HCV may often help to achieve normoglycaemia. Pegylated interferon (Peg-IFN) forms the mainstay of antiviral treatment and can improve glucose tolerance on its own by increasing hepatic glucose clearance and by decreasing availability of free fatty acid.\textsuperscript{62} Moreover, when combined with ribavirin, it not only achieves a sustained virological response (SVR) but also causes a two-third reduction in the onset of type 2 diabetes in the post-treatment follow up period.\textsuperscript{63} Similar results have also been echoed by other authors who believe that the attainment of SVR in chronic HCV
non-alcoholic fatty liver disease (NAFLD) with or without diabetes is inconsistent. It may improve serum transaminase levels and IR by reducing hepatic inflammation and fibrosis, but effects are often not sustained. In view of these findings, the use of insulin sensitizers to enhance the response of antiviral treatment are not routinely recommended.

Incretin-based therapies, such as the glucagon like peptide 1 (GLP-1) receptor agonists and oral inhibitors of dipeptidyl peptidase-4 (DPP-4; gliptins) have been also studied in chronic liver disease of any aetiology. Among the GLP-1 analogues, only liraglutide has beneficial action on liver inflammation markers, fibrosis and also improved body weight in NAFLD patients with type 2 diabetes. Pharmacokinetic studies of liraglutide have shown no major increase in liver enzymes but it should be used cautiously in advanced liver disease. The DPP-4s (e.g. sitagliptin, linagliptin and vildagliptin) increase the levels of endogenous GLP-1 and are minimally metabolised in the liver and excreted unchanged by the kidney. As results have shown, they are safe to use in patients with cirrhosis and diabetes and they do not show any worsening of hepatic impairment after drug exposure. There is overwhelming evidence to suggest that they are also very effective in managing NODAT as they reduce fasting glucose, post-prandial glucose and HbA1c after transplantation.

Selective renal sodium glucose co-transporter (SGLT2) inhibitors, such as dapagliflozin, canagliflozin and empagliflozin, improve glycaemic control by inducing glycosuria and osmotic diuresis. In pharmacokinetic studies, these drugs lead to higher systemic exposure to patients with moderate to severe hepatic impairment. Although the drugs are well tolerated and reported toxicities are low (mainly renal), the decision to use these drugs in chronic liver disease should be done on an individual basis as there is no evidence currently about their long-term safety in this cohort of patients. Moreover, they do not show any benefit on hepatic fat content nor on liver histology in patients with NAFLD and type 2 diabetes.

In the prevention of hypoglycaemia, insulin has been considered as the drug of choice in patients with diabetes and decompensated liver disease, due to its short half-life. Insulin requirement can be high in compensated cirrhosis due to IR, whereas it may be low in decompensated patients due to a reduction in hepatic clearance and gluconeogenesis. A short-acting insulin is usually preferred as its metabolism and clearance are usually not affected by hepatic dysfunction. Longer-acting insulins, e.g. degludec, have a stable pharmacokinetic profile and show no difference with drug absorption nor clearance in patients with advanced liver disease. Dose adjustments with insulin should be done carefully to avoid hypoglycaemia.

In recent times, newer molecular targets have been identified which can potentially reverse the IR that develops in chronic HCV infection. As HCV up-regulates phospho-S6K1, bringing about phosphorylation of S-1 at serine residues and decreasing its tyrosine residues thereby stimulating IRS-1 degradation, targeting phospho-S6K1 would be beneficial to reduce HCV induced insulin resistance.

Furthermore, HCV up-regulates the expression of suppressors of cytokine signalling 3 (SOCS3) and TNF-α which are important mediators of inflammation and fibrosis. Selective inhibition of these molecular targets will be paramount in reducing the development and progression of IR in these settings.

Finally, regulation of weight, improvement of diet and making substantial lifestyle changes will remain as important as they would have been for the treatment of diabetes without HCV infection.

Conclusion

The complex interplay between the HCV and the host metabolic pathways is a fascinating one. The direct effects of HCV on pancreatic β cells and HCV’s influence on creating an environment of inflammation, fibrosis and steatosis lead to dysglycaemia or diabetes in genetically predisposed individuals who have the conventional risk factors such as strong family history and obesity. As the relationship between diabetes and HCV is mutually reciprocal, clinicians should develop strategies for early detection of diabetes in HCV infected individuals to minimise and mitigate the morbidity and mortality risk that arises when these two diseases co-exist. It is also important to establish whether the incidence of diabetes and its adverse outcomes can be reduced by viral clearance in a cost-effective manner. Novel approaches for treatment are already being used but newer therapies against specific molecular targets should be developed to reduce HCV viral load, inflammation, steatosis and fibrosis, and the chances of development of auto-immune process – which will in turn improve the metabolic parameters and reduce the risk of development of diabetes in patients with chronic HCV infection.

Declaration of interests

There are no conflicts of interest declared.

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References are available online at www.practicaldiabetes.com.
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