

Hepatitis C, Insulin Resistance, and Steatosis

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Chronic hepatitis C (CHC) and nonalcoholic fatty liver disease (NAFLD) are two frequently identified liver diseases worldwide. NAFLD is related to obesity and insulin resistance, which may also be a preexisting condition in patients with CHC. The complex relationship among obesity, steatosis, and insulin resistance as it pertains to the pathogenesis, treatment, and outcomes in CHC is discussed in this article.

Introduction

The current prevalence of hepatitis C in the United States is estimated to be roughly 1.6%, with 1.3% having chronic hepatitis C (CHC) infection. This equates to 3.2 million people in the United States alone [1]. The worldwide prevalence is somewhat higher, with approximately 2% of the world's population infected with hepatitis C [2]. Recent analysis predicts that death from chronic hepatitis C virus (HCV) complications will continue to rise to about 13,000 people annually in 2030 in the United States, compared with 4200 people predicted to die as a result of HIV [3]. Even more alarming is the growing prevalence of nonalcoholic fatty liver disease (NAFLD), which is estimated to occur in approximately 30% of the US population [4]. A subset of individuals with NAFLD will have nonalcoholic steatohepatitis (NASH), the more aggressive form of NAFLD, which places them at risk for developing cirrhosis, liver failure, and hepatocellular carcinoma. The association of obesity, insulin resistance, and NAFLD is well characterized, and as obesity and diabetes become more prevalent, it is likely that NAFLD will as well.

Given the commonality of both these liver diseases, overlap and coexistence of hepatitis C infection and NAFLD are to be expected. Moreover, recent investigation has shown that the hepatitis C virus can promote

insulin resistance and hepatic steatosis in a manner unrelated to host metabolic dysregulation. Additionally, the natural history of hepatitis C infection and its response to antiviral therapy have been shown to be affected significantly by coexistence with NAFLD or NASH.

Epidemiology

The prevalence of hepatic steatosis in CHC has been well described and appears to be around 50%. This is clearly higher than the 20% to 30% seen in the general population and is independently associated with increased body mass index (BMI), insulin resistance, diabetes, older age, alcohol abuse, genotype 3 infection, hepatic inflammation, and fibrosis [5,6]. The degree of fatty infiltration is usually mild and involves less than 33% of the parenchyma. Based on the prevalence of steatosis on liver biopsy in CHC patients along with an estimated prevalence of CHC and NAFLD of 1.8% and 20%, respectively, previous investigators calculated the expected concurrence of HCV infection and steatosis to be 0.36%, or 20% of all cases of CHC [6]. This is much lower than the true 50% prevalence rate and suggests that steatosis occurs 2.5 times more often than would be expected, implying that a direct relationship between steatosis and the virus exists. The coexistence of NASH with CHC has been estimated to occur in 5% to 10% of all cases [7–9].

Pathogenesis of Steatosis in HCV Infection

The mechanisms linking hepatic steatosis and hepatitis C are complex and often involve both host and viral factors (Fig. 1). Host-dependent factors include alcohol ingestion and certain medications related to hepatic steatosis, as well as metabolic factors such as obesity, insulin resistance, and diabetes mellitus. The amount of hepatic steatosis in patients with CHC correlates with BMI and insulin resistance [9,10]. The prevalence of being overweight or obese among these patients varies with ethnicity and geographic region, but studies suggest that up to 37% of US veterans are overweight or obese [11]. Hispanics with CHC appear to have even higher rates of obesity (up to 47%) [10]. Central obesity is associated with increased visceral fat, which secretes numerous cytokines involved in regulating

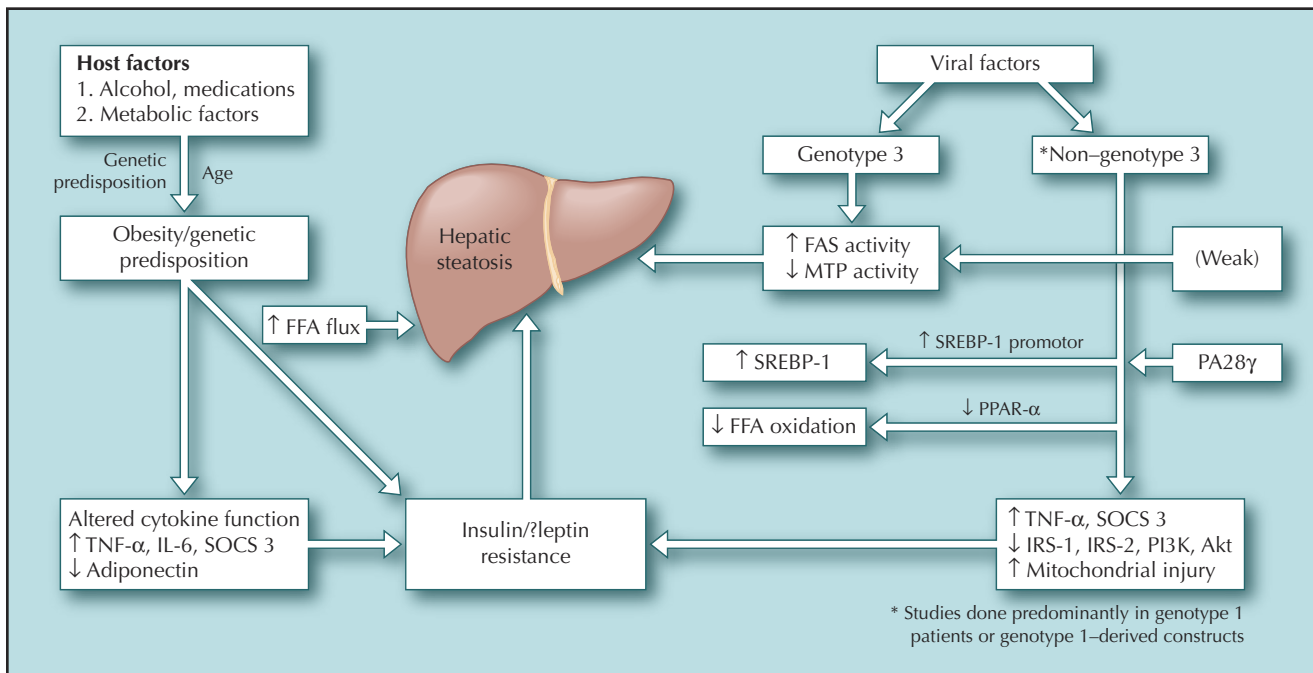


Figure 1. Pathogenesis of steatosis in hepatitis C virus infection. FAS—fatty acid synthase; FFA—free fatty acid; IL-6—interleukin-6; IRS—insulin resistance substrate; MTP—microsomal triglyceride transfer protein; PI3K—phosphatidy inositol 3-kinase; PPAR- α —peroxisomal proliferator activator receptor- α ; SOCS 3—suppressor of cytokine signaling 3; SREBP-1—sterol regulatory binding protein-1; TNF- α —tumor necrosis factor- α .

glucose and lipid metabolism, including tumor necrosis factor- α (TNF- α) and adiponectin. The proinflammatory cytokines TNF- α and interleukin-6 (IL-6) are elevated in patients with CHC, which may lead to inhibition of insulin signaling in part via up-regulation of the protein SOCS 3 (suppressor of cytokine signaling 3), which is elevated in obese genotype 1 patients [12]. Alternatively, adiponectin has been shown to down-regulate TNF- α and is decreased in obese patients with diabetes, CHC, and nonalcoholic steatohepatitis [13]. Data from recent studies show an independent association between low adiponectin levels and hepatic steatosis and insulin resistance [14,15]. Leptin, another protein secreted by adipocytes, may induce insulin resistance via further up-regulation of proinflammatory cytokines, is increased in patients with CHC compared with healthy controls [16], and is associated with steatosis development in genotype 1 CHC patients [17]. Insulin resistance, as a consequence of obesity, leads to enhanced lipolysis within visceral fat, resulting in increased free fatty acid (FFA) flux. This increase in FFA flux alters insulin signaling within skeletal muscle and the liver, leading to inefficient glucose metabolism, enhanced gluconeogenesis, altered FFA metabolism, and impaired triglyceride export, resulting in hepatic steatosis.

The hepatitis C virus may also contribute to insulin resistance and subsequent hepatic steatosis. In a recent study by Lecube et al. [18], nondiabetic patients with CHC were found to be significantly more insulin resistant than a group of patients with chronic hepatitis equally matched for age, gender, BMI, waist-to-hip ratio, family history

of diabetes, fasting blood glucose, and degree of fibrosis. Indeed, population-based studies provide support for a strong association of hepatitis C with diabetes mellitus. In a large cross-sectional survey of Americans older than 40 years, individuals with HCV were three times more likely to have type 2 diabetes mellitus [19]. Other studies have confirmed the association between type 2 diabetes and HCV, and this has led to attempts to show a cause-and-effect relationship between hepatitis C and diabetes. A prospective case-cohort study followed 1084 adults 44 to 65 years old for 5 years to see if they developed diabetes mellitus [20]. The incidence of hepatitis C in this population was 0.8%. Patients were risk stratified based on BMI and age for their risk of diabetes; high-risk patients with hepatitis C infection were 11 times more likely to develop diabetes compared with uninfected high-risk patients. Regardless of risk factors, HCV-infected patients in this study were two times more likely to develop diabetes.

Experimental data support an independent role of HCV in the development of insulin resistance and hepatic steatosis via genotype-specific mechanisms. In a transgenic murine model carrying the core gene of genotype 1b HCV, insulin resistance was noted within the first month, before liver injury, and was associated with a twofold increase in TNF- α [21]. Administration of anti-TNF- α antibody reversed the insulin resistance. In earlier studies by the same authors, HCV core protein-producing transgenic mice were shown to develop steatosis after the age of 3 months [22], suggesting insulin resistance precedes development of steatosis in this animal model.

Both in vivo and in vitro data suggest that TNF- α and SOCS 3 are increased and expression of insulin resistance substrate-1 (IRS-1) and IRS-2 is diminished in genotype 1 virus, leading to downstream inhibition of phosphatidylinositol 3-kinase (PI3K) and Akt, and impaired insulin signaling [12,23,24]. This process may be regulated by PA28 γ , a proteasomal activator that may also serve as a cofactor for sterol regulatory binding protein-1 (SREBP-1) up-regulation via HCV core protein [25,26]. Support for this mechanism of impaired insulin signaling in genotype 1 virus is demonstrated by Kawaguchi et al. [23], who showed that patients achieving a sustained virologic response (SVR) had a threefold increase in IRS-1/2 expression with improved insulin signaling, adding support for a direct viral link to development of insulin resistance.

It has also been proposed that the HCV core protein induces mitochondrial injury, leading to oxidative stress and eventual hepatic steatosis [27]. This is consistent with the observation that an increase in lipid peroxidation precedes steatosis in HCV core protein-producing transgenic mice [28,29].

Peroxisomal proliferator activator receptor- α (PPAR- α) regulates fatty acid import into mitochondria and β -oxidation of FFA within mitochondria, microsomes, and peroxisomes. Recently, the expression of PPAR- α was shown to be decreased in vitro among genotype 1-derived constructs and in vivo (although genotype-specific responses were not recorded), likely potentiating the development of hepatic steatosis [30,31].

Genotype 3 virus is associated with a greater prevalence and higher severity of steatosis [32] than non-genotype 3 virus, and is closely related to levels of viremia. Hourieux et al. [33] compared the amount of lipid in sections of cells producing genotype 1a HCV core protein with genotype 3-specific core protein and found that cumulative lipid droplet area was significantly greater in HCV genotype 3 cells ($P < 0.001$). Another study comparing HCV-3a and HCV-1b core proteins found that HCV-3a core protein induced significantly higher fatty acid synthase (FAS) promoter activity, which is crucial in de novo lipid synthesis and hepatic steatosis [34]. A recent study by Mirandola et al. [35] also showed significantly reduced liver microsomal triglyceride transfer protein activity when compared with other HCV genotypes ($P = 0.004$). This protein is essential for hepatic lipoprotein assembly and secretion in the form of very-low-density lipoprotein. Collectively, these studies support the notion of a viral steatosis effect of genotype 3 infection that occurs independently of metabolic risk factors for steatosis, such as obesity.

Steatosis and Association With Fibrosis

A negative consequence of the presence of steatosis in patients with CHC appears to be fibrosis. Despite some data to suggest otherwise, the preponderance of data demonstrates an association of steatosis with fibrosis. A

recent meta-analysis of more than 3000 CHC patients from 10 clinical centers around the world demonstrated that steatosis was independently associated with fibrosis regardless of genotype, although genotype 2 patients had less fibrosis [5••]. Data from the lead-in phase of the HALT-C (Hepatitis C Antiviral Long-term Treatment Against Cirrhosis) trial showed similar findings in more than 1100 patients, with the caveat that the correlation was lost in cirrhotic or diabetic patients [36]. To further this concept, a correlation of steatosis with fibrosis progression has also been shown. Castera et al. [37] examined paired liver biopsies of untreated patients over an average 48-month period and showed that worsening of steatosis was associated with fibrosis progression ($P < 0.0003$), a finding others have supported. Whereas an association is evident in patients with genotypes 1 through 4, this relationship is particularly evident in genotype 3-infected patients. In the dual liver biopsy analysis by Westin et al. [38] of 98 patients followed over a mean of 5.8 years without treatment, the prevalence and grade of steatosis was strongly associated with genotype 3 infection ($P = 0.0006$) and steatosis was directly related to fibrosis progression, especially in genotype 3 patients.

However, others have not been able to show a relationship between hepatic steatosis and fibrosis. Although study design, patient demographics, histopathologic grading criteria, and statistical analysis varied among these studies, which may explain some of the discrepancy, it is probable that the confounding variable of insulin, at least in non-genotype 3 patients, may be the reason for this association. Indeed, several recent studies have confirmed an independent association of insulin resistance with hepatic fibrosis on multivariate logistic regression analysis [39–41].

The mechanisms for hepatic stellate activation and subsequent collagen matrix deposition are still under investigation but are thought to mirror those of NASH patients. This pathway may involve the aforementioned satiety hormone, leptin, which has been shown to enhance the secretion of TNF- α and other proinflammatory cytokines and to up-regulate the secretion of transforming growth factor- β , a cytokine involved in fibrogenesis. In a study comparing 77 patients with CHC to 22 healthy controls, leptin was associated with BMI and glycemia and was the only independent variable associated with severity of fibrosis [42]. This study also speculated that TNF- α production triggered by increased leptin was an important pathway in the development of fibrosis.

Effect of Steatosis and Insulin Resistance on Treatment Outcomes

Several recent studies have supported the observation that patients with significant insulin resistance and steatosis at the beginning of treatment are less likely to obtain an SVR (Table 1). In a large retrospective analysis of 1428 patients, Poynard et al. [43] showed that SVR in all genotypes is

Table 1. Steatosis, genotype, and sustained virologic response (SVR) rate

Study	Country	Patients, <i>n</i>	SVR, %			
			Non-genotype 3		Genotype 3	
			Steatosis	No steatosis	Steatosis	No steatosis
Harrison [52]	USA	315	23	34	42	78
Poynard et al. [43]	International	1428	35	57	76	85
Patton et al. [44]	USA	574	4.6	10.1	22.4	24.8
Romero-Gomez et al. [47••]	Spain	159	18.2	53.7	*	*
Westin et al. [45]	Europe	231	46	65	88	100
Yaginuma et al. [69]	Japan	80	30.4	57.9	*	*
Tarantino et al. [70]	Italy	40	45	82.5	*	8
Guidi et al. [71]	Italy	102	33	44	*	*

*Genotype 3-specific data are not available.

decreased in patients with hepatitis C and hepatic steatosis. This complex analysis compared SVR among four grades of steatosis—0%, 1% to 5%, 6% to 32%, and 33% to 100%—and found that patients with even small amounts of steatosis had a significantly decreased SVR, from 66% to 52% ($P < 0.001$). Steatosis remained significant even after adjusting for viral load, genotype, fibrosis, and age. Another retrospective analysis of 574 HCV patients showed that those who achieved SVR had less pretreatment steatosis compared with nonresponders, 4.6% versus 10.1% ($P = 0.02$) [44]. Additionally, genotype 1-infected patients with an early virologic response (> 2 log reduction in HCV RNA or virus negativity at week 12) were more likely to have grade 0 steatosis compared with those without an early response, 71% versus 42% ($P = 0.003$).

A more recent prospective study of 231 patients confirmed the negative impact of steatosis in obtaining an SVR [45]. Among non-genotype 3 patients with and without steatosis, the SVR was 46% and 65%, respectively ($P = 0.01$). Genotype 3 patients with and without steatosis had an SVR of 88% and 100%, respectively, which was not statistically significant. One notable exception to the relationship between steatosis and decreased SVR was shown in the previously mentioned study by Lok et al. [36]. In this retrospective analysis of CHC patients undergoing retreatment with peginterferon alfa-2a and ribavirin, steatosis was associated with a decreased SVR in nondiabetic patients only. This lack of association between steatosis and decreased SVR in patients with diabetes is unique to this study, and further investigation seems warranted.

The effect of significant steatosis and/or NASH on treatment outcome has also been assessed retrospectively. One study enrolling 315 patients compared HCV treatment with either interferon (IFN)/ribavirin or pegylated IFN/ribavirin between two groups: patients who had CHC and steatosis greater than 33% with or without NASH on initial biopsy and patients without NASH and with less

than 33% steatosis [46]. The SVR was 28% in patients with steatosis/NASH versus 44% in those without steatosis or NASH ($P = 0.001$). This reduction in response to therapy is even more dramatic when one looks at genotype 2 and 3 patients alone, with SVR of 42% in patients with steatosis/NASH versus 78% in those without ($P = 0.008$).

Although these studies implicated steatosis or NASH as the variable responsible for the decreased SVR, others showed that increased BMI, not steatosis, was responsible. Taken together, these studies suggest that a cofactor seen in both steatosis and increased BMI likely plays a role. Insulin resistance is common to both conditions. The results of a recent study by Romero-Gomez et al. [47••] of 159 patients treated with peginterferon plus ribavirin suggested that insulin resistance, BMI, and fibrosis are associated with decreased SVR. This study showed a large difference between SVR based on a patient's initial degree of insulin resistance as measured by the homeostasis model of assessment insulin resistance index (HOMA-IR), which is calculated by the quotient of the fasting insulin level and fasting glucose divided by 22.5. Patients with no insulin resistance had an SVR of 60% compared with an SVR of 20% for patients with a significantly altered HOMA-IR greater than 4. Among genotype 1 patients, hepatic steatosis was associated with a decreased SVR, 18.2% versus 53.7% ($P = 0.001$).

Potential Mechanisms for a Decreased Sustained Virologic Clearance

The significant negative impact of obesity, insulin resistance, and hepatic steatosis on SVR has led investigators to explore potential pathways for this occurrence (Fig. 2). Obesity seems to be the most unifying clinical variable and has been hypothesized to affect the hepatitis C response to antiviral therapy via several mechanisms.

First, obesity is associated with altered cytokine function. White adipose tissue secretes numerous cytokines

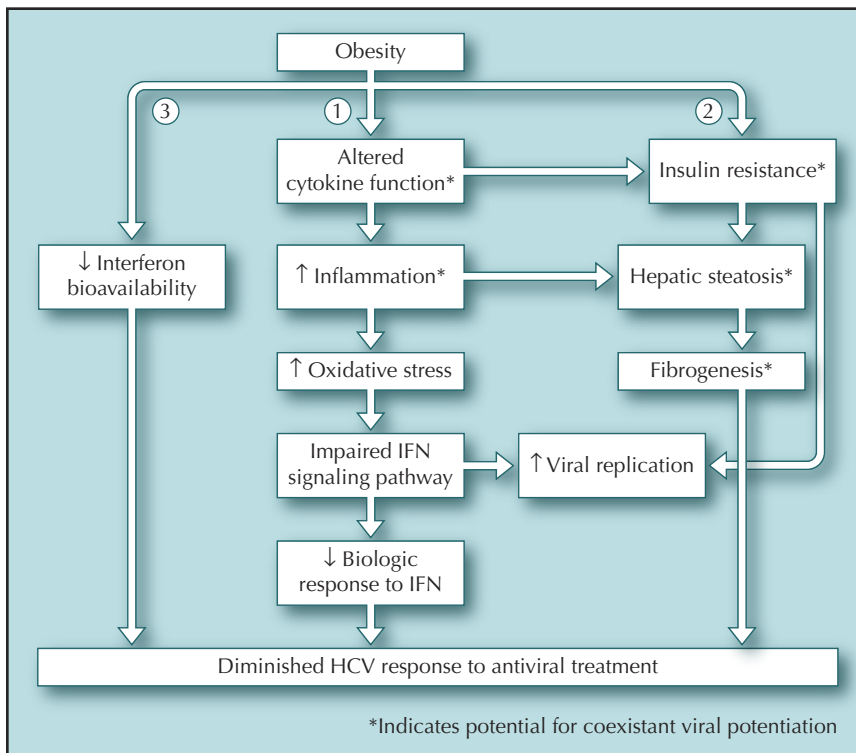


Figure 2. Pathogenetic mechanisms for decreased sustained virologic response. HCV—hepatitis C virus; IFN—interferon.

involved in glucose and lipid metabolism as well as host immune responses. The proinflammatory cytokines leptin, TNF- α , and IL-6 are up-regulated and may modulate both development of systemic inflammation and insulin resistance. Chronic systemic inflammation may lead to increased oxidative stress, and this has been shown in patients with CHC [48]. A recent study demonstrated that oxidative stress is associated with altered IFN- α signaling via decreased phosphorylation of the JAK/STAT pathway [49]. Furthermore, increased TNF- α -mediated expression of SOCS 3 has been identified in obese, genotype 1 patients. Overexpression of SOCS 1 and SOCS 3 further inhibits IFN- α -induced JAK/STAT activation and subsequent transcription of IFN-stimulated genes [50].

Second, obesity-related insulin resistance may lead to development of hepatic steatosis and fibrosis, as previously mentioned [27]. The presence of steatosis impairs the early viral response to pegylated IFN- α . Hepatic steatosis likely leads to fibrosis development in a manner similar to that seen in NASH patients, and increased stages of fibrosis are associated with a decreased SVR. Additionally, insulin resistance has been associated with increased viral replication *in vitro* [51] and *in vivo* [52]. The mechanisms surrounding this have yet to be well developed.

Finally, obesity may result in impaired bioavailability of IFN. Pegylated IFNs are injected subcutaneously and are preferentially taken up by the lymphatic system. Patients with large amounts of subcutaneous fat may have impaired absorption of drug due to decreased lymphatic uptake of interferon [53]. Although the pegylated IFNs are dosed differently (pegylated IFN- α -2b is dosed

at 1.5 $\mu\text{g}/\text{kg}$ of body weight, and pegylated IFN- α -2a is dosed at a fixed 180 μg), the maximum recommended weekly subcutaneous dose is 150 μg of pegylated IFN- α -2b and 180 μg of pegylated IFN- α -2a. Patients weighing more than 100 kg may subsequently receive a suboptimal dose of pegylated IFN- α -2b if dosed according to guidelines. Recent data suggest that 180 μg of pegylated IFN- α -2a may also be suboptimal in heavier patients. Patients weighing more than 85 kg treated with 270 μg of pegylated IFN- α -2a were found to have higher serum trough concentrations of drug and a better overall SVR [54,55]. Further investigation is under way to assess the efficacy of higher fixed doses of pegylated IFN- α -2a in obese patients.

Unique Applications to African-American and Hispanic Populations

There is emerging evidence that specific demographics are prone to more advanced liver disease, perhaps secondary to greater prevalence of metabolic disturbances. In a recent comparison of 169 Hispanics with 63 non-Hispanic whites (NHWs) with hepatitis C, there were profoundly increased rates of obesity, diabetes, and hepatic steatosis among the Hispanic population [10]. These patients also had more histologically advanced disease, with 35% of Hispanics having cirrhosis on their index liver biopsy versus 22% of NHWs. This study is important because it emphasizes the link between increased insulin resistance, increased BMI, hepatic steatosis, and severity of liver disease, particularly in this at-risk population.

African Americans (AAs) are also of special interest given their known decreased rates of responsiveness to therapy for CHC. Some think these lowered rates are partly the result of the increased rates of genotype 1 infection in AAs, but the role of increased insulin resistance is also under investigation [56]. Conjeevaram et al. [9] looked at the differences in baseline characteristics and response to therapy of Caucasian Americans (CAs) versus AAs infected with genotype 1 virus. This study is particularly interesting because historically AAs have a lower prevalence of NAFLD despite having a higher prevalence of risk factors for fatty liver. Indeed, this was confirmed in the study, as AAs were approximately half as likely to have hepatic steatosis as were CAs when accounting for metabolic factors such as BMI and HOMA-IR. Patients with any degree of steatosis were noted to have a trend toward decreased SVR when compared with those without steatosis (37% vs 46%, $P = 0.09$). There was a significant stepwise decrease in SVR as the HOMA-IR increased, providing further evidence of the importance of insulin resistance in obtaining an SVR. Further studies are needed to assess why AAs overall have less steatosis than CAs despite their higher rates of obesity, diabetes, and insulin resistance.

Future Therapies

Improving oxidative stress

The growing body of literature that correlates insulin resistance to hepatic steatosis, more severe liver disease, and decreased SVR has led to the question of whether modification of metabolic factors before, or concomitantly with, treatment for hepatitis C infection leads to improved outcomes. Several trials assessing the benefits of antioxidant therapy in addition to pegylated IFN and ribavirin have been performed. Melhem et al. [57] studied the effects of an oral antioxidant cocktail (glycyrrhizin, schisandra, silymarin, ascorbic acid, lipoic acid, L-glutathione, and α -tocopherol) given daily for 20 weeks as well as an intravenous preparation of glycyrrhiza, ascorbate, L-glutathione, and B-complex given twice weekly for the first 10 weeks on liver enzymes, HCV viral load, and histopathology in 50 CHC patients (66% genotype 1) [57]. Treatment was well tolerated, and 44% of patients normalized their liver enzymes, HCV viral load decreased by at least 1 log in 25% of patients, and 36% of patients had at least a two-point reduction in their hepatic activity index. Another study using the weak antioxidant ursodeoxycholic acid (UDCA) as part of a treatment regimen for CHC with IFN- α showed no difference in SVR, but the UDCA group did have lower relapse rates; however, it is unclear if this was attributable to UDCA [58]. Other studies with vitamin E, in doses ranging from 544 to 1200 IU/day, have shown down-regulation of the fibrogenesis cascade, greater reductions in viral load, and improved end-of-treatment response [59,60]. However, these stud-

ies were of limited duration and did not improve relapse rates. Overall, antioxidant therapy, although associated with biochemical and/or histopathologic improvement in small studies, has not been rigorously assessed in large prospective trials with SVR as an end point. Subsequently, its utility as adjuvant therapy is still questioned.

Modulating host lipid metabolism

It has been proposed that targeting host lipid metabolism may improve response rates to treatment [61]. This proposal is based on an HCV infectivity model using the low-density lipoprotein (LDL) receptor as a means of cell entry [62]. Decreasing the number of LDL receptors, via lifestyle modification or pharmacologic agents, may decrease the ability of HCV to enter hepatocytes. A recent in vitro study identified the HMG-CoA reductase inhibitor atorvastatin as a direct inhibitor of HCV replication [63]. This result was not supported by a subsequent small pilot trial of 10 patients who were given 20 mg of atorvastatin daily for 12 weeks without a statistically significant decrease in HCV RNA levels [64]. It remains to be seen whether combining a cholesterol biosynthesis inhibitor with conventional therapies for CHC, or using increased dosages of these lipid-modifying medications, will provide significant suppression of HCV replication.

Weight loss

The effect of weight loss on liver histology and biochemistry has also been evaluated in CHC patients. In a study of 19 patients who lost a mean of 5.9 kg, mean fasting insulin was decreased from 16 to 11 mmol/L ($P < 0.002$) and serum alanine aminotransferase fell progressively with weight loss [65]. Even more intriguing was the improvement in steatosis in nine of 10 patients who underwent paired liver biopsies ($P < 0.005$); the degree of improvement was associated with percentage of weight lost ($P = 0.005$). Patients with reduced steatosis also had a trend toward reduced fibrosis (five of nine patients, $P = 0.04$). This study was limited by its small patient population, but it supports the idea that modifying insulin resistance with weight loss before initiation of therapy for hepatitis C may improve prognosis.

Insulin-sensitizing medication

Pharmacologic means of reducing insulin resistance provide another intriguing area of study in an effort to improve response rates to therapy. One group of medications, the thiazolidinediones (TZDs), has been shown to improve insulin sensitivity through activation of PPAR- γ in adipocytes and skeletal muscle [66]. Pioglitazone, one of two currently available PPAR- γ ligands, decreases insulin resistance and TNF- α ; increases adiponectin, thereby increasing PPAR- α ligand activity; and decreases hepatic steatosis in NASH patients [67]. Further data suggest pioglitazone also decreases SOCS 3 expression [68]. Ultimately, if insulin resistance-mediated increased SOCS

3 expression and oxidative stress inhibit IFN- α -mediated JAK/STAT signaling, leading to an inadequate host immune response to virus, then treatment with the TZD class of drugs may improve response to therapy. Prospective trials are needed to assess the effect of combination therapy with a TZD plus pegylated IFN and ribavirin on innate immunity and SVR.

Another medication used to reduce insulin resistance that may be of benefit is metformin, a biguanide that decreases the production of glucose in hepatocytes and increases the use of glucose within skeletal muscle. Metformin does not increase adiponectin levels, however, and its effect in NASH patients is less robust than the TZDs. Studies are under way in Europe, however, to assess the efficacy of metformin as adjunctive therapy with pegylated IFN and ribavirin in the treatment of insulin-resistant CHC patients.

Conclusions

In summary, adjuvant therapy aimed at improving insulin sensitivity (lifestyle modification or insulin-sensitizing medication) may hold the most promise for improving outcomes of antiviral therapy. Studies that are adequately powered and designed to assess both innate immune response and ultimately SVR are urgently needed. The nonresponder population may also benefit from this type of therapeutic approach, and future studies should include this group of patients. If the results of these studies are positive, future treatment regimens may be individually tailored according to the degree of insulin resistance as well as genotype and stage of disease.

Disclaimer

The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or reflecting the view of the Department of the Army or the Department of Defense.

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