Insulin resistance and chronic liver disease

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Abstract

Increased insulin resistance is frequently associated with chronic liver disease and is a pathophysiological feature of hepatogenous diabetes. Distinctive factors including hepatic parenchymal cell damage, portal-systemic shunting and hepatitis C virus are responsible for the development of hepatogenous insulin resistance/diabetes. Although it remains unclear whether insulin secretion from pancreatic beta cells is impaired as it is in type 2 diabetes, retinopathic and cardiovascular risk is low and major causes of death in cirrhotic patients with diabetes are liver failure, hepatocellular carcinoma and gastrointestinal hemorrhage. Hemoglobin A1c is an inaccurate marker for the assessment and management of hepatogenous diabetes. Moreover, exogenous insulin or sulfonylureas may be harmful because these agents may promote hepatocarcinogenesis. Thus, pathogenesis, cause of death, assessment and therapeutic strategy for hepatogenous insulin resistance/diabetes differ from those for lifestyle-related type 2 diabetes. In this article, we review features of insulin resistance in relationship to chronic liver disease. We also discuss the impact of anti-diabetic agents on interferon treatment and hepatocarcinogenesis.

INTRODUCTION

An association between diabetes mellitus (DM) and liver cirrhosis was first described by Bohan in 1962 and named as hepatogenous diabetes by Megyesi et al., in which 57% of cirrhotic patients showed increased insulin resistance. Various pathogenetic factors are involved in development of the insulin resistance. Serum insulin levels are higher in diabetic patients with chronic liver disease than those in patients with lifestyle-related DM, suggesting that besides over-eating, obesity and physical inactivity, distinctive factors may underlie the pathophysiology of hyperinsulinemia in patients with chronic liver disease.

Since blood glucose is delivered to the liver through the portal vein, hyperinsulinemia in patients with liver cirr-
rhosis may be secondary to either hepatic parenchymal cell damage or to portal-systemic shunting\(^6,12\). The rate at which insulin is degraded in the liver is reduced in patients with liver cirrhosis\(^8,12\). Moreover, despite peripheral hyperinsulinemia, insulin levels in the portal and hepatic veins are decreased in cirrhotic patients with portal systemic shunting\(^8,10\). However, hyperinsulinemia is also seen in patients with chronic hepatitis C virus (HCV) infection who do not show both severe hepatic parenchymal cell damage and portal-systemic shunting\(^8,10,13-16\), indicating that increased hepatic insulin resistance is another factor related to hyperinsulinemia in patients with liver disease, particularly in HCV-related chronic liver disease\(^8,13-21\).

PATHOGENESIS OF INSULIN RESISTANCE IN PATIENTS WITH CHRONIC HEPATITIS C

Insulin resistance parallels the liver fibrosis stage\(^22-24\) and is associated with a reduced level of sustained virological response (SVR) to pegylated interferon and ribavirin\(^25,38\). Thus, insulin resistance is involved in the disease progression and success of treatment and it is important to understand the pathogenesis of insulin resistance in patients with chronic hepatitis C.

Changes in serum levels of leptin, adiponectin, tumor necrosis factor-alpha and interleukin-6 are known to be associated with the development of insulin resistance\(^8,13-16\). However, in patients with chronic hepatitis C, changes in these cytokines are not always correlated with insulin resistance\(^17-30\). On the other hand, insulin resistance is increased in the HCV core cDNA-transfected hepatoma cell lines and mice\(^37,39\) and serum levels of HCV core protein are associated with the development of insulin resistance in patients with chronic hepatitis C\(^39-41\). Furthermore, insulin resistance is correlated with HCV viral kinetics\(^8,13,42\) and is improved by clearance of HCV by interferon therapy\(^44-47\). These findings suggest that HCV per se is an important factor for the development of insulin resistance.

Recently, the relationship between HCV genotype and insulin resistance has been revealed. HCV genotypes 1, 3 and 4 are associated with more severe insulin resistance\(^24,42,48\). In human hepatoma cell lines, HCV genotype 1 up regulates suppressor of cytokine signaling (SOCS) 3 and causes ubiquitination of insulin receptor substrate (IRS)1/2, which subsequently suppresses insulin-induced phosphorylation of the p85 subunit of phosphatidylinositol-3-kinase and Akt and reduces glucose uptake (Figure 1)\(^49\). These changes are not seen in hepatoma cell lines infected with HCV genotype 2, suggesting that IRS1/2 degradation through up-regulation of SOCS3 is a genotype-specific mechanism\(^49\). In agreement with these results of basic research, hepatic expression of SOCS3 is higher in patients with HCV genotype 1 than in those with genotype 2 and increased hepatic expression of SOCS3 is correlated with poor response to antiviral treatment\(^50-53\). Two further mechanisms are reported in HCV genotype 1: activation of the p85 subunit of phosphatidylinositol 3-kinase and Akt and reduces glucose uptake (Figure 1).

Figure 1  Scheme for HCV genotype difference in the molecular pathogenesis of insulin resistance and hepatocarcinogenesis. HCV: Hepatitis C virus; STAT: Signal transducer and activator of transcription; SOCS: Suppressor of cytokine signaling; mTOR: Mammalian target of rapamycin receptor; PPAR: Peroxisome proliferator-activated receptor; IGBP: Insulin-like growth factor binding protein; IGF: Insulin-like growth factor; IRS: Insulin receptor substrate; MAPK: Mitogen-activated protein kinase.

The mammalian target of rapamycin\(^52\) and up-regulation of serine phosphorylation of IRS1(Figure 1)\(^43\). In addition, amino acid substitutions in the core region of HCV genotype 1b [Gln70 (His70) and/or Met91] have recently been reported as significant predictors of severe insulin resistance\(^51,54\). Although the underlying molecular mechanisms remain unclear, these findings indicate a unique molecular pathogenesis for insulin resistance in HCV genotype 1.

HCV genotype 3 also causes down-regulation of IRS1; however, the molecular pathogenesis differs from that of HCV genotype 1. HCV genotype 3 promotes down-regulation of IRS1 by up-regulating SOCS7 but not SOCS3 (Figure 1)\(^52,53\). SOCS-7 mRNA expression is independent of signal transducer and activator of transcription 3 and is modulated by peroxisome proliferator-activated receptor gamma activity (Figure 1)\(^52,53\). HCV genotype 4 is the most common variant in the Middle East and Africa and is increasing in prevalence in Western countries\(^56\). Infection with HCV genotype 4 is associated with a high prevalence of hepatic steatosis and obesity; however, the impact of
adiponectin on insulin resistance remains controversial\(^\text{[27,58]}\) and specific mechanisms of insulin resistance in HCV genotype 4 infection also remain unclear.

Besides direct association of HCV with intracellular insulin signaling, hepatic steatosis is associated with increased BMI and insulin resistance and HOMA index is reported to be a predictor of SVR in patients with HCV non 3 genotypes\(^\text{[27,39,42]}\). In patients with HCV genotype 3, hepatic steatosis directly correlates with circulating and hepatic viral load, which is mediated by an impaired very-low-density lipoprotein assembly and secretion and by an up-regulation of the sterol depending protein signaling pathway, which regulates de novo lipogenesis and inhibits mitochondrial fatty acid b-oxidation\(^\text{[65,66]}\).

### Changes in Pancreatic Beta Cells in Patients with Liver Disease

A decrease in islet mass and/or beta-cell dysfunction is a pathogenesis for type 2 DM\(^\text{[63,66]}\). In patients with chronic liver disease, impairment of insulin secretion is also reported\(^\text{[11,27]}\); however, insulin resistance/hyperinsulinemia is also characteristic in such patients\(^\text{[61,17-21]}\) and it therefore remains unclear whether the pathogenesis of hepatogenous DM is same as that of type 2 DM.

Pancreatic islet hypertrophy is reported in surgical biopsy tissue of patients with liver cirrhosis\(^\text{[69]}\). Islet hypertrophy and hyperplasia are also reported in thioacetamide-treated rats\(^\text{[69]}\) and in HCV-core transgenic mice\(^\text{[80]}\). Moreover, Takei et al reported that islets in patients with cirrhosis show higher proliferation and lower apoptosis compared to those in patients with no chronic liver disease\(^\text{[70]}\). These findings suggest that hyperinsulinemia in cirrhotic patients may be caused by an adaptive response of the pancreatic beta cells to increased insulin resistance.

Although cross-talk between the pancreas and liver is an important issue in the development of insulin resistance, little is known about this relationship. Further studies regarding morphological and pathological changes of pancreatic alpha-or beta cells are required to characterize the pathogenesis of insulin resistance in patients with liver disease.

### Causes of Death in Diabetic Patients with Liver Disease

The prevalence of DM in patients with chronic liver disease is reportedly 18%-71%\(^\text{[18,19,77-79]}\). DM leads to several complications including cardiovascular disease. Generally, the therapeutic strategy in DM is to reduce the incidence of cardiovascular disease and to prevent a subsequent decrease in quality of life and improve prognosis. However, hepatogenous DM is less often associated with a positive family history, retinopathy and cardiovascular diseases\(^\text{[40,47-50]}\). In fact, major causes of death in cirrhotic patients with DM relate to liver disease or its complications, such as chronic liver failure, hepatocellular carcinoma (HCC) and gastrointestinal hemorrhage\(^\text{[18,19,77-79]}\). Therefore, the management of DM in patients with liver cirrhosis should aim to reduce such hepatic complications and to improve prognosis. Because the incidence of HCC has been well demonstrated to relate to DM\(^\text{[80]}\), a major target in the management of DM should be to reduce the incidence of HCC in patients with liver cirrhosis.

### Assessment of DM in Patients with Liver Disease

Plasma glucose and hemoglobin A1c (HbA1c) are generally used for routine assessment and management of patients with type 2 DM, whereas there is less information regarding the association between these markers and HCC incidence or prognosis in patients with liver cirrhosis. HbA1c level in patients with HCC is higher than in patients with liver cirrhosis or in control subjects\(^\text{[81]}\). In patients with liver cirrhosis, however, HbA1c does not properly represent glycemic control status in cirrhotic patients because of the short lifespan of erythrocytes caused by hypersplenism\(^\text{[82,83]}\). These data indicate that assessment and management of hepatogenous DM using HbA1c is inaccurate, although poor glucose control is associated with HCC incidence.

Strict control of blood glucose levels may improve survival in HCV patients. In patients with HCV-related liver cirrhosis, the prognosis for patients with hyperglycemia (fasting plasma glucose \(\geq 7.0 \text{ mmol/L} \approx 126 \text{ mg/dL}\)) was worse than for those with normoglycemia\(^\text{[84]}\). Therefore, fasting plasma glucose \(\leq 7.0 \text{ mmol/L (126 mg/dL)}\) appears to be meaningful in hepatogenous DM.

Fasting serum insulin and homeostasis model assessment of insulin resistance (HOMA-IR) are also used as markers of glucose tolerance. In patients with HCV infection, HCC development is associated with increased fasting serum insulin level and by HOMA-IR\(^\text{[85]}\). Moreover, HCC recurrence has also been demonstrated to be related to HOMA-IR\(^\text{[86,87]}\). In addition, prognosis is worse in HCC patients with increased fasting serum insulin level or HOMA-IR\(^\text{[88]}\). These data suggest that the assessment of insulin is also meaningful in patients with liver cirrhosis. Taken together, fasting plasma glucose and either serum insulin or HOMA-IR are candidate markers for the assessment of hepatogenous insulin resistance/DM. However, further studies are required to clarify the utility of these markers and their target values in terms of complications induced by liver cirrhosis including HCC or prognosis.

### Impact of Anti-diabetic Agents in Patients with Liver Disease

**Exogenous insulin and sulphonylureas**

Despite the recognition of this potential link between insulin resistance and life-threatening complications including HCC, there is no common therapeutic strategy for...
insulin resistance in patients with chronic liver disease. Since insulin is a growth-promoting hormone with mitogenic effects, exogenous insulin and sulphonylureas, which increase serum insulin levels, are considered to enhance carcinogenesis. In fact, a large-scale cohort study has reported that exogenous insulin increases the risk of malignancies in patients with DM. Exogenous insulin and sulphonylureas are known to promote breast cancer, colorectal cancer, and pancreatic cancer in patients with DM. Recently, a possible link between anti-diabetic agents and the risk of cancer is noted in the consensus statement from the American Diabetes Association and the American Cancer Society.

An association between anti-diabetic agents and hepatocellular carcinoma (HCC) was first described in 1986 by Lawson et al. In addition, we, along with others, have recently shown that use of exogenous insulin or sulphonylurea increases the development and recurrence of HCC in patients with chronic hepatitis C (Table 1). Exogenous insulin or second-generation sulphonylurea increases serum insulin levels. Since insulin has mitogenic and cell proliferative effects, these anti-diabetic agents could be a carcinogenic factor. Insulin binds to insulin receptors and activates the mitogen-activated protein kinase pathway. Insulin also cross-reacts with insulin like growth factor (IGF)-1 receptor and activates the Raf cascade, leading to mitosis and cell proliferation. Moreover, excess insulin binds to IGF-binding proteins, resulting in increased levels of free serum IGF-1 (Figure 1). Thus, hyperinsulinemia induced by use of exogenous insulin or sulphonylurea may enhance hepatocarcinogenesis through multiple pathways.

The association of exogenous insulin or second-generation sulphonylurea with HCC was more evident in females than in males. Sex affects the development of HCC and females are less prone to HCC than males; therefore, we assume that use of exogenous insulin or a 2nd-generation sulphonylurea may accelerate development of HCC mainly in patients who have negative factor for the development of HCC.

Metformin

Metformin is an oral biguanide with insulin-sensitizing effects. However, biguanides are reported to predispose patients with liver cirrhosis to lactic acidosis and are considered as a contraindication in this situation. Recently, Romero-Gomez et al first reported that adding metformin to peginterferon and ribavirin is safe and improved insulin sensitivity in treatment-naive patients with HCV genotype 1 infection and DM. In an intent-to-treat analysis, no beneficial effects of metformin on SVR were seen; however, in female patients with insulin resistance, adding metformin to antiviral treatment doubled the SVR rate (58% vs 29%). Although the reason for this sex difference is still unclear, elevated estradiol-to-testosterone ratio is known to be associated with better response to metformin treatment, suggesting a possible association between sex hormones and metformin-induced high SVR rate. Donadon et al and our research group have reported that metformin reduced risk of HCC in patients with DM and chronic liver disease. Metformin is also known to attenuate the response of cancer cells to insulin in vitro. Thus, metformin has potential benefits as an insulin sensitizer for patients receiving antiviral treatment or those with liver cirrhosis.

Pioglitazone

Pioglitazone is a thiazolidinedione with insulin-sensitizing effects. Recently, Overbeck et al reported that adding pioglitazone to pegylated interferon-alpha and ribavirin improves insulin resistance; however, none of the patients achieved a satisfactory virological response after 12 wk of treatment. On the other hand, Khattab et al reported that pioglitazone improved sustained virological response to antiviral therapy in hepatitis C patients with insulin resistance. The effect of pioglitazone on SVR therefore remains controversial; however, a difference in enrolled subjects may account for this discrepancy. The study by Overbeck et al enrolled patients with chronic hepatitis C who previously failed to respond to peginterferon plus ribavirin therapy, whereas the

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**Table 1 Effects of anti-diabetic agents in patients with chronic liver disease**

| Anti-diabetic agent | Subjects | Outcome | Reference |
|---------------------|----------|---------|-----------|
| Exogenous insulin or sulphonylurea | Patients with liver cirrhosis or HCC | Increased HCC risk | [100] |
| Exogenous insulin or sulphonylurea | Patients with chronic hepatitis C | Increased HCC risk | [101] |
| Exogenous insulin | Chronic viral hepatitis patients who had undergone curative resection for HCC | Increased risk of HCC recurrence | [102] |
| Metformin | Treatment-naive female patients with HCV genotype 1-related chronic hepatitis and insulin resistance | Increased SVR rate | [16] |
| Metformin | Patients with diabetes mellitus and liver cirrhosis or HCC | Decreased HCC risk | [101] |
| Metformin | Patients with liver cirrhosis or HCC | Decreased HCC risk | [112] |
| Pioglitazone | Chronic hepatitis C patients who had previously failed to respond to antiviral therapy | No increase in EVR rate | [115] |
| Pioglitazone | Treatment-naive chronic hepatitis C patients with insulin resistance | Increased SVR rate | [116] |

HCC: hepatocellular carcinoma, EVR: early virological response, SVR: sustained virological response.
Dipeptidyl peptidase-4 inhibitors

Dipeptidyl peptidase (DPP)-4 inactivates incretin hormones including glucagon-like peptide-1 (GLP-1) [117,118], which enhances insulin secretion and reduces body weight [121]. DPP-4 inhibitors are therefore used as anti-diabetic agents [122]. DPP-4 is also known as CD26, an immune-regulation molecule expressed on T-cells [122], and transfection of a HCV non-structural genome region is reported to increase DPP-4 expression in a hepatoma cell line [122]. Treatment of HCV-infected patients with interferon decreases serum DPP-4 activity, which is related to interferon-induced immune activation [123]. Although changes in DPP-4 activity after interferon treatment may just represent indirect evidence, one would think that changes in DPP-4 activity could be involved in the pathogenesis of HCV-related insulin resistance.

Although changes in GLP-1 and DPP-4 remain unclear in hepatogenous insulin resistance, we previously investigated changes of these molecules in patients with HCV infection [124]. The serum level of the active GLP-1 in HCV-infected patients is significantly lower than that in hepatitis B virus-infected patients and healthy subjects. On the other hand, DPP-4 is up-regulated in the serum, ileum and liver of HCV-infected patients more than that of hepatitis B-infected patients and healthy subjects. Taken together, it seems that inactivation of GLP-1 through up-regulation of DPP-4 is a possible pathogenetic mechanism for HCV-related insulin resistance.

DPP-4 inhibitors are now available in the clinical setting and decrease plasma glucose levels as well as HbA1c levels with a low incidence of hypoglycemia in patients with type 2 diabetes mellitus [125,126]. Unlike other anti-diabetic agents, DPP-4 inhibitors are metabolized in the kidney and rarely cause hepatic dysfunction [127,128]. Moreover, GLP-1 analogs improve insulin sensitivity in insulin-resistant obese fa/fa Zucker rats [129] and DPP-4 inhibitors increase hepatic glucose uptake [130]. Thus, further study will be focus on the effects of DPP-4 inhibitors on HCV-related insulin resistance.

COFFEE CONSUMPTION

In various studies including a large prospective study, patients with HCV-related liver disease with a regular coffee consumption show a lower rate of disease progression such as hepatic fibrosis [131-133] and HCC [134-135]. Recently, it was also reported that more than 3 cups per day coffee drinkers are three times more likely to have a virological response to peginterferon plus ribavirin treatment than non-drinkers [136]. Since coffee consumption increases insulin sensitivity [137] and inhibits the development of non-alcoholic fatty liver disease in healthy subjects [138], coffee intake may be protective by mechanisms modulating insulin sensitivity and resulting in a reduced extent of liver steatosis in patients with HCV infection.

CONCLUSION

In this paper, we summarize the features of insulin resistance in relationship to chronic liver disease. Pathogenesis, assessment and cause of death in insulin resistance related to liver disease differ from those of lifestyle-related insulin resistance. Furthermore, exogenous insulin or sulfonylureas may be harmful because these agents may promote hepatocarcinogenesis. There is, therefore, a need for a unique therapeutic strategy for hepatogenous insulin resistance.

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