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EDITORIAL

Importance of hepatitis C virus-associated insulin resistance: Therapeutic strategies for insulin sensitization

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Abstract

Insulin resistance is one of the pathological features in patients with hepatitis C virus (HCV) infection. Generally, persistence of insulin resistance leads to an increase in the risk of life-threatening complications such as cardiovascular diseases. However, these complications are not major causes of death in patients with HCV-associated insulin resistance. Indeed, insulin resistance plays a crucial role in the development of various complications and events associated with HCV infection. Mounting evidence indicates that HCV-associated insulin resistance may cause (1) hepatic steatosis; (2) resistance to anti-viral treatment; (3) hepatic fibrosis and esophageal varices; (4) hepatocarcinogenesis and proliferation of hepatocellular carcinoma; and (5) extrahepatic manifestations. Thus, HCV-associated insulin resistance is a therapeutic target at any stage of HCV infection. Although the risk of insulin resistance in HCV-infected patients has been documented, therapeutic guidelines for preventing the distinctive complications of HCV-associated insulin resistance have not yet been established. In addition, mechanisms for the development of HCV-associated insulin resistance differ from lifestyle-associated insulin resistance. In order to ameliorate HCV-associated insulin resistance and its complications, the efficacy of the following interventions is discussed: a late evening snack, coffee consumption, dietary iron restriction, phlebotomy, and zinc supplements. Little is known regarding the effect of anti-diabetic agents on HCV infection, however, a possible association between use of exogenous insulin or a sulfonylurea agent and the development of HCC has recently been reported. On the other hand, insulin-sensitizing agents are reported to improve sustained virologic response rates. In this review, we summarize distinctive complications of, and therapeutic strategies for, HCV-associated insulin resistance. Furthermore, we discuss supplementation with branched-chain amino acids as a unique insulin-sensitizing strategy for patients with HCV-associated insulin resistance.

Key words: Hepatitis C virus; Diabetes mellitus; Insulin resistance; Complications; Treatments; Branched-chain amino acid

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INTRODUCTION

Insulin resistance is frequently seen in patients with

hepatitis C virus (HCV) infection[1,2]. Although in the general population, lack of exercise and overeating are major causes of insulin resistance, in patients with HCV infection, hepatic inflammation, activated inflammatory cytokines, and HCV-induced impairments of insulin and lipid signaling molecules are also important factors for the development of insulin resistance[3-14]. Therefore, the prevalence of insulin resistance is higher in patients with HCV infection compared to that in the general population and patients with other hepatobiliary disorders[6,15].

Generally, insulin resistance results in the development of type 2 diabetes mellitus and increases the risk of life-threatening complications such as cardiovascular diseases, renal failure, and infections. However, these complications are not major causes of death in cirrhotic patients with insulin resistance[16]. On the other hand, the development of intrahepatic complications, including hepatocellular carcinoma (HCC), is known to be associated with insulin resistance[17-21]. Insulin resistance is also reported to be involved in the development of extrahepatic manifestations of HCV infection including gastric cancer[22-24].

Reduction of fasting blood glucose and hemoglobin A1c (HbA1c) is a well-established therapeutic strategy for prevention of complications in diabetic patients[25,26]. However, in patients with chronic liver diseases, fasting blood glucose and HbA1c are not always available for evaluation of glucose metabolism because of decreased hepatic glycogen content[27] and increased turnover of hemoglobin[28]. Furthermore, an association between the use of exogenous insulin or sulfonylurea agents and the development of HCC has recently been reported[29,30]. Although therapeutic guidelines for inhibiting the distinctive complications of HCV-associated insulin resistance are not yet available, amelioration of insulin resistance is considered to inhibit complications and improve prognosis. Here, we summarize treatments that could reduce HCV-associated insulin resistance.

In this review, we summarize distinctive complications of, and therapeutic strategies for, HCV-associated insulin resistance. In addition, we discuss the merits of branched-chain amino acid (BCAA) supplementation as a unique insulin-sensitizing strategy for patients with HCV-associated insulin resistance.

DISTINCTIVE COMPLICATIONS OF HCV-ASSOCIATED INSULIN RESISTANCE

Complications of HCV-associated insulin resistance are different from those of lifestyle-associated insulin resistance[16]. Cardiovascular diseases are major causes of death in patients with lifestyle-associated insulin resistance[31]. However, these complications are not major causes of death in patients with HCV-associated insulin resistance[16]. In contrast, HCV-associated insulin resistance is involved in the development of various complications associated with HCV infection. Here, we summarize events associated with insulin resistance that are distinctive complications of HCV-associated insulin resistance (Figure 1).

Hepatic steatosis

Hepatic steatosis is commonly observed[32,33] and is an independent risk factor for disease progression in patients with HCV infection[34]. Various mechanisms are operative in the development of hepatic steatosis. HCV core protein induces production of reactive oxygen species and lipid peroxidation[35]. HCV core protein also regulates secretion of very low-density lipoprotein, triglycerides, and apoliprotein B through regulation of fatty acid synthase, microsomal triglyceride transport protein, peroxisome proliferator-activated receptor γ (PPARγ), and sterol regulatory element binding protein-1c[9,36-38]. Thus, HCV itself is directly involved in the development of hepatic steatosis. In addition, insulin is an anabolic hormone and promotes hepatic lipogenesis through activation of hydroxymethylglutaryl-CoA reductase and acetyl-CoA carboxylase[39]. In addition, insulin inhibits lipolysis through regulation of phosphodiesterase type 3B[19]. In HCV core gene transgenic mice, the development of insulin resistance precedes the development of hepatic steatosis, suggesting that insulin resistance may induce hepatic steatosis[8,40]. However, hepatic steatosis could also cause insulin resistance[41,42], and therefore, the initial step in HCV-related metabolic disorders remains unclear in patients with HCV infection.

Resistance to anti-viral treatment

Insulin resistance is associated with a poor response to anti-viral treatment in patients with HCV genotype 1, 2, and 3 infections[10,43-46]. Although the reason for an association between insulin resistance and resistance to anti-viral treatment is largely unknown, the following are possibilities. Insulin resistance is known to increase hepatic lipid synthesis[47]. Since the lipid droplet is an important organelle for HCV replication[48], accumulation of hepatic lipid droplets may increase HCV replication and result in poor responses to anti-viral treatment, even in patients with HCV genotype 2 and 3[45].

Alternatively, HCV core protein is reported to upregulate suppressor of cytokine signaling (SOCS) 3[6,49-52], which acts as an adaptor to facilitate the ubiquitination of signaling proteins, leading to subsequent proteasomal degradation of SOCS3[19]. HCV core protein-induced SOCS3 upregulation promotes proteasomal degradation of insulin receptor substrate (IRS) 1 and IRS2, resulting in the development of insulin resistance in patients with HCV infection[6,19,44]. Simultaneously, SOCS3 is also known to inhibit interferon-alpha-induced expression of the anti-viral proteins 2',5'-oligoadenylate synthetase and myxovirus resistance A through inactivation of Janus kinase, a signal transducer and activator of the transcription pathway[49]. Thus, SOCS3 seems to be a key molecule for a cross-talk between insulin resistance and resistance in patients with HCV infection. In fact, hepatic expression of SOCS3 has predictive value for the outcome of anti-viral therapy in patients with HCV infection[53,54].

Hepatic fibrosis and esophageal varices

Insulin resistance is closely associated with progression

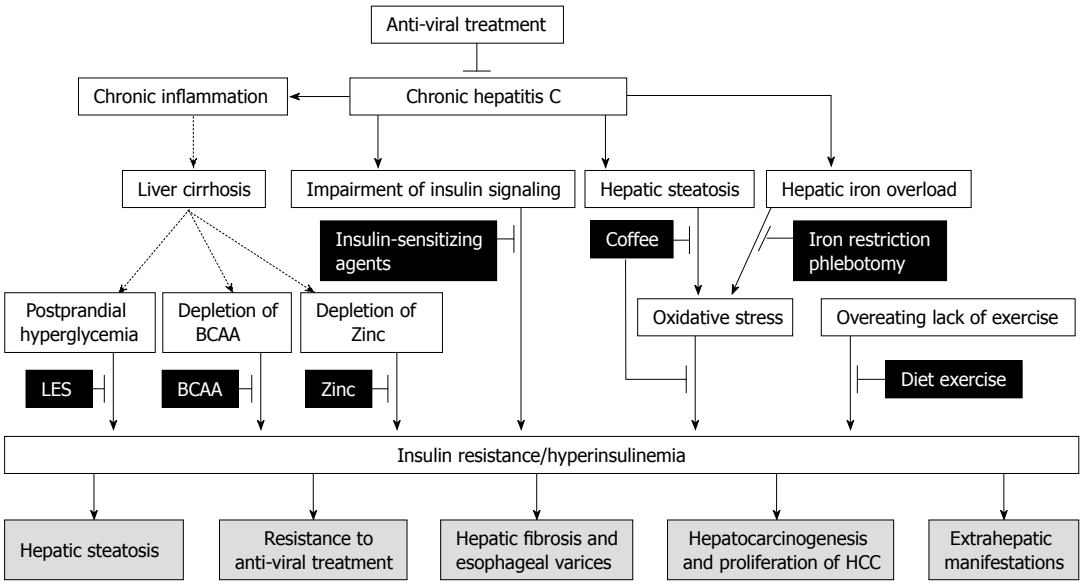

Figure 1 Pathogenic mechanisms and therapeutic strategies for hepatitis C virus (HCV)-associated insulin resistance. Black squares indicate therapeutic strategies for HCV-associated insulin resistance. Proper diet, exercise, iron restriction, phlebotomy, and coffee intake are recommended to any stage of liver disease. In cirrhotic patients, a late evening snack (LES), branched-chain amino acid (BCAA) supplementation, and a zinc supplement are also recommended. Insulin-sensitizing agents can be used in patients with chronic hepatitis C, however, the agents are not always recommended for patients with liver cirrhosis because of severe adverse effects.

of hepatic fibrosis in patients with HCV infection[6,11,55]. The hepatocyte is known to degrade circulating insulin, and, therefore, hepatic fibrosis may reduce insulin clearance, resulting in increased serum insulin levels regardless of the presence of insulin resistance[56]. However, insulin resistance is seen in early stages of chronic hepatitis C[6]. Furthermore, even in patients that have received a liver transplantation for HCV-related liver cirrhosis, insulin resistance is a risk factor for rapid progression of hepatic fibrosis[57]. These findings suggest that insulin resistance promotes hepatic fibrosis. Insulin resistance may directly affect hepatic stellate cells and increase connective tissue growth factor (CTGF), which causes production of extracellular matrix[58]. Alternatively, insulin resistance-induced hepatic lipid accumulation may increase oxidative stress, resulting in progression of hepatic fibrosis[32].

Insulin resistance is also a risk factor for esophageal varices in cirrhotic patients with HCV infection[59]. As the hepatic fibrosis is correlated with the development of esophageal varices, insulin resistance may be associated with the development of esophageal varices through progression of hepatic fibrosis[60]. In addition, insulin modulates the endothelial synthesis of nitric oxide and endothelin[61], regulators of sinusoidal blood flow[62]. Thus, insulin-induced hepatic fibrosis and vasoconstriction may be possible mechanisms for the development of esophageal varices.

Hepatocarcinogenesis and proliferation of HCC

Liver cirrhosis, aging, and being a male are well-known risk factors for the development of HCC in patients with HCV infection[18,63]. In addition, insulin resistance is now recognized as an independent risk factor for the development of HCC worldwide[18,63]. Diabetes is reported as the only independent risk factor for HCC in patients with chronic hepatitis C[21]. Moreover, development of diabetes-related HCC is reported to be independent of viral hepatitis and alcoholism[64]. These findings suggest that insulin resistance has direct effects on hepatocarcinogenesis. Although precise mechanisms for this effect remain unclear, the following explanations may be put forward. Insulin resistance causes lipid accumulation[19]. Visceral adiposity results in changes in serum adipocytokine levels, including reduction of adiponectin, which suppresses effects for hepatocarcinogenesis[65]. Hepatic lipid accumulation also increases oxidative stress, which may be responsible for the development of HCC[18,63]. Besides these possibilities, insulin has a mitogenic effect[19,30], suggesting that insulin may be directly linked to hepatocarcinogenesis[19].

Insulin resistance may be associated not only with hepatocarcinogenesis, but also with proliferation of HCC. We have examined the significance of insulin resistance on the prognosis in patients with HCV-associated HCC and found that insulin resistance is an independent risk factor for poor prognosis[20]. As no significant difference was seen in disease-free survival between patients with and without insulin resistance, these findings indicate that insulin resistance accelerates the proliferation of HCC[20]. In good accordance with our results, Saito *et al*[66] reported that reduction of serum insulin levels by continuous infusion of octreotide significantly suppressed proliferation of HCC. Although the mechanisms for insulin-induced proliferation of HCC remain obscure, insulin exerts growth-promoting activity through activation of a mitogen-activated protein kinase pathway[19]. In addition, overexpression of transducing molecules for insulin signaling, IRS1[67] and IRS2[68],

and downregulation of suppressing molecules for insulin signaling, phosphatase and tensin homologue[69], and SH2 domain-containing inositol phosphatase- 2[20] occur in HCC. Thus, HCC may be sensitive to insulin stimulation.

Extrahepatic manifestations

HCV causes extrahepatic manifestations including mixed cryoglobulinemia, Sjögren's syndrome, and non-Hodgkin lymphoma, oral lichen planus, oral squamous cell carcinoma, and malignancies other than HCC[22-24,70-73]. In patients with extrahepatic manifestations of HCV, fasting insulin levels and homeostasis model assessment for insulin resistance are significantly higher than for patients without extrahepatic manifestations[22]. Among various extrahepatic manifestations, insulin resistance is associated with oral lichen planus[23], oral squamous cell carcinoma[24], and multiple primary cancers including gastric cancer[24]. Although reasons for this association remain unclear, a high prevalence of precancerous lesions and cancers are seen in patients with type 2 diabetes mellitus[74,75], suggesting that insulin resistance or hyperinsulinemia may enhance carcinogenic activities.

DISTINCTIVE THERAPEUTIC STRATEGY FOR HCV-ASSOCIATED INSULIN RESISTANCE

Despite awareness of the increased risk of insulin resistance, therapeutic guidelines to inhibit distinctive complications of HCV-associated insulin resistance have not yet been established. HCV itself has a significant impact on the development of insulin resistance, and eradication of HCV improves insulin resistance[44,46,76]. Thus, anti-viral therapy is a fundamental therapeutic strategy for patients with HCV infection. In addition, amelioration of insulin resistance is considered to inhibit complications and improve prognosis. Here, we summarize treatments which could improve HCV-associated insulin resistance as therapeutic strategies (Figure 1).

Late evening snack

Proper diet and exercise are fundamental for patients with lifestyle-associated insulin resistance as well as patients with HCV-associated insulin resistance[77-80]. As a nutritional treatment for liver cirrhosis, divided energy intake (4 to 6 meals/d) has been recommended[77,79]. As postprandial hyperglycemia is characteristic of HCV-associated insulin resistance[77-80], a decrease in energy intake per meal reduces postprandial hyperglycemia and hyperinsulinemia. In particular, a late evening snack is reported not only to improve glucose intolerance[81-84], but also to suppress hepatocarcinogenesis in cirrhotic patients[85].

Coffee consumption

Coffee consumption reduces the risk of elevated serum alanine aminotransferase activity[86], hepatic fibrosis[87], and disease progression in chronic hepatitis C[88]. Coffee consumption also reduces the risk of HCC independent of HCC etiology[89]. Caffeine is metabolized by hepatic cytochrome P450 1A2 into 3 metabolites, the dimethylxanthines paraxanthine, theobromine, and theophylline. Of these metabolites, theophylline inhibits transforming growth factor-β-stimulated CTGF expression through PPARγ and Smad 2/3-dependent pathways. Since CTGF and transforming growth factor-β are important factors associated with progression of hepatic fibrosis and hepatocarcinogenesis, a metabolite of caffeine, theophylline, may have an inhibitory effect on the development of complications associated with HCV infection. In addition, coffee has significant effects on glucose metabolism[90]. In an animal experiment, the insulin-sensitizing effects of coffee have been demonstrated[91]. Similarly, in a human study, coffee consumption reduced fasting glucose and insulin levels[90,92]. Although the mechanisms for the coffee-induced insulin-sensitizing effect remain unclear, some possibilities exist. Chlorogenic acids, a constituent of coffee, inhibits hepatic glucose-6-phosphate translocation[90,93], limits glucose absorption from the gut by inhibiting Na^+-dependent transport[94], and increases the secretion of glucose regulating hormone, glucagon-like peptide (GLP)-1, from the gut[90,95,96]. These findings suggest that a constituent of coffee, chlorogenic acid, directly ameliorates HCV-associated insulin resistance. Furthermore, coffee modulates lipid metabolism[97,98] and lowers body weight[90], indicating that coffee may suppress the lipid-induced increase in oxidative stress and ameliorates HCV-associated insulin resistance.

Phlebotomy

Hepatic iron overload produces oxidative stress and is a factor responsible for the development of HCV-associated insulin resistance[4,99-101]. Although the pathogenesis of hepatic iron overload remains unclear, recent studies showed that iron-regulating molecules are modulated by HCV infection. Hepcidin is a negative regulator of duodenal iron absorption and macrophage iron release[100] and decreased hepatic expression of hepcidin is seen in both HCV polyprotein transgenic mice[102] and patients with HCV infection[103-105]. In addition, upregulation of hepatic expression of transferrin receptor 2, a mediator of iron uptake, is responsible for hepatic iron overload[106].

In order to reduce hepatic iron deposition, dietary iron restriction and phlebotomy are effective. Dietary iron restriction (less than 7 mg/d) decreases serum alanine aminotransferase levels in patients with HCV infection[107]. Phlebotomy reduces oxidative stress as well as insulin resistance in patients with HCV infection[101,108,109]. A long-term combination treatment with phlebotomy and dietary iron restriction reduces the risk of development of HCC in patients with HCV infection[110].

Supplementation of zinc

Zinc plays a crucial role in the metabolism of protein, carbohydrate, lipid, nucleic acid, and ammonia[111-113]. In fact, zinc supplementation improves glucose disposal in patients

with cirrhosis[114]. Zinc also inhibits hepatic inflammation[115] and hepatic fibrosis[116]. More recently, zinc supplementation was shown to lower the cumulative incidence of HCC in patients with HCV infection[117]. It is unclear whether these inhibitory effects of zinc on progression of liver disease are mediated by amelioration of insulin resistance. However, zinc participates in the synthesis, storage and secretion of insulin[118] and regulates the binding ability of insulin to bind to its receptor[113]. As the serum zinc level is decreased in patients with HCV infection[115,117], supplementation of zinc could be a therapeutic option.

Anti-diabetic agents

Exogenous insulin and sulfonylurea agents: Anti-diabetic agents are effective for decreasing plasma glucose and HbA1c levels, leading to prevention of diabetes mellitus-associated complications including cardiovascular diseases[119,120]. However, it has never been determined whether anti-diabetic agents prevent complications or improve prognosis in patients with HCV infection. Use of exogenous insulin or sulfonylurea agents may worsen hyperinsulinemia. In fact, we, along with others, recently reported an association between exogenous insulin or sulphonylurea treatment and the development of HCC in patients with HCV infection[29,30,121]. Use of exogenous insulin is also reported to be associated with the development of colon cancer[122] and other malignancies[123]. Although a causal relationship between exogenous insulin and the development of HCC remains controversial[124], the reduction of serum insulin levels is a first line therapeutic strategy for insulin resistance[125-128].

Insulin-sensitizing agents: Insulin resistance is associated with a poor response to anti-viral treatment in patients with HCV infection[10,43-46]. Amelioration of insulin resistance may improve the response to anti-viral treatment. However, the impact of insulin-sensitizing agents, biguanides and thiazolidinediones, on sustained virologic response (SVR) rates has not yet been established. Recently, metformin, a biguanide agent, has been reported to ameliorate HCV-associated insulin resistance, and increase the SVR rate in HCV genotype 1 infected patients with normalization of homeostasis model assessment for insulin resistance at week 24 of therapy[129]. Pioglitazone, a thiazolidinedione agent, has also been reported to ameliorate insulin resistance and increase SVR rates in patients with HCV genotype 4 infection[130]. Although the insulin-sensitizing mechanisms of metformin and pioglitazone are different, both agents are known to upregulate IRS[131,132], which is the molecule responsible for HCV-associated insulin resistance[3,6,50], and to improve HCV-associated insulin resistance. Because both agents have severe adverse effects, neither is recommended for patients with liver cirrhosis. Biguanides predispose cirrhotic patients to lactic acidosis[133]. Thiazolidinediones cause overproduction of hydrogen peroxide leading to severe hepatotoxicity[134]. Thus, further validation for safety is required.

Dipeptidyl peptidase Ⅳ (DPPIV) inhibitor is a new therapeutic agent[135] and its clinical efficacy in type 2 diabetes has been shown[136]. Although no study has examined the effect of DPPIV inhibitor on HCV-associated insulin resistance, we found that activation of DPPIV is a factor responsible for HCV-associated insulin resistance[27]. Thus, a DPPIV inhibitor may be suited for ameliorating HCV-associated insulin resistance.

BCAA supplementation, a possible insulin-sensitizing agent

BCAA are constituents of proteins and are required for protein synthesis[19,78,137,138]. In addition, BCAA are reported to modulate glucose metabolism. Leucine and isoleucine induce glucose transporter 1 and 4 translocation to the plasma membrane of muscle cells and improve glucose metabolism in a carbon tetrachloride-induced cirrhotic rat model[139]. In addition, leucine enhances the insulin-induced activation of the Akt/mammalian target of the rapamycin pathway in adipocytes of db/db mice[140]. Moreover, isoleucine increases hepatic phosphatidylinositol 3-kinase activity and improves insulin resistance in Zucker fa/fa rats, a model of severe insulin resistance[141]. Recently, knockout of the mitochondrial BCAA aminotransferase gene in mice, in which results in elevated plasma BCAA levels, was found to ameliorate insulin resistance[142]. Thus, BCAA improve insulin signaling in various animal models *via* several pathways. In good agreement with these results in animals, in human studies, we have recently shown that BCAA-enriched supplementation reduces insulin resistance in patients with HCV infection[143,144]. In a multicenter, randomized, controlled trial, BCAA supplementation led to a reduction in the risk of HCC in cirrhotic patients[145]. This suppressive effect on hepatocarcinogenesis was more evident in obese patients with HCV infection[145]. Both obesity and HCV induce the development of insulin resistance. Thus, BCAA may improve insulin resistance and subsequently inhibit insulin resistance-induced hepatocarcinogenesis[19,145].

CONCLUSION

In this review, we summarize the distinctive complications of, and therapeutic strategies for, HCV-associated insulin resistance. Although cardiovascular diseases, renal failure, and infections are well-known complications of lifestyle-associated insulin resistance, these complications are not major causes of death in cirrhotic patients with insulin resistance. HCV-associated insulin resistance rather causes (1) hepatic steatosis, (2) resistance to anti-viral treatment, (3) hepatic fibrosis and esophageal varices, (4) hepatocarcinogenesis and proliferation of HCC, and (5) extrahepatic manifestations. These complications are life-threatening, and therapeutic strategies for HCV-associated insulin resistance have to be considered on the basis of its pathogenic mechanisms.

Pathogenic mechanisms for HCV-associated insulin resistance differ from those for lifestyle-associated insulin resistance. Postprandial hyperglycemia, lipid-induced oxi-

dative stress, hepatic iron overload, and depletion of zinc are responsible for the development of HCV-associated insulin resistance. Therefore, a late evening snack, coffee consumption, dietary iron restriction, phlebotomy, and supplementation of zinc are recommended therapeutic strategies. No clinical guidelines for the use of anti-diabetic agents are available for patients with HCV-associated insulin resistance. However, use of exogenous insulin or sulphonylurea may increase the risk for HCC. On the other hand, insulin-sensitizing agents may improve the SVR rate of anti-viral treatment. In addition, BCAA supplementation has an insulin-sensitizing effect as well as a suppressive effect on hepatocarcinogenesis. Thus, in order to ameliorate HCV-associated insulin resistance, various therapeutic approaches are required.

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