Medicine

THE INFLUENCE OF STEATOSIS AND CONJUGATE FACTORS OF RESPONSE TO ANTIVIRAL TREATMENT IN CRONIC HEPATITIS C

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ABSTRACT:
HEPATITIS C VIRUS (HCV) IS A MAJOR CAUSE OF CHRONIC LIVER DISEASE WORLDWIDE. AN INCREASED PREVALENCE OF STEATOSIS IN PATIENTS WITH HCV IS WELL ESTABLISHED. MOST STUDIES HAVE REPORTED APPROXIMATELY 50% PREVALENCE OF STEATOSIS AMONG PATIENTS UNDERGOING A LIVER BIOPSY BECAUSE OF HCV. IN COMPARISON, AMONG PATIENTS WITH AUTOIMMUNE HEPATITIS AND HEPATITIS B (HBV), STEATOSIS IS NOT COMMONLY OBSERVED. HEPATITIS C VIRUS (HCV) INFECTION IS AN IMPORTANT RISK FACTOR FOR INSULIN RESISTANCE (IR). THE LATTER IS THE PATHOGENIC FOUNDATION UNDERLYING METABOLIC SYNDROME, STEATOSIS AND CIRRHOSIS, AND POSSIBLY HEPATOCELLULAR CARCINOMA (HCC). WHEREAS THE OVERALL PREVALENCE OF IR IS 10%-25% OF THE POPULATION, THE PREVALENCE IR IN HCV INFECTION REACHES FIGURES RANGING BETWEEN 30% TO 70%. OBESITY AND/OR STEATOSIS IN PATIENTS WITH CHRONIC HCV HAS CONSISTENTLY BEEN SHOWN TO BE ASSOCIATED WITH AN IMPAIRED RESPONSE TO ANTIVIRAL TREATMENT WITH INTERFERON THERAPY. IT IS NOT CLEAR WHETHER THIS ASSOCIATION BETWEEN OVERWEIGHT OR OBESITY AND POOR RESPONSE TO ANTIVIRAL THERAPY IS DUE TO STEATOSIS AND MIGHT NOT ONLY BE LINKED TO OBESITY. ACCUMULATING EVIDENCE SUGGESTS THAT STEATOSIS PLAYS A ROLE IN HCV-RELATED FIBROSIS, AND SUPPORT FOR THIS ALSO COMES FROM STUDIES SHOWING THAT WEIGHT REDUCTION IN THESE PATIENTS LEADS NOT ONLY TO A DECREASE IN STEATOSIS BUT ALSO IMPROVEMENT IN FIBROSIS SCORE.

KEY WORDS: HEPATITIS C VIRUS, STEATOSIS, NON-ALCOHOLIC FATTY LIVER, INSULIN RESISTANCE, INTERFERON THERAPY

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INTRODUCTION

Hepatitis C virus (HCV) is a major cause of chronic liver disease worldwide. According to the most recent WHO estimate the prevalence of HCV is approximately 2.2%, affecting approximately 123 million people in the world. Factors that may influence the rate of disease progression and response to therapy have been extensively investigated. These variables include age at infection, gender, alcohol consumption, duration of infection, race, HCV genotype, viral burden and the stage of fibrosis[6.]

Other possible factor is steatosis - a common yet non-specific histologic feature of chronic HCV infection, with prevalence rates of 30 – 70%. Due to the increased recognition of the potential for some forms of fatty liver to result in progressive liver disease, the role of steatosis in HCV infection has become an area of interest[7].

Hepatitis C virus (HCV) infection causes chronic hepatitis and leads to liver fibrosis and hepatocellular carcinoma. Pegylated-interferon and ribavirin is the current standard therapy for chronic hepatitis C. However, the therapy is only effective in 50% of the patients. Over the last decade it has become apparent that liver steatosis in the setting of HCV infection is a distinct condition with specific clinical and prognostic features. epidemiological studies have shown that hepatic steatosis among people who do not drink alcohol, or drink only small amounts of alcohol—nonalcoholic fatty liver disease (NAFLD). Non-alcoholic fatty liver disease (NAFLD) is a pathological clinical syndrome that ranges from isolated liver steatosis to non-alcoholic steatohepatitis (NASH), which can progress to advanced fibrosis and cirrhosis. Estimates based on imaging studies and autopsies suggest that approximately 20%-30% of American adults and those from Western countries have an accumulation of liver fat, and approximately 10% of these individuals have NASH. This is frequently associated with adult age, female gender, obesity, diabetes mellitus (DM) type 2, hypertriglyceridemia, dyslipidemia and other conditions characterized by resistance to insulin and hyperinsulinemia[8].

MAIN TEXT

RELATIONSHIP BETWEEN STEATOSIS AND HCV INFECTION

An increased prevalence of steatosis in patients with HCV is well established. Most studies have reported approximately 50% prevalence of steatosis among patients undergoing a liver biopsy because of HCV. In comparison, among patients with autoimmune hepatitis and hepatitis B (HBV), steatosis is not commonly observed[9].

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Although concomitant steatosis and HCV infection may in some cases be due to alcohol, it has been demonstrated that NAFLD is a more common explanation in most patients. The most common denominator of steatosis in HCV-infected patients in general is the concomitant presence of obesity correlating positively with body mass in- dex (BMI) in most studies. The prevalence of obesity in HCV-infected patients has been reported to be

17-38% in Europe, North America, and Asian countries. Several large studies have consistently found the association between obesity and other features of the metabolic syndrome and presence of steatosis in patients with HCV infected with the genotypes 1 and 2, but such an association is rather weak in HCV genotype 3-infected patients.

Thus, it has been convincingly shown that genotype 3 per se can specifically induce liver steatosis without metabolic risk factors. Steatosis in patients with genotype 3 correlates with viral load and intrahepatic replication indicating a direct steatogenic effect of this specific genotype. Furthermore, steatosis has been shown to resolve with a successful eradication of HCV genotype 3 and returns with relapse, whereas this is not seen in those infected with genotype 1[10].

By pooling data from different studies, steatosis has been found to occur in approximately 74% in genoype 3 vs. approximately 50% in patients with genotypes other than 3. High titers of in- trahepatic strand HCV RNA of patients with genotype 3 have been shown to correlate significantly with the grade of steatosis in these patients, indicating that steatosis in- duced by genotype 3 might be due to cytopathic effects of this particular genotype. The presence and intensity of liver steatosis is considered a marker of liver disease progression in patients with CHC, and it also seems to have an impact on sustained virological response (SVR) in these patients when submitted to antiviral therapy. It is possible that hyperinsulinemia could block the inhibition of HCV replication by interferon, since insulin and interferon share signal transduction factors, such as p38 MAP kinase; PI3 kinase and IRF-1 also might be associated. The presence and intensity of liver steatosis is considered a marker of liver disease progression in patients with CHC, and it also seems to have an impact on sustained virological response (SVR) in these patients when submitted to antiviral therapy. It is possible that hyperinsulinemia could block the inhibition of HCV replication by interferon, since insulin and interferon share signal transduction factors, such as p38 MAP kinase; PI3 kinase and IRF-1 also might be associated[11].

INSULIN RESISTANCE AND HCV

Hepatitis C virus (HCV) infection is an important risk factor for insulin resistance (IR). The latter is the pathogenic foundation underlying metabolic syndrome, steatosis and cirrhosis, and possibly hepatocellular carcinoma (HCC). IR is a complex pathophysiological condition where higher-than-normal concentrations of insulin are needed to maintain a normal glycemia and adequate glucose utilization in insulin target tissues. IR is of global importance since is closely linked to the epidemic condition of obesity it precedes and predicts the development of type 2

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diabetes mellitus (T2DM) and increases the risk of life-threatening complications such as cardiovascular diseases, renal failure, and infections. IR is extremely common in patients with chronic HCV infection and has been associated with increased disease severity, extrahepatic manifestations and decreased response to antiviral therapy[12].

Causes of insulin resistance it represent by genetic and acquired factors. Obesity is associated with IR, hepatic steatosis and over expression of tumor necrosis factor-α (TNF-α). All of these factors increase the risk of fibrosis and decreased antiviral efficacy. Also, obesity decreases interferon bioavailability and impairs immune stimulating properties of interferon. Hepatic steatosis, nonalcoholic steatohepatitis and fibrosis are associated with release of reactive oxygen species (ROS), which contribute to decreased HCV response to interferon (IFN). Moreover, obesity is associated with decreased number and downregulation of insulin receptors and impairment of postreceptor signaling. Overflow of free fatty acids (FFAs) from adipose tissue interferes with intrahepatic insulin signaling pathway via increased levels of pro-inflammatory cytokines such as TNF-α, and proteasomal degradation of the insulin receptor substrates (IRS)[13].

Hepatitis C virus induces insulin resistance

Whereas the overall prevalence of IR is 10%-25% of the population[14], the prevalence IR in HCV infection reaches figures ranging between 30% to 70%[15]. Moreover, IR with HCV infection is increased at early stages of liver disease without liver fibrosis, and is on average significantly higher than that found in patients with chronic hepatitis B, matched for age and body mass index[16].

The causal relationship of HCV infection and IR development has been demonstrated by the increased prevalence of IR (insulin resistance) in chronic HCV infection.HCV virus, through both direct and indirect pathways, affects the insulin signaling pathways, promoting IR at a cellular level. Insulin effects are elicited after binding of insulin to its receptor that is linked to a complex signaling pathway that involves sequential activation of IRS, PI3K, Akt, a protein kinase which is a downstream of PI3K activation, and protein kinase C. This cascade of events eventually results in stimulation of glucose uptake after translocation of the GLUT4 to the plasma membrane. IR results from defects at any level of the insulin receptor-related signaling pathway

Following inflammatory response in the liver to HCV infection, a profound impairment of insulin signaling occurs at the level of IRS tyrosine phosphorylation and PI3K activation. HCV core protein induces expression of TNF-α, which activates SOCS-3, leading to subsequent

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proteasomal degradation of IRS1 and IRS2, resulting in the development of IR. Meanwhile, SOCS-3 inactivates PI3K, which in turn inhibits translocation of GLUT-4 to cell membrane, thus blocking intracellular glucose uptake[17].

It has been also suggested that increased levels of pro-inflammatory cytokines such as interleukin 1, TNF-α, IL-6 and leptin, and reduced levels of adiponectin may directly contribute to the occurrence of HCV-related IR.

STEATOSIS AND PROGRESSION OF FIBROSIS

Multiple factors may influence the progression of fibrosis in patients with HCV such as age, sex, concomitant alcohol use, and/or co-infections with hepatitis B or HIV. Steatosis has been shown to influence the progression of fibrosis among patients with HCV. Some studies have only identified genotype 3 to influ- ence the progression of fibrosis, whereas others have found that steatosis may influence fibrosis associated with genotype 1. Several studies have found steatosis to be independently associated with progression of fibrosis[18].

It is uncertain if steatosis per se is the cause of fibrosis progression in patients with HCV. Steatosis might be the consequence of more severe liver injury and a marker of necroinflammatory activity, which has been closely linked to fibrosis progression in chronic HCV.

That steatosis plays an indirect role probably mediated by he- patic inflammation is further supported by the recent meta-analysis demonstrating that the association between steatosis and fibrosis was dependent on a simultaneous as- sociation between steatosis and hepatic inflammation[19].

IMPACT OF STEATOSIS ON THE EFFECT OF TREATMENT

Obesity and/or steatosis in patients with chronic HCV has consistently been shown to be associated with an impaired response to antiviral treatment with interferon therapy. It is not clear whether this association between overweight or obesity and poor response to antiviral therapy is due to steatosis and might not only be linked to obesity. Patton et al. observed that pa- tients with genotype 1 who achieved SVR had a lesser de- gree of steatosis compared to nonresponders. Other authors have previously shown steatosis to be more prevalent in poor responders (65%) than in those patients who achieved SVR (47%). However, this poor response associ- ated with steatosis seems to be limited to the ‘‘metabolic’’ fat, in contrast to ‘‘viral’’ fat, because viral steatosis associ- ated with genotype 3 was not associated with an impaired response to antiviral therapy.

In fact, it has been demonstrated that steatosis may result in altered liver function, which might contribute to the normal response to antiviral therapy although that has not been tested in well-designed studies. Weight reduction has been suggested as a potential tool in order to improve the therapeutic efficacy of antiviral therapy but so far has not been tested[20].

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HCV AND LIPID METABOLISM

Lipid metabolism is involved in the life cycle of many viruses. The resulting metabolites work as physiologically active molecules such as eicosanoids and so on,and some of them are incorporated into the lipid raft membrane. A lipid raft is distinct from other lipid membranes. It is enriched in cholesterols and sphingolipids and is detergent-resistent. Lipid rafts play an important role in virus entry, replication, and assembly. HCV also forms a replication complex on the lipid raft membrane structure. Therefore, the depletion of the cholesterol and sphingolipid from the lipid raft leads to the inhibition of HCV RNA replication[21].

DIFFERENT ANTI-HCV EFFECTS OF STATIN

Statins are one of the most worldwide used reagents for the treatment of hypercholesterolemia and they are beneficial in the prevention of coronary heart disease. In the cholesterol biosynthesis pathway, the production of mevalonate by HMG-CoA reductase, resulting in decreased production of isoprenoids as well as cholesterol. The activites of some cellular proteins are regulated by the attachement of isoprenoides (prenylation). The combination therapy of PEG-IFN and ribavirin is a current standard therapy for patients with CH-C. Ribavirin by itself possessed no anti-HCV effect for the patients[22].

HCV ANT ANTIVIRAL THERAPY

Because of the lack of randomised studies, a reliable estimation of the impact of antiviral treatment on the long-term outcome of patients with HCV infection is very difficult to appreciate. Several cohort studies, designed to assess the response to Interferon (IFN) therapy in cirrhotic patients, documented a better prognosis for patients who received IFN regardless of HCV-RNA eradication. Two retrospective reports confirmed these data, and altogether these studies have demonstrated that sustained virological response (SVR) is significantly associated with a reduction of decompensation rate, HCC occurrence, and liver-related mortality. Therefore, liver disease mortality and morbidity is dependent on successful antiviral therapy, and peginterferon plus ribavirin is, at present time, the treatment of choice before direct-acting antivirals (DAAs) will be available[23].

The patients treated with Interferon-based therapy, with sustained viral response showed an improvement of reduction of progression to cirrhosis and development of HCC. However, still remains a residual risk of hepatocellular carcinoma indicating the need for careful follow-up using ultrasonography every six months in cirrhotic patients, even in those showing persistently normal ALT and undetectable HCV RNA levels after antiviral therapy[24].

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The negative impact of IR on response to antiviral therapy has been demonstrated in several studies. Romero-Gómez et al, showed marked differences in the rates of SVR in HCV infected patients with and without IR, assessed by HOMA-IR. In this study, 23 of 70 (32.8%) patients with genotype 1 CHC and IR (HOMA-IR > 2) achieved a SVR vs 26 of 43 (60.5%) genotype 1 CHC patients without IR. These findings were independently confirmed, and extended to genotypes 2 and 3.

In a recent large-scale study in CHC patients, pretreatment HOMA-IR was associated with SVR to combination therapy with (PEG-IFN)/ribavirin, in particular among ‘‘difficult-to-treat” patients (genotype 1b and high baseline viral loads). These findings suggest that pretreatment measurement of HOMA-IR, in combination with tests of HCV genotypes and viral load, may be used as the determinants for selecting regimens in CHC patients.

EFFECT OF IMPROVING INSULIN RESISTANCE ON SUSTAINED VIROLOGIC RESPONSE.

Since IR is considered a factor that can be modified and improved by various interventions, it would be valuable to evaluate by prospective studies whether the improvement of IR before initiation of the combination therapy for CHC can significantly increase the SVR rate. It has been proved that weight reduction will have an impact on both liver histology and biochemistry in patients diagnosticated with CHC[25].

CONCLUSION

Patients with chronic HCV have an increased prevalence of steatosis. Accumulating evidence suggests that steatosis plays a role in HCV-related fibrosis, and support for this also comes from studies showing that weight reduction in these patients leads not only to a decrease in steatosis but also improvement in fibrosis score. Whether weight reduction might improve response to antiviral therapy is an important unanswered question that requires further study.

Morbidity and mortality in cirrhosis is mainly associated with complications of liver cirrhosis and HCC occurrence. Therefore, the main goal of therapy is to inhibit viral replication and decrease liver necroinflammation that is directly related to development of cirrhosis and HCC.

Among patients treated with IFN-based therapy, those with SVR showed a significant deacreased of progression to cirrhosis and development of HCC. However, a residual risk of hepatocellular carcinoma still remains, indicating the need for careful follow-up using ultrasonography every six months for patients with cirrhosis, even in those showing persistently normal ALT and undetectable HCV RNA levels after antiviral therapy.

IR is one of the pathological features in patients with HCV infection. IR plays a crucial role in the development of various complications and events associated with HCV infection. Mounting evidence indicates that HCV-associated IR may cause hepatic steatosis, hepatic fibrosis, resistance to anti-viral treatment, hepatocarcinogenesis and proliferation of hepatocellular carcinoma; and extrahepatic manifestations.

Thus, HCV-associated IR is a therapeutic target at any stage of HCV infection.

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