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Hepatitis C Virus Infection, Metabolic Disorders and Non-alcoholic Fatty Liver Disease: A Literature Review

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Authors' contributions

This work was carried out in collaboration between all authors. Authors MEGC and MA performed the literature search, and authors HK and ST prepared the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Aims: Non-alcoholic fatty liver disease (NAFLD) is a prevalent metabolic disorder both in industrialized and developing countries that makes a large health and financial burden to the patients and the society. In the current article, we review the existing literature to find evidence for interactions between these two conditions.
Methodology: A comprehensive review of the literature has been performed to find associations between HCV infection and NAFLD disease, Pubmed database was our primary search source, and then related citations were found through Google Scholar search.
Discussion and Conclusion: The literature suggest that in NAFLD patients with HCV, attention

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should be paid not only to optimize the antiviral response but also to screen for and treatment of the various components of the metabolic syndrome. Prospective studies are needed for confirming our data.

Keywords: Hepatitis C virus; HCV; metabolic disorders; non-alcoholic fatty liver disease; NAFLD.

1. INTRODUCTION

Hepatitis C Virus (HCV) infection is a major cause of chronic liver disease with an estimated number of 200 million people infected worldwide. The severity of the HCV infection-associated liver diseasevaries largely from nonspecific, minimal inflammatory changes to cirrhosis and hepatocellular carcinoma [1]. The behavior of chronic HCV infection also depends on many factors, mostly host-related, such as age, gender, alcohol consumption, weight, diabetes mellitus status, and existence of other infections [2,3]. Steatosis, usually defined as an increased fat content of the liver, has been observed in several conditions associated with hepatic injury, and is the hallmark of non-alcoholic fatty liver disease (NAFLD), where liver fat accumulation develops as a result of increased free fatty acid influx from adipocytes and *de novo* hepatic triglyceride synthesis [4].

Representing a wide spectrum of liver injury ranging from simple steatosis to Non-alcoholic Steatohepatitis (NASH), NAFLD is the most frequently diagnosed chronic liver disease in all age categories [5,6]. Research indicates strong association between NAFLD and HCV infection. The main mechanisms through which HCV infection can lead to NAFLD have been suggested to be either metabolic or viral. NAFLD and its components have been mostly observed in patients infected with genotypes 1 & 2 HCV and less in other genotypes [7,8]. Moreover, chronic infection by other virus genotypes seems to affect liver steatosis through different routes [9]. On the other hand, metabolic factors, especially insulin resistance and diabetes mellitus are both associated with HCV infection and NAFLD [10,11]. In the current article, we review the existing literature on aspects of associations of HCV infection and NAFLD.

2. METHODOLOGY OF LITERATURE SEARCH

We searched the literature using Pubmed. Terms having been used for the search included, “non-alcoholic fatty liver disease”, “NAFLD”, “hepatitis C virus”, “HCV”, “metabolic syndrome”, “insulin resistance”, “pegilated interferon α” “PEG-IFN”, “ribavirin”, “sustained viral response” “viral response”, “SVR”, “steatosis”, “fatty change”, “adverse effect”, “body mass index”, and “BMI”. Different combinations of the abovementioned terms have been used for the search. When studies very related to our subject were finding, we tried to find their citations, in an attempt to more directly search the literature.

3. LITERATURE REVIEW

3.1 How HCV Affects NAFLD: HCV and Fat Accumulation in the Liver?

HCV infection often ends with chronic liver disease which is associated with a wide range of hepatic pathologies. Fatty change is one of these pathologies that affect livers of HCV infected patients. The prevalence of steatosis in patients with chronic HCV has been reported up to 80% [12] when there are other risk factors including alcohol consumption, obesity and so on, and up to 40%, when all other risk factors are excluded, which are quite higher than that for other liver pathologies [13,14]. On the other hand, the degree of steatosis is directly correlated with the HCV replication level confirmed by analysis of sera or liver specimens of the patients [15-17]. These undoubtedly confirm causative effects of HCV on steatosis.

The rationale behind HCV-associated hepatic damage includes several mechanisms with disturbances in lipid metabolisms as the leading. Three major levels of lipid metabolisms have been suggested to be affected by HCV: Secretion, synthesis, and degradation [18]. These lipid disturbances have been recommended as the main factors of steatosis development in HCV infection. Nonetheless, other factors including HCV-induced metabolic syndrome have also been implicated as significant factors [19]. In molecular levels, Shlomai et al. [20] have suggested that the metabolic regulator peroxisome proliferator-activated receptor-gamma co-activator 1α is strongly induced following HCV infection, resulting in an upregulated gluconeogenic response; This observation provides evidence for

a linkage between HCV infection and hepatic insulin resistance. In cellular level, HCV infection has been suggested to induce organelle dysfunction which leads to the development of NAFLD [21]. In HCV infected patients who don't drink alcohol, being overweight even minimally (BMI>25 kg/m^2) has been suggested as an independent risk factor for development of fatty liver [14,16,22].

3.2 How HCV Affects NAFLD: HCV Genotypes and NAFLD Disease?

Evidence for correlations between HCV infection and steatosis is most highlighted when the patients is infected with the genotype 3 HCV infection [23,24]. For example, successful antiviral treatment of patients infected with genotype 3 HCV is strongly correlated with improvements in liver steatosis, while this association is less prominent in other HCV genotypes [9,22]. Authors have also suggested that genotype 3 HCV more significantly induces accumulation of triglycerides in hepatocytes [18]. Associations between host and metabolic factors and steatosis in HCV infected patiens have also been suggested to be HCV genotype-related. BMI and hepatic fat accumulation have been more prominent in genotype 3 HCV infection, while in genotype 1, fat distribution especially visceral obesity, is the dominant factor in the steatosis development [16,25]. Nevertheless, according to the abovementioned issues, one should not assume that there is a clear distinction in the pathogenesis of infection-related steatosis and different HCV genotypes, because all the mentioned factors more or less interfere in disease processes associated with any of the HCV genotypes.

3.3 How NAFLD Affects HCV Disease Course?

HCV infection and NAFLD are common entities that can have synergistic effects on the liver. Fatty changes are frequently observed in HCV infected liver and seem to have a considerable impact on the natural history of the chronic HCV infection. It has been demonstrated that insulin resistance is associated with a lower sustain viral response (SVR) rate; Moreover, SVR is also correlated with reductions in insulin resistance [26-28]. This association is such strong that authors have suggested insulin sensitizers and anti-metabolic syndrome treatment to achieve higher levels of viral response to treatment [3,29]. Kawaguchi et al. put their HCV infected patients on a 6 months period of treatment with IFN-α based treatment. They found that patients experiencing SVR represent significant decreases in their homeostatic model assessment (HOMA) values following treatment, an indicator of reduced insulin resistance, while HOMA was unchanged in non-responders. Grasso et al. [30], Evaluating factors associated with viral response to treatment in HCV genotype 1 infected patients found that HOMA is the strongest factor independently associated with a viral response in multivariable logistic regression. A meta-analysis by Eslam et al. [31] Also showed that HOMA, as a surrogate marker of insulin resistance, was inversely associated with antiviral response in HCV infected patients receiving pegylated interferon (PEG-IFN)-α plus ribavirin treatment. The same findings were found for insulin resistance and HCV in another Meta analysis by Deltenre et al. [32]. Romero-Gomez et al. [26] studied the effects of host factors on SVR in HCV infected receiving PEG-IFN plus ribavirin. They found that SVR was correlated with insulin resistance, BMI, serum leptin levels, age and levels of g-glutamyl transpeptidase. HCV genotype 1 represented a significant reduced SVR rate with increasing insulin resistance. Similar results have been reported by Conjeevaram et al. [27] Where they demonstrated that insulin resistance was independently associated with a lower rate of HCV clearance; However, they failed to find such a relationship for steatosis. On the other hand, SVR appears to improve insulin resistance, too [28].

3.4 How NAFLD and Metabolic Factors Affect Hepatitis C Virus Treatment?

The simultaneous presence of liver steatosis and HCV infection has deleterious effects on the response rate of IFN-α–based therapy for HCV. Data suggests a reduction in SVR rates of combination IFN-α and ribavirin therapy in HCV infected patients when they have steatosis greater than 30% [33]. Moreover, multivariate analyses have also shown an independent role for hepatic steatosis in reducing viral response rates in HCV infection [34]. In a multicenter randomized study by Westin et al. [35] Patients with steatosis represented lower response to antiviral treatment than those without liver steatosis. Poynard and colleagues also found a significant difference in SVR rates regarding liver steatosis status of patients [22].

As mentioned before, both hepatic steatosis and obesity are independent risk factors for reduced viral clearance rates in HCV infected patients, which can be attributed to insulin resistance as the unifying factor at the root of those conditions. The specific mechanism through which these interactions occur has not been clearly understood. It has been proposed that bioavailabilty of IFN-alpha is reduced in obese patients with HCV. Giannini et al. [36] suggested that lipid droplets which forms due to accumulation of fat in hepatocytes, act as a physical barrier between the virus and treatment drugs, and effectively prevents bioavailability of the drug. Due to the comparative poor lymphatic circulation in obese individuals, this effect can also limit the serum levels of PEG-IFN-α and leads to a reduction in SVR rate [37]. Disruptions in the IFN-α signaling pathway in obese individuals provides another explanation for this observation. Obese patients are found to have increased messenger RNA expression of SOC-3, which inhibits insulin signaling and IFN-α expression, leading to lower SVR rates in treatment nonresponders [38].

3.5 How Antiviral Treatment Affects Metabolic Factors?

Since 1986 through which interferon has been introduced as an effective agent in the management of non-A non-B hepatitis [39], this agent became the cornerstone of controlling this infection. Soon after, PEG-IFN and ribavirin have become the standard treatment protocol for HCV infection. Despite the recent progressions in the development of newly introduced potent agents, especially HCV protease inhibitors, these two drugs remain the backbone of the therapeutic regimens for HCV infection. However, these drugs, despite their beneficial effects, have their own problems which can adversely affect patients' health.

Several authors have investigated adverse effects of PEG-IFN and ribavirin in their patient populations. A mild increase in serum transaminase levels has been reported in HCV patients treated with PEG-IFN and ribavirin [40]. The rationale behind this elevation can be either ongoing viral activity in non-responders, or even a good virological response due to an immunemodulating effect of interferon in patients with more significant raise [40]. On the other hand, some authors have reported a simultaneous development of viral response and decrease in serum transaminases suggestive of a significant correlation between viral response and serum ALT levels during the first 4 weeks of treatment [41]. Kim et al [42], retrospectively analyzed data of 168 patients undergoing PEG-IFN and ribavirin therapy found that a decrease in serum ALT levels is independently associated with achieving SVR. On the other hand, it has also been observed that long-term therapy with PEG-IFN and ribavirin is associated with a late increase in the mentioned serum biochemical factors, suggesting accumulation of polyethylene glycol in the hepatocytes is the accountable [43]. It has also been demonstrated that PEG-IFN therapy can affect the immune system and induce autoimmune diseases including type 1 diabetes mellitus [44,45]. Moreover, compared to the general population, HCV infected persons untreated with PEG-IFN and ribavirin, have higher total cholesterol (TC), low-density lipoprotein (LDL-C), and triglyceride (TG) levels [46]; However, treatment with PEG-IFN and ribavirin appears to result in increased lipid levels in HCV-infected patients who achieve SVR, but not in those who do not [47-48]. PEG-IFN plus ribavirin therapy has also been associated with an improvement in pancreatic β-cell function measured by HOMA-IR. This effect was most prominent when the patient well responds to the antiviral therapy [49]. Moreover, another study showed that rosuvastatin reduces non-alcoholic fatty liver disease in patients with chronic hepatitis C treated with α-interferon and ribavirin.

4. CONCLUSION

Hepatitis C virus, NAFLD and metabolic abnormalities including the insulin resistance obesity and particularly high BMI levels have interactions with each other and can be concomitantly observed in the same patient. On the other hand, pharmacotherapy for each of the abovementioned factors can directly or adversely affect other factors. For example, PEG-IFN therapy in HCV infected patients can result in metabolic disorders and insulin resistance which themselves have confirmed effects on viral response in HCV infected patients. On the other hand, insulin sensitizing agents as well as treatment of metabolic disorders improves HCV response to antiviral therapy. All these data suggests that attention should be paid not only to optimize the antiviral response but also to screen and treatment of the various components of the metabolic syndrome. These mean that besides caring for obesity and insulin resistance, physicians should take care of the waist circumference, elevated triglycerides, reduced

HDL-C, elevated blood pressure and elevated fasting glucose, since these factors can also directly or indirectly influence the main interfering factors. Controlling all these factors not only improve treatment of HCV infection and associated liver injuries, including the NAFLD, it will also have several other beneficial effects including lowering the risk of cancers and cardiovascular diseases which has the potential both to improve the quality and duration of our patients' lives.

CONSENT

This is a unanimous retrospective report of our series and a literature review, and we belive it does not need to get informed consent from the patients.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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