Chapter 6

Metabolic Factors and Their Influence on the Clinical Course and Response to HCV Treatment

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Abstract

Nowadays, direct-acting antivirals (DAA) have been used for hepatitis C virus (HCV) treatment leading to cure in 90–95% of non-cirrhotic patients depending on genotype, treatment experience, and regimen used. It was observed rates of antiviral response above 90% in compensated cirrhotic patients that should be treated for long time and/or ribavirin may be required. Metabolic syndrome, obesity, and insulin resistance are increasing worldwide and further contribute to hepatic steatosis and have long been recognized as a cause of lipid deposition in the liver. These factors affect the rate of antiviral response to interferon-based therapy, but it seems not impact DAA treatment. The effect of HCV eradication on hepatic steatosis and progression to fibrosis, cirrhosis, and hepatocellular carcinoma warrants further study in the era of direct-acting antivirals. Other factors that could be related to increase liver damage are vitamin D and associated polymorphisms. Patients with low concentration of total vitamin D [25(OH)D] presented high degree of fibrosis and high values of total cholesterol and triglycerides. In this chapter, we review the challenges and metabolic pathology associated with HCV infection and, discuss the influence of some metabolic factors which can cause liver damage.

Keywords: hepatitis C, metabolic syndrome, insulin resistance, vitamin D, genetic polymorphism

1. Introduction

Hepatitis C virus (HCV) infection is a serious health problem with an estimated 71 million of people having chronic HCV worldwide [1]. During chronic hepatitis C (CHC), it is observed many extrahepatic manifestations that could lead to rapid progression of the

disease, increasing the risk of developing hepatocellular carcinoma (HCC) and advanced fibrosis [2, 3]. The effect of HCV eradication on hepatic steatosis and progression to fibrosis, cirrhosis, and hepatocellular carcinoma warrants further study in the era of direct-acting antivirals. Now, with HCV eradication possible in virtually everyone, the sequelae of steatosis, fibrosis and its drivers will garner more attention. People infected by HCV genotype other than three presenting high BMI and visceral obesity have high risk of hepatic steatosis. It is believed that insulin resistance (IR) is the primary pathologic mechanism that leads to abnormal lipid accumulation within hepatocytes. But it is not defined if IR is due to host factors, presence of HCV infection, or a combination. These data become extremely relevant due to the high prevalence of obesity and metabolic syndromes observed worldwide [3].

Nowadays antiviral treatment for HCV demonstrated to be very effective (>90%), but it is important to recognize and identify irreversible and associated metabolic damage, thereby reducing the morbidity and mortality associated with HCV [3]. IR has been associated to CHC [4, 5], which is characterized by hyperinsulinemia in patients with normal fasting blood glucose and with an increased risk of developing diabetes mellitus type II (DM2), heart disease, and nonalcoholic fatty liver disease [6–8].

One of the consequences of persistent IR may be the development of DM2. DM2 is a metabolic disease characterized by hyperglycemia that can occur due to defects in insulin secretion and/or action involving specific pathogenic processes, such as the destruction of insulin-producing pancreatic beta cells or resistance to insulin action. It is the most common metabolic disease and the one with the highest prevalence among individuals with hepatitis C compared to those infected with the hepatitis B virus (HBV), for example [9, 10]. DM2 comprises approximately 90% of cases and may have a genetic and environmental component. Type 1 diabetes, comprising about 10% of the cases, results in the destruction of beta cells, which may lead to absolute insulin deficiency, thus requiring the exogenous administration of it to avoid ketoacidosis and coma.

HCV core protein is involved in the development of IR, however little is known about the clinical impact of HCV core region on IR [11, 12]. Patients infected with HCV genotype 1b who had 70Q core mutation had higher rates of IR compared to those without the mutation, indicating that this substitution is associated with the development of IR [11]. Mutation at core 70Q have been associated to higher incidence of HCC and mutations in 70 and/or 91 core HCV are important predictors of IR in patients without cirrhosis or DM [13, 14]. However, this finding was not seen in Brazilian population [12].

Other factor that could be related to increase liver damage is vitamin D and associated polymorphisms. Vitamin D, whose active form is 1,25-dihydroxy vitamin D3, is essential for calcium and bone homeostasis, and its deficiency has been associated to several diseases, such as cancer, cardiovascular and autoimmune diseases, IR, and infectious disease [15–19].

Vitamin D is an important immunomodulator and plays an important role in metabolic and inflammatory diseases in the liver, including HCV infection. Vitamin D deficiency is common in healthy worldwide populations [20]. Despite this, patients with liver diseases such as CHC are at substantially higher risk for hypovitaminosis D [15, 21, 22]. The polymorphism of the

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vitamin D receptor (VDR) gene was associated with rapid progression to fibrosis [bAt haplotype (CCA)] among HCV patients [23]. This information together demonstrates the potential of VDR-vitamin D axis association in viral hepatitis and highlights the importance of vitamin D as an immunomodulator, indicating an association between vitamin D deficiency and the absence of sustained virological response (SVR) in patients with hepatitis C [24, 25].

Studies have found a relationship between vitamin D concentration and decreased response to antiviral treatment in hepatitis C patients with genotype 1, 2 and 3 in double therapy with peg-interferon (PEG-IFN) and ribavirin [15, 24]. Bitetto et al. [26] observed that the vitamin D concentration and polymorphism in rs12979860 of IL28B gene were independent predictors of response to treatment. Patients who did not present the CC (IL28B) and vitamin D deficient genotype presented a greater risk of not responding to antiviral treatment. In addition, vitamin D concentration supplementation improves response to antiviral treatment in double therapy with PEG-IFN and ribavirin for recurrent hepatitis C [27]. Scalioni et al. [28] demonstrated that patients with lower concentration of 25(OH)D presented high degree of fibrosis and higher values of total cholesterol and triglycerides.

Currently, studies have been conducted correlating vitamin D and SVR levels in patients under direct-acting antivirals (DAAs) treatment. Backsteadt et al. [29] evaluated the association of vitamin D levels with cirrhosis in an HCV-infected cohort. In addition, they assessed pre-treatment vitamin D levels up to week 12. A higher prevalence of vitamin D deficiency was observed in cohorts of HCV-cirrhotic patients, but changes in vitamin D levels did not influence SVR rates [29]. Belle et al. [30] evaluated the impact of vitamin D levels in treatment-naive genotype 1 patients and submitted to conventional double therapy (PEG-IFN + ribavirin) in a French cohort. No impact was observed between vitamin D levels and response to antiviral therapy [30]. Studies have also evaluated genetic polymorphisms related to vitamin D cascade in Thai population and have observed that polymorphism in the DHCR7 gene may be a predictive marker of response to dual therapy (PEG-IFN + ribavirin) in a patient with HCV genotype 1 [31].

Egypt has the highest prevalence rate of HCV infection in the world, where hepatitis C is considered a major health problem. The standard treatment of HCV is combination therapy of PEG-IFN and ribavirin where SVR is only achieved in 30% of the patients. Due mainly to the adverse effects and cost of treatment, discontinuation of treatment is an important approach. In this way, Abdelsalam et al. [32] evaluated the association between vitamin D concentration and VDR polymorphisms with SVR acquisition, where the concentration of vitamin D, FokI and TaqI was considered as predictors for the antiviral response with the combination of pegylated interferon and ribavirin.

2. HCV disease progression in patients with metabolic alterations

Recently, epidemiological, clinical, and experimental studies have related HCV to liver steatosis and several metabolic derangements [33–35]. There is also evidence that HCV infection can induce IR through different mechanisms [34]. Insulin metabolism is affected by HCV directly

and indirectly leading to the production of several proinflammatory cytokines. The process of replication, assembly, and release of HCV from hepatocytes depend on close interactions with lipid droplets and host lipoproteins. The role of HCV in lipid metabolism of hepatocytes can lead to hepatic steatosis, especially in HCV patients infected by genotype 3 [36].

In genotype-1 patients, liver steatosis is directly related to metabolic factors including IR [37]. The impact of IR on the progression of liver disease has been debated and many evidence suggest that patients who have IR have a worse prognosis concerning multiple disease outcomes including progression of hepatic fibrosis and development of hepatocellular carcinoma [37]. Before the era of DAA for HCV infection treatment, IR also had an impact on treatment response, which has now been overcome by the high efficacy of these drugs. However, even with DAA treatment, IR is improved after the achievement of SVR [33].

There are several studies that analyze the association of HCV infection with IR and a meta-analysis of 34 studies found a positive correlation between HCV infection and increased risk of DM2 in comparison to the general population in both retrospective and prospective studies [38].

Regarding the studies that evaluated response to HCV treatment with interferon-containing regimens, it was observed that attaining SVR was associated with the improvement of IR defined by a lower homeostatic model assessment (HOMA)-IR after treatment [39, 40]. In addition, among patients submitted to treatment, those with a lower HOMA-IR had a higher chance of SVR [41].

Many studies found an association between higher HOMA-IR and fibrosis as well as the association of hepatocellular carcinoma with IR. Petit et al. [42] studied 123 HCV infected patients to investigate the host and viral specific factors associated with diabetes mellitus and IR in chronic hepatitis C patients. In diabetic patients, a score F4 was one of the factors related to the presence of diabetes mellitus and in patients without diabetes the HOMA-IR of METAVIR F 0 and F1 patients was significantly different compared to F2 and F3/F4 patients. They concluded that IR in non-diabetic HCV-infected patients was related to grading of liver fibrosis and occurred already at an early stage during HCV infection [42].

Hickman et al. [43] hypothesized that host metabolic factors might be associated with increased body mass index (BMI) and might play a role in liver disease progression. Thus, they studied 160 HCV patients at the time of liver biopsy and collected their serum for the assessment of the levels of insulin, c-peptide and leptin. They found that insulin was independently associated to fibrosis (P = 0.046) but not inflammation (P = 0.83). In addition, serum leptin levels were not associated to stage of fibrosis. So, in HCV patients infected by any genotype, increasing circulating insulin levels may be a factor responsible for the association between BMI and fibrosis [43].

Cua et al. [44] confirmed the impact of IR on fibrosis where they found that increased steatosis was related to high viral load (p = 0.001) but was not related to fibrosis (p = 0.1) in HCV genotype 3 patients. In HCV genotype I, body mass index (p = 0.04) and HOMA-IR (p = 0.01) contributed directly to steatosis. HOMA-IR was independently associated to fibrosis for HCV genotype 1 (OR, 3.22; p = 0.02) and genotype 3 (OR, 3.17; p = 0.04). [44].

Petta et al. [45] aimed to assess whether increasing degrees of IR, up to overt diabetes, were associated to steatosis and higher stages of fibrosis in patients with CHC resulting from genotype 1 HCV. About 201 genotype −1 HCV-infected patients were evaluated by liver biopsy and anthropometric and metabolic measurements, including IR, by the HOMA-IR (nondiabetic patients were defined as insulin resistant if HOMA-IR was >2.7). They evaluated three different groups concerning IR profile: 96 patients were noninsulin resistant (group 1), 76 were insulin resistant without diabetes (group 2), and 29 were diabetic (group 3). At multivariate analysis, fibrosis of >/=3 was independently associated with high necroinflammatory activity, low platelets, low cholesterol, high ferritin, and a high prevalence of IR. Diabetic patients were twice as likely to have severe fibrosis (60%) than those with IR but no diabetes (30%) ($p = 0.006$). This study concluded that in genotype 1 HCV infected patients, IR and overt diabetes are major determinants of advanced fibrosis, regardless of the degree of steatosis, mainly in the presence of severe necroinflammation.

Mohammed et al. [46] also concluded in a study that evaluated HCV infected patients compared to control group of non-infected HCV patients that IR may increase the rate of fibrosis progression in non-diabetic patients with chronic HCV. They suggested that follow up of hyperinsulinemia by serial assessment of HOMA-IR in non-diabetic HCV infected patients may be a biochemical indicator for progression of liver fibrosis [46]. On the other hand, some studies found no association between insulin resistance and liver fibrosis, like the one from Carvalho et al. who concluded that patients with chronic hepatitis C have significant metabolic alterations (hyperadiponectinemia and high HOMA-IR values) that are independent of HCV viremia and liver fibrosis [47].

Another issue that deserves discussion is the association of HCC and IR. Although the exact delineated mechanism is not yet established, there are some evidences to emphasize the involvement of HCV induced chronic inflammation, oxidative stress, IR, endoplasmic reticulum stress, liver steatosis and liver fibrosis in the progression of HCV chronic disease to hepatocellular carcinoma [48]. Possibly, IR is only one step involved among a complex interplay among factors that lead to HCC development. The impact of IR on HCC development is possible related to the fact that HCV interferes with insulin signaling by degradation of insulin receptor substrate 1 (IRS-1) and IRS-2 by suppressor of cytokine signaling (SOCS) protein or PI3K/Akt/mTOR pathway. IRS-1 is inactivated by TGF-α and PI3K/Akt also [49]. Based on these facts, the early stage of chronic HCV infection with increasing steatosis and IR creates an environment to develop hepatocarcinogenesis.

To investigate the role of IR and serum adiponectin level in hepatocellular carcinoma associated with chronic hepatitis C. Hung et al. analyzed three groups of patients and found that diabetes mellitus was more prevalent among HCV patients (35.6%, n = 59) compared to those infected by hepatitis B virus (HBV; 12.7%, n = 63), and non-HBV, non-HCV patients (7.1%, n = 28). Among HCV patients, age, serum insulin, HOMA-IR, DM and male gender were independently associated with HCC. This result was similar even when diabetic individuals were excluded from the analysis [50].

Noteworthy, most studies that evaluated the association of IR and HCV fibrosis are transversal studies. Longitudinal studies evaluating truly fibrosis progression and HCC development

in patients with and without insulin resistance are needed to better understand this link. However, in the new DAA era one must reevaluate the impact of IR in fibrosis progression since the elimination of the virus per se will probably improve liver histology as well.

3. HCV treatment in patients with metabolic syndrome and vitamin D deficiency

HCV infection may contribute to hepatic steatosis and to metabolic syndrome, forming a positive feedback that may further increase steatosis and culminate in steatohepatitis and fibrosis. As HCV infection is considered a curable disease, fibrosis can regress in some patients after therapy response [51, 52]. However, based on data from IFN era, infected patients have comorbidities, as metabolic syndrome, that may prevent fibrosis regression, leading eventually to a continued liver damage, even after viral eradication.

Vitamin D is an important physiological regulator that contributes to various biological, immunological, and metabolic functions in liver diseases. Previous *in vitro* results indicated that 25-OH vitamin D appeared to be significant associated with treatment response, particularly in the aspect of the rapid virological response (RVR) [53], which is an important predictive factor for SVR achievement [54, 55]. Patients with RVR have an approximately 90% of chance of treatment success after receiving PegIFN/RBV combined therapy, regardless of the viral genotypes [56–58]. The achievement of this early goal provides greater flexibility for tailoring the treatment duration on an individual basis and enhances the cost-effectiveness of treatment [55]. However, the impact of 25-OH vitamin D deficiency on RVR and the precise mechanisms underlying the inhibition of HCV replication were not thoroughly elucidated.

Some cross-sectional studies have shown associations between a higher 25-OH vitamin D level and response to therapy with PEG-IFN and ribavirin [15, 59, 60], while low levels are associated with poor response and its supplementation improves SVR rates. On the other hand, studies conducted in French HCV patients did not observed an impact of vitamin D levels in response to double therapy [30]. No causality can be established by cross-sectional studies and discordant results have been observed [61]. Associations may occur because healthier people are more exposure to sunlight and perform more physical exercises, which lead to a higher 25-OH vitamin D level. Also, chronic inflammation can shorten the half-life of 25-OH vitamin D and hepatic production of vitamin D-binding protein is reduced in patients with advanced liver disease and this may accelerate vitamin D turnover. Indeed, some studies pointed that its level before antiviral therapy has no impact on the efficacy of antiviral therapy, regardless the genotype [62]. On the other hand, an Italian study found high frequency of vitamin D deficiency among decompensated cirrhosis showing that vitamin D may play a role in the development of infections in patients affected by liver cirrhosis [63].

Potential relationship of vitamin D gene pathway has been suggested in the pathophysiology of HCV infection. Studies conducted in Asian and Latin America population did not find an association of VDR gene polymorphism to SVR in double therapy [28, 64]. On the other, studies conducted among European patients infected by genotypes 1, 2 and 3 found that VDR gene polymorphisms are independently related to the response to Peg-IFN + RBV therapy in CHC. These differences could be related to genetic differences among these studies [65, 66].

Few studies have evaluated the impact of vitamin D metabolism in therapy with direct-acting antivirals (DAAs). Recently, Cusato et al. [67] evaluated the impact of polymorphisms in genes (*CYP27B1*, *CYP24A1*, *VDBP* and *VDR*) related to vitamin D pathway on sofosbuvir and GS-331007 plasma levels in HCV mono-infected patients at 1 month of treatment. They found that genetic polymorphisms involved in vitamin D pathway influenced drug concentration. In future, it might be useful to understand if these polymorphisms can affect other DAAs concentrations; and to understand their role in the prediction of clinical variables, such as the probability to develop hepatocarcinoma or to influence the viral load decay.

High rates of early tumor recurrence were recently reported after therapy with DAAs in 103 HCV-infected patients with prior HCC [68]. Despite therapy with DAAs, the occurrence of liver cancer could not be reduced in cirrhotic patients with SVR [69]. Recently, a study conducted in Italy found an association of HCC risk factors to age, ribavirin administration, IL28B rs12979860 CC and previous treatments; VDR FokI CC, sex and insulin resistance were protective factors [67]. However, three distinct prospective cohorts showed no increased risk of HCC recurrence in 267 patients after DAA treatments [70]. Whether DAA treatments increase HCC occurrence or recurrence rates will remain a subject for debate until have emerged with a proper control arm to assess this important question [71].

With the efficacious DAAs regimens, comorbidities appear not to impair SVR. Long-term studies in very large patient cohorts treated with DAAs will elucidate the degree to which steatosis, steatohepatitis, and/or fibrosis reverse with SVR. The persistence of these comorbidities may prevent complete return to health in HCV-cured patients.

4. Conclusion

In conclusion, several metabolic alterations, such as, insulin resistance and DM2 have been observed among CHC patients. During double therapy with PEG-IFN and ribavirin, IR and vitamin D levels were important to define high successful rates of virological response. Nowadays, with the advent of DAAs, the rate of SVR have been increased, however high rates of early tumor recurrence were recently reported after therapy with DAAs. In addition, the role of vitamin D levels and genetic polymorphisms involved in vitamin D metabolism could be important predictors for viral response and evolution of clinical cases. Further studies should be necessary to confirm the impact of these factors during new antiviral regimens.

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Conflict of interest

The authors declare no conflict of interest.

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