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EDITORIAL

Hepatic steatosis: A benign disease or a silent killer

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Abstract

Steatosis is a common feature of many liver diseases, namely non-alcoholic steatohepatitis (NASH) and hepatitis C virus (HCV) infection, but the pathogenic mechanisms differ. Insulin resistance (IR), a key feature of metabolic syndrome, is crucial for NASH development, associated with many underlying genetically determined or acquired mitochondrial and metabolic defects and culminates to inflammation and progression to fibrosis. This may have potential implications for new drug therapy. In HCV-related disease, steatosis impacts both fibrosis progression and response to treatment. Steatosis in HCV-related disease relates to both viral factors (HCV genotype 3), and host factors (alcohol consumption, overweight, hyperlipidemia, diabetes). Among others, IR is a recognized factor. Hepatic steatosis is reported to be associated with disturbance in the signaling cascade of interferon and downregulation of its receptors. Thus, hepatic steatosis should not be considered a benign feature, but rather a silent killer.

Key words: Metabolic steatosis; Hepatitis C virus steatosis; Insulin resistance; Fibrosis progression

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INTRODUCTION

Both hepatitis C infection and non-alcoholic fatty liver disease (NAFLD) are major causes of liver related morbidity and mortality. Hepatitis C virus (HCV) is a major cause of chronic liver disease with about 170 million people infected worldwide. The severity of disease varies widely from asymptomatic chronic infection to cirrhosis and hepatocellular carcinoma (HCC)[1].

NAFLD represents a spectrum of liver diseases characterized mainly by macrovesicular steatosis that occurs in the absence of alcoholic consumption. The hepatic histology varies from isolated hepatic steatosis alone "first hit" to fatty liver accompanied by hepatocellular damage plus inflammation known as steatohepatitis "second hit" which is followed by the development of fibrosis.

Adipose tissue is now recognized as not simply a storage depot for excess energy, but rather an active endocrine organ that secretes a number of molecules termed, adipocytokines. A number of these adipocytokines have been linked to alterations in insulin sensitivity, including adiponectin, leptin, resistin, and tumor necrosis factor-α (TNF-α)[2,3].

Insulin resistance (IR) is a major pathogenic feature leading to hepatic fat accumulation. In the meantime, hepatitis C infection promotes IR. Two types of IR are found in chronic hepatitis C patients: "viral" and "metabolic" IR. IR in chronic hepatitis C is relevant because it promotes steatosis and fibrosis[4]. Metabolic IR is thought to be triggered by hepatic FFA accumulation that may exacerbate overall IR[5].

METABOLIC SYNDROME

Metabolic Syndrome (X-syndrome) is a cluster of disorders including central obesity, IR with or without type 2 DM, dyslipidemia and hypertension. Recent findings linking the components of the metabolic syndrome with NAFLD and the progression to non-alcoholic steatohepatitis (NASH), fibrosis and cirrhosis will be reviewed. Metabolic syndrome was first described in 1988 by Reaven GM[6]. Whether hepatic IR causes cellular injury and inflammation in the liver or is

the result of both inflammation and steatosis is still unrevealed[7]. Hepatic steatosis is caused by imbalance between the delivery of fat in the liver and its subsequent secretion or metabolism. In other words, fat accumulates when the delivery of fatty acids to the liver, either from the circulation or by de novo synthesis within the liver, exceeds that capacity of the liver to metabolize the fat by β-oxidation or secrete it as very low-density lipoproteins (VLDL). Derangements in any of these pathways alone or in combination causes fat to accumulate in the liver.

Delivery of fatty acids from peripheral stores to the liver

Triglycerides (TAG) are stored in adipose tissue and released as FFAs into the circulation through the actions of lipoprotein lipase. FFAs released from peripheral stores are hydrophobic and are strongly bound to circulating albumin. FFAs are transported by albumin to the liver where they can then be used as a substitute for β-oxidation, stored as TAG, or exported as VLDL.

Excess glucose is converted to the liver, the backbone of most amino acids, can be converted to pyruvate and then to acetyl-coenzyme A (acetyl-CoA), which feeds directly into cytosolic fatty acid synthesis.

Processes that can lead to excessive FFAs delivery or impaired β-oxidation or secretion can lead to hepatic steatosis, increased mitochondrial reactive oxygen species (ROS) and lipid peroxidation products[8,9].

Fate of fatty acids in the liver

In the fasting state, adipocyte TAG is hydrolyzed to release FFAs, which are transported to the liver where they can serve as substrates for mitochondrial β-oxidation. β-oxidation of fatty acids is a major source of energy needed to maintain liver viability during fasting. It is also the source of the ketone bodies, acetoacetate and acetone. These are released into the blood and are essential fuel sources for peripheral tissues, when glucose is in short supply. Defects in hepatic β-oxidation cause microvesicular steatosis of the liver, increase in oxidative stress due to extramitochondrial oxidative stress. ROS and peroxidation products lead to cytotoxic events, release of proinflammatory cytokines and activation of hepatic stellate cells and fibrosis[8,9].

Formation and secretion of VLDL

In the fed state, β-oxidation of fatty acids is not required as an energy source, and fatty acids delivered to the liver are mainly converted to TAG. Insulin regulates the metabolic path that fatty acids take in the liver. Without insulin, creatinine palmitoyl transferase-I (CPTI) commit fatty acids to mitochondrial β-oxidation; when insulin levels are high, glycerol-3-phosphate acetyltransferase commits fatty acids to the formation of TAG. This bulk of acetyl CoA entering the citric acid cycle, results in delivery of electrons to the respiratory chain, where they generate ROS.

DEVELOPMENT OF STEATOHEPATITIS

Steatosis *per se* does not always lead to hepatocellular injury suggesting that a two-step model involving additional secondary insults is required for the inflammatory component of steatohepatitis "second hit"[10].

Factors that lead to progressive liver injury are multifactorial and may include increased lipid peroxidation, FA toxicity, mitochondrial impairment, cytokine mediated hepatotoxicity, and oxidative injury. Hyperinsulinemia in the insulin-resistant state leads to increased FA oxidation promoting the development of ROS and oxidative injury[11-13]. Although there are no reliable human data supporting a causal role of oxidative injury in human NASH, animal data have suggested a potential role for oxidative injury[14-16].

Excess fat in the liver predisposes to hepatocellular injury. This may be caused by direct cellular cytotoxicity of excess FFAs, oxidative stress, lipid peroxidation or other mechanisms. In the meantime, IR may contribute to hepatic fat accumulation and plays a key role in the development of steatohepatitis and disease progression[4]. Furthermore, TNF-α secreted by the macrophages of the adipose tissue which directly impairs insulin signaling and is crucial for the passage of steatosis to steatohepatitis[17] through induction of several proinflammatory cytokines. In addition, FFAs may lead to hepatocyte apoptosis which is one mechanism of cell injury in NAFLD[5].

Hepatocellular injury may cause inflammatory response with subsequent cytokine induction, mitochondrial dysfunction and progressive fibrosis in a subset of patients[10].

In animal models, development of steatohepatitis depends on additional factors, such as endotoxin exposure, acute liver injury (for example, ischemia-reperfusion), alcohol, excess dietary polyunsaturated fatty acids, or aging. A unifying hypothesis envisages that all causes capable of changing the redox equilibrium of the hepatocyte may result in liver inflammation and fibrogenesis activation. ROS may promote hepatic stellate cell activation and collagen fiber deposition[18]. Lipid peroxidation products may elicit activation of nuclear factors that lead to procollagen type I overexpression[19].

Some investigators have used a taxonomic distinction of secondary NASH, or that attributable to readily identifiable drugs, toxins, or genetic abnormalities, and primary NASH, which is probably related to IR[20].

FIBROSIS PROGRESSION IN NASH

Progression of fibrosis in NASH has been histologically demonstrated in 32%-37% of the patients[21,22]. Estimated rates of cirrhosis development over 10 years of 5%-20% have been reported by 3 independent studies [23-25]. NASH patients with advanced fibrosis are at risk of developing liver complications[25]. Obesity, diabetes, IR and the initial severity of the fibrosis are the factors most conspicuously associated with fibrotic progression[23-25].

The mechanisms by which IR promotes fibrosis progression include: steatosis, hyperleptinemia, increased

TNF production, impaired expression of PPAR-γ receptors[4]. Hepatic injury in NASH induces oxidative stress, ROS and peroxidation products which lead to cytotoxic events, release of proinflammatory cytokines that activate hepatic stellate cells and deposition of collagen[8,9].

HCC has been detected in several NASH patients, most often at the time of diagnosis, and rarely, during follow up[23,26,27]. In the larger Olmsted County Community Study[26], 2 of 420 NAFLD patients developed HCC during a 7-year follow-up period. The estimated rate of liver-related deaths over 10 years was 12% for NASH patients[24,25].

ROLE OF HYPERTENSION

Hypertension is one of the main components of metabolic syndrome. The renin-angiotensin system (RAS) plays a role in progression of chronic liver disease to fibrosis, and HCC and this action is mediated *via* several mechanisms such as direct effect on activated HSCs and neovascularization[28].

RAS is frequently activated in patients with chronic liver disease. In animal models, evidence has shown that angiotensin 2 receptor antagonist and angiotensin-converting enzyme (ACE) inhibitors display antifibrotic characteristics *via* the hepatic stellate cell proliferation[29]. In a pilot study examining the therapeutic efficacy of angiotensin 2 receptor antagonist, losartan was studied in patients with NASH and hypertension. Seven patients were treated with losartan (50 mg/d) for 48 wk. After 48 wk, patients not only showed a significant decrease in blood markers of hepatic fibrosis, but also an improvement in serum aminotransferase levels[30]. However, recent evidence that angiotensin 2 receptor antagonists and ACE inhibitors are antifibrotic in animal models of hepatic fibrosis suggests that these agents are worth examining in clinical trials[29]. Hypertension should be sought and treated appropriately in patients with NAFLD, particularly those with type 2 DM in whom tight blood pressure control (< 140/80 mmHg) with an ACE inhibitor or a β-blocker significantly reduces the risk of cardiovascular morbidity, sudden death, stroke and peripheral vascular disease[31,32].

BIOLOGICAL ROLE OF INSULIN

Insulin, after binding its receptor, induces the phosphorylation of receptor substrates in the liver and muscles, and triggers several steps toward the transactivation of glucose transporter-4 (GLUT-4). This increases glucose uptake by cells and its storage as glycogen, and inhibits the net production of glucose by the liver, thus blocking glycogenolysis and neoglycogenesis. Moreover, insulin promotes lipid storage by inhibiting lipolysis. When insulin is unable to induce glucose uptake, pancreatic β-cells increase insulin production and the hyperinsulinemic state prevents hyperglycemia. Thus, IR depends on insulin secretion and insulin sensitivity.

IR

IR is defined as a condition in which higher-than-normal insulin concentrations are needed to achieve normal metabolic responses or, alternatively, normal insulin concentrations are unable to achieve normal metabolic responses[33].

Hyperinsulinemia appears as a consequence of the inability of insulin to induce its effect on glucose metabolism, and hence, an abnormally large amount of insulin is secreted to achieve a biological response with consequent several abnormalities in target organs such as the liver, endothelium, and kidneys, and this represents the main feature in the metabolic syndrome[4].

IR is measured by many ways. The most accurate is euglycemic-hyperinsulinemic clamp method whereas the less accurate, but widely applied, is Homeostasis Model Assessment (HOMA). Mean HOMA index increases with the stage of fibrosis and could help to differentiate stages of fibrosis[34].

Pathogenesis of IR

Pathogenesis of IR is not fully understood. IR is thought to be the key pathogenic feature leading to hepatic fat accumulation. It causes an increase in FFA influx into the liver that drives hepatic triglyceride production. Increased serum insulin and glucose levels also promote *de novo* lipogenesis by upregulating lipogenic transcription factors. NAFLD may in turn result in hepatic IR, which is thought to be triggered by hepatic FFA accumulation and their metabolites that may exacerbate overall IR[5].

TNF-α is liberated by macrophage of adipose tissues of obese persons and worsens IR. Typically patients with NASH have also low serum adiponectin which is considered a potent insulin enhancer[17].

IR in hepatitis C

HCV directly associates with IR independent of the visceral fat area in non-obese and non-diabetic patients[35]. The mechanisms by which hepatitis C induces increased IR and the risk for development of diabetes has not been completely understood. Liver fibrosis progression has been considered, for a long time, responsible for the appearance of IR and type 2 diabetes in patients with chronic liver diseases[4].

Recent data support a connection between HCV replication and IR, and HOMA decreased when the virus was eradicated. Besides, the incidence of diabetes type 2 is different in cured patients than in non-responders, supporting a better control of IR after HCV clearance[36]. Therefore, hepatitis C promotes IR and IR induces interferon resistance, steatosis and fibrosis progression in a genotype-dependent manner[4].

Extensive evidence supports a central role of TNF-α and other proinflammatory cytokines in the development of obesity-associated IR and fatty liver[37].

HCV infection promotes IR, mainly by increased TNF-α production together with enhancement of suppressor of cytokine (SOC)-3; both events block PI3K and Akt phosphorylation. Two types of IR can

be found in chronic hepatitis C patients: "viral" and "metabolic" IR[4].

Both HCV and TNF-α downregulate IRS-1, 2 phosphorylation *via* upregulation of SOCS-3, which degrades the insulin receptor. Furthermore, HCV core protein *per se*, or its inflammatory cytokine (TNF-α), interfere with normal insulin signaling which impairs translocation of CLUT-4 transporters to plasma membrane limiting glucose uptake and increases blood glucose/insulin level leading to IR. In the mean time, TNF-α impairs expression of PPAR-γ receptor which in turn, decreases insulin sensitivity[4].

STEATOSIS IN CHRONIC HEPATITIS C

In chronic hepatitis C patients, the prevalence of steatosis ranges from 40% to 86% (mean, 55%)[38,39]. The majority of patients with steatosis (78%) have mild steatosis affecting less than 30% of hepatocytes. Thus, steatosis occurs more frequently in patients with chronic hepatitis C (55%) than in the general population (20%-30%) of adults in the Western world[40]. Macrovesicular steatosis is found in the periportal region of the liver-different from the centrilobular distribution characteristic of NASH patients. Mild steatosis had been reported in nearly 40% of patients with HCV genotype 4[41].

Moderate or severe steatosis is significantly less frequent in genotype 4 than 3 chronic hepatitis C patients and similar between genotype 4 and 1. In non-diabetic, overweight patients, moderate or severe steatosis is present in only 10%-15% of genotype 4 or 1 compared with 40% of genotype 3 patients. Thus, hepatic steatosis in genotype 4 is mostly associated with metabolic factors, similar to those in genotype 1[41,42].

It has been shown that HCV genotype 3 is associated with higher quasispecies heterogeneity than genotype 1[43]. Serum levels of apolipoprotein B and cholesterol are reduced in patients in whom steatosis responds to antiviral therapy[44]. Hypocholesterolemia in patients with chronic hepatitis C (especially genotype 3) has been reported by others[45,46]. Instead, after antiviral treatment, virus-related steatosis disappears whereas host associated steatosis remains unaffected[1]. Thus the disappearance of steatosis correlates with normalization of apolipoprotein B and cholesterol levels.

Pathogenesis of steatosis in chronic hepatitis C

IR emerges as a very important host factor, mainly because it has been related to steatosis development, fibrosis progression and non-response to peg-interferon plus ribavirin. HCV directly associates with IR independent of the visceral fat area in non-obese and non-diabetic patients. HCV is directly associated with IR in a dose-dependent manner, independent of the visceral adipose tissue area[35].

Factors associated with steatosis in chronic hepatitis C are: (1) viral factor (HCV genotype 3); (2) host factors (alcohol consumption, overweight, hyperlipidemia, diabetes, insulin resistance), and (3) drug therapy (corticosteroids, amiodarone, methotrexate, *etc*)[1]. The mechanisms underlying the development of parenchymal steatosis in HCV infection are not exactly known[47].

The first mechanism supposes that HCV core protein may block assembly of Apo-A_1-A_2 with TAG. This will result in decreased export of TAG bound to apolipoprotein-β (Apo-β) as VLDL out of hepatocyte, which is corrected by antiviral therapy[1]. Others propose that the core protein induces oxidative stress within the mitochondria that contributes to lipid accumulation[48]. Though the exact mechanism remains elusive, it seems that HCV itself can directly induce steatosis in genotype 3[49] by the cytopathic effect of high titer of intracytoplasmic negative strand HCV RNA[39].

The second proposed mechanism recognizes IR as the major mechanism in the pathogenesis of hepatic steatosis[49-53]. It has been reported that IR plays a central role in NAFLD. However, the mechanisms of development of IR in patients with chronic HCV infection are not well understood[54,55]. IR causes impaired metabolic clearance of glucose, compensatory hyperinsulinemia, and increased lipolysis. The latter leads to increased plasma FFAs; increased hepatic uptake of FFAs by the liver which results in steatosis[9]. Furthermore, it has been suggested that IR may result from excess FFAs, TNF-α and suppressor of cytokine signaling (SOCS) which could downregulate insulin receptor substrate (IRS)-1 signaling[20]. This will result in the impaired translocation of GLUT-4 transporters to the plasma membrane which limits glucose uptake; increases blood glucose and cause a compensatory increase in insulin[56-58]. Recently, Pazienza *et al* reported that both genotype 3a and 1b downregulates IRS-1 through genotype-specific mechanisms[59]. Furthermore, Fartoux L *et al* reported that IR depends mainly on the age of the patient[34]. It has been suggested that age associated decline in mitochondrial function could contribute to IR[34,60].

The main deleterious effect of IR in chronic hepatitis C is the ability to promote fibrosis progression. High serum glucose levels have been found associated with an increased rate of fibrosis progression, even greater than overweight[61].

Steatosis and fibrosis progression in HCV

High levels of TNF-α have also been observed in human chronic hepatitis C patients[40]. TNF-α has been shown to induce IR in experimental animals and cultured cells[62,63]. Inhibition of tyrosine phosphorylation of IRS 1 and 2 may be one of the mechanisms by which a high level of TNF-α causes IR[63-65]. Administration of an anti-TNF-α antibody restores insulin sensitivity[66]. These results provide direct experimental evidence for the contribution of HCV in the development of IR. There are experimental arguments for a direct role of insulin in fibrosis progression in HCV infection[1].

Epidemiological studies indicating that the state of IR now associated with NASH is also associated with an increased risk of HCC. It is worth mentioning that diabetes increases the risk of chronic liver disease and HCC[67].

RESPONSE TO INTERFERON THERAPY IN HCV INFECTION

The current treatment for patients with chronic hepatitis C is the addition of ribavirin to interferon-based therapies for 24 to 48 wk. Unfortunately, a sustained virological response (SVR) is achieved in only 42%-52% of treatment-naive patients, and the rest either show no response or experience a relapse when therapy is stopped[68].

The mechanisms underlying the failure of interferon therapy are not well understood, but evidence indicates that in addition to viral factors, several host factors are also involved[69]. Among host factors, IR has been found to impair virological response to combined therapy in chronic hepatitis C patients[70].

Hyperinsulinemia interferes with IFN signaling cascade[71] through upregulation of SOCS and activation of phosphatidylinositol-3-kinase (PI3K) that inhibit phosphorylation of STAT1.

In addition to IR, HCV core protein and TNF-α cytokine, derived primarily from macrophages of adipose tissue, upregulate SOCS-3 which binds to Janus Kinase inhibiting phosphorylation of STAT1, eventually interfering with interferon signaling[4]. SOCS-3 also causes degradation of IRS-1, in turn leading further to interference with insulin signaling and hyperinsulinemia that interferes eventually with interferon signaling[71].

Recent data support a connection between HCV replication and IR and HOMA decreased when the virus was eradicated[4]. HCV directly associates with IR independent of the visceral fat area in non-obese and non-diabetic patients[35].

In addition to IR, obesity and hepatic steatosis have been recognized as independent risk factors for a poor response to IFN-α therapy[72,73]. In obese individuals, subcutaneous fat could cause a reduction in the initial absorption and bioavailability of interferon given subcutaneously[72]. In the meantime, obesity and hepatic steatosis impair immune responses to HCV and increase fibrosis progression in obese patients[73].

Furthermore, hyperleptinemia in obese is an independent risk factor for non-response to antiviral therapy[74]. Hyperferritinemia downregulates the response to interferon therapy[75,76].

From this review, we have noted that steatosis, either metabolic or cytopathic, contributes to the development of NASH and progression to fibrosis, cirrhosis and HCC. Accordingly, we can conclude with confidence that hepatic steatosis is not a benign disease, but rather a silent killer.

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