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Involvement of Metabolic Fatty Liver Disease in Patients with Hepatitis C Virus in Sustained Viral Remission Treated with Direct-Acting Antivirals

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ABSTRACT

Introduction: *MAFLD is a metabolic fatty liver disease not associated with alcohol or other liver disease, which is characterized by a finding of greater than 5% of hepatic steatosis associated with metabolic syndrome criteria. It is an asymptomatic disease, with a wide spectrum of diseases ranging from fibrosis to cancer, which is currently on the rise in Western life. HCV infection is currently curable with DAAs, and depending on the time at which it is treated, liver damage can be definitively halted. Therefore, based on the updated MAFLD concept, it would be important to know the coexistence of both pathologies and to measure liver damage with their respective complications, in order to stop them in time.*

Objective: *To determine the implication on the morbidity and mortality of MAFLD in patients with HCV infection in SVR who received treatment with ADD, at the Central Military Hospital in a period from 2016-2019.*

Methods: *It is an observational, descriptive, retrospective and cross-sectional study, the patients who presented cirrhosis (84) and those who did not (51) were classified into 3 groups: MAFLD, HCV, MAFLD + HCV, to correlate with the demographic data obtained and by the Kruskal-Wallis test to compare Fib4 in non-cirrhotic patients, and MELD and Child Pugh in cirrhotic patients.*

Results: *In patients without cirrhosis, we were able to document that the degree of fibrosis is statistically significantly higher in HCV patients (p 0.015) compared to MAFLD patients, and slightly higher in the HCV+ MAFLD group. Contrary to what we would expect from the presence of dyslipidemia in the HCV group, it was higher in the HCV+ MAFLD group. In patients with cirrhosis, we could see that there is no statistically significant difference in the degrees of fibrosis between the three groups. There is a greater presentation of dyslipidemia in the MAFLD group, with a lower presentation in the HCV group, and there is also a statistically significant difference in the prognosis of the MAFLD group evaluated with Child Pugh and MELD ($p<0.001$), being worse in the MAFLD group.*

Conclusions: *MAFLD is a common disease that every clinician should be aware of in order to be able to treat when it is still reversible and avoid liver involvement, which can even have a worse outcome than HCV infection or HCV+ MAFLD, which otherwise will result in higher health costs, emphasizing that these diseases depend heavily on the habits of patients and that they are within the reach of anyone to prevent irreversible situations.*

Keywords
Direct acting antivirals, MAFLD, Sustained viral remission, VHC.

Abbreviations
MAFLD: Metabolic fatty liver disease, NAFLD: No alcoholic fatty liver disease, DT2: Type 2 diabetes, RI: Insulin resistance, OSA: Obstructive sleep apnea, PAD: Peripheral arterial disease, CAD: Coronary artery disease, CVD: Cardiovascular disease, CKD: Chronic kidney disease, PCOS: Polycystic ovary syndrome, HD: Hepatic steatosis, Chol-HDL: High-density protein-bound cholesterol, CRP: C-reactive protein, VLDL: Very low density lipoproteins, ROS: Reactive oxygen species, HCV: Hepatitis C virus, IFN-α:Interferon alpha, SVR: Sustained viral remission, FIB4: Serological non-invasive index to estimate liver fibrosis, MELD: Model for End-stage liver disease, prognostic index of mortality in patients with liver cirrhosis, useful for prioritizing patients awaiting transplantation, Child Pugh: Staging system used to evaluate the prognosis of chronic liver disease, DAA: Direct acting antivirals.

Introduction
The term MAFLD refers to fatty liver disease associated with metabolic dysfunction, and is similar to the earlier term NAFLD, which refers to non-alcoholic fatty liver disease (NAFLD), this acronym being highly unspecific as it does not reflect pathogenesis nor does it help in patient stratification for treatment [1].

The diagnostic criteria for this condition are based on histologic (biopsy), imaging, or blood biomarker evidence of fat accumulation in the liver, plus one of the following 3 criteria: overweight/obesity, presence of type 2 diabetes, or evidence of metabolic dysregulation. Metabolic dysregulation is defined by the presence of at least two metabolic risk abnormalities: 1.-waist circumference greater than or equal to 102/88 cm in Caucasian men and women respectively with greater than or equal to 90/80 cm in Asian men and women respectively. 2.-Blood pressure greater than or equal to 100/85 mmgHg. 3.- Plasma triglycerides greater than or equal to 150 mg per deciliter. 4.-cholesterol linked to high-density lipoproteins (Chol-HDL) plasma less than 40 mg over deciliter for men and less than 50 mg over deciliter for women. 5.Pre-diabetes, i.e., fasting glucose of 100-125 mg per deciliter or two-hour post-load glucose levels of 140-199 mg per deciliter or glycosylated hemoglobin of 5.7-6.4%. 6.-Index of insulin resistance greater than or equal to 2.5. 7.-PCR greater than 2 mg per liter.

MAFLD is currently one of the main causes of chronic liver disease in the Western world, with a worldwide prevalence reported in the general population of 25%, and it is estimated that it will be the first underlying cause of liver transplantation within the next 10 years [2]. The highest rates are in South America, the Middle East, Asia, the United States of America and Europe [3] however, in Mexico, population-based studies have estimated a prevalence of around 14.3-50% in the asymptomatic population [4].

Pathophysiology of MAFLD. The relevant event is the accumulation of triglycerides in the cytoplasm of hepatocytes, to avoid this, there are two mechanisms for their elimination: the oxidation performed in mitochondria, and the export of very low density lipoproteins (VLDL), but when these mechanisms fail, an imbalance is generated between the acquisition of lipids (fatty acid uptake and lipogenesis) and their elimination (mitochondrial oxidation of fatty acids and export as a component of VLDL particles). This imbalance will condition a disorder called HD, which will generate reactive oxygen species (ROS) and toxic lipid species triggering lipotoxicity [5].

Lipotoxicity, caused by the accumulation of free cholesterol in the liver, refers to the injury and cell death caused by fatty acids and their intermediates. The metabolism of free fatty acids occurs in their packaging in triglycerides or in VLDL, but when this does not occur because there is an excess, it is done through their oxidation, generating ROS that are eliminated through antioxidant pathways, but when a patient presents MAFLD , these pathways are highly saturated, the oxidative stress generates damage to liver cells and activates their necrosis. Free cholesterol also produces ROS that further stress mitochondrial mechanisms and increase mitochondrial dysfunction [6].

HCV infection is associated with dyslipidemia, through lower total cholesterol and triglyceride levels, and hypobetalipoproteinemia, because lipids are important for HCV replication and virion assembly; and lipoproteins are necessary for HCV circulation in the blood [7].

The multifaceted interaction between HCV and lipid metabolism has been reported in several studies, and have suggested the complex effects of fatty acid metabolism on HCV replication. For example, in 2012, Negro F. et al. demonstrated that fatty acids, especially polyunsaturated fatty acids, inhibit HCV replication. In another study by Yamane et al. demonstrated that lipid peroxidation, which is a hallmark of MAFLD, restricts HCV replication in hepatocytes [8]. In contrast, Hofmann et al. demonstrated that the elimination of fatty acid elongases and desaturases, which are responsible for de novo fatty acid synthesis, could disrupt HCV replication in hepatocytes [9]. These results suggest the existence of a complex network that regulates HCV RNA replication in fatty liver.

HD, which is frequently found in patients with chronic hepatitis C, accelerates fibrosis and progression of hepatocellular carcinoma and is associated with poor response to IFN-α-based therapy. In patients with HCV genotype 3 infection, the severity of HD showed a correlation with viral load and improved after successful antiviral treatment. In addition, chronic HCV infection is associated with an increased risk of T2D and higher levels of IR, which in turn contributes to a sustained diminished response to IFNα-based therapy [9].

Fatty liver disease is the most common liver disease, affecting 17-47% of the western population and ¼ of the adult world population, being the third cause of cirrhosis worldwide. In Mexico, there is a prevalence of 17-30% in the population [10]. In patients with MAFLD, it is estimated that approximately 25% progress to HD, increasing the risk of end-stage liver disease [11].

HCV hepatitis has a worldwide prevalence of around 170 to 180 million people and prevalence rates for Latin America are estimated to vary from 1 to 2.6%. There are 58 million people with chronic HCV infection and about 1.5 million new infections occur each year. In the pediatric/adolescent population, 3.2 million people are chronically infected [12]. In Mexico, the number of people over 20 years of age is approximately 700,000 with a prevalence of 1.4%, with a prevalence of up to 10.2% in the at-risk population. The World Health Organization estimates that "in 2019 approximately 290,000 people died due to hepatitis C, mainly due to cirrhosis and hepatocellular cancer".

HCV infection is a current epidemiological problem, which is sought to eradicate and offer treatment with timely diagnosis to avoid consequences, however, the fact of coexisting with MAFLD conditions an outcome that is not as good as expected.

To date there are few studies and none in our population that demonstrate the association or certain complications that relate HCV with MAFLD and, therefore, little is known about it, so it is important to identify the relationships of complications and comorbidities involved in this relatively recent disease in order to manage it and give a better prognosis to the patient with HCV.

Material and Methods

Observational, descriptive, retrospective and cross-sectional study. Digital and physical clinical records of military and entitled patients with HCV were taken; those who had specific retroviral treatment with AAD in SVR were classified, in order to later compare the morbimortality they presented when they presented hepatic complications and associations. This search was conducted at the Central Military Hospital during the period from January 1, 2016 to November 1, 2021, with convenience sampling.

Inclusion Criteria

Records of patients diagnosed with HCV who received treatment with DAA in SVR, patient records with one or more criteria for MAFLD, files of patients older than 18 years old, records of female and male patients. Exclusion criteria: files of patients who were transplanted, files of patients with other causes of hepatopathy. Elimination criteria: incomplete records, files of patients who did not complete their treatment, files of patients who did not complete their follow-up.

Materials

Clinical records of patients meeting inclusion criteria, software R 4.2.1. , SPSS software, Microsoft Excel software.

A review of patient records of patients seen in the gastroenterology service of the Hospital Central Militar was carried out to obtain general data and data on patients who attended for consultation in the period from January 1, 2016 to November 1, 2021.

We included records of patients diagnosed with HCV who were in sustained viral remission, and who presented one or more criteria for MAFLD. The review of the records to obtain the information was done through the Digital Health System, a system used at the Central Military Hospital to store clinical record information.

Patients who presented decompensation or some of those who died were reported for hospitalization; however, the rest were followed up in the outpatient clinic during this period, using a non-probabilistic convenience sampling. Our data included clinical data, such as diagnosis, pharmacological treatment used, complications, and comorbidities. Similarly, patients with and without cirrhosis were classified into 3 groups: MAFLD, HCV, MAFLD + HCV, to correlate with the demographic data obtained. The Kruskal-Wallis test was used because the variables were independent, not paired.

Results

In (Table 1) we can see that there is a higher prevalence of MALFD in the female sex, unlike the patients who only present hepatitis C virus, in which the most affected sex was male. We can note that the distribution by gender in the MALFD + HCV group was also more predominantly female and that this group presented greater morbidities. On the other hand, although we found a higher mortality in the HCV group, this process was due to infections.

Table 1: Demographic table of patients without cirrhosis.

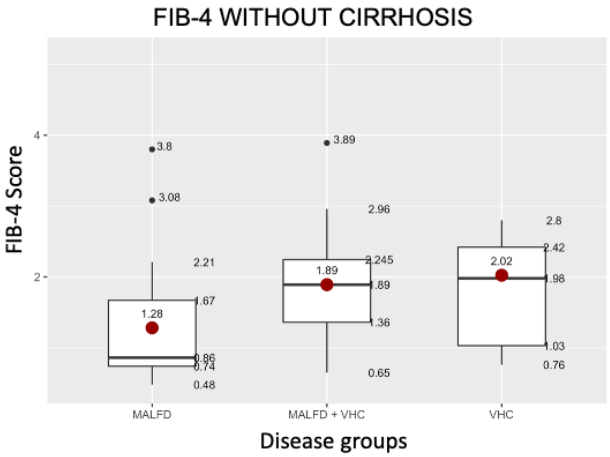
Patients without Cirrhosis	MALFD (n 25)	HCV (n 11)	MALFD + HCV (n 15)
Sex	M 9 W 16	M 6 W 5	M 4 W 11
Age	52 + 10	58 + 21.3	73 + 6.3
BMI	29.3 + 6.87	20.8 + 2.5	28.1 + 2.4
Systemic arterial hypertension	8 (32%)	2 (18%)	7 (46%)
Diabetes	6 (24%)	0	6 (40%)
Low HDL	9 (36%)	0	7 (46%)
Hipertriglyceridemia	6 (24%)	1 (9%)	6 (40%)
Descompensations	0	1 (9%)	0
Mortality	0	2* (18%)	0

Within the group of patients with liver cirrhosis (Table 2), we obtained that there is a higher prevalence of MAFLD and MAFLD + HCV in the female sex, in contrast to the HCV group, in which the male sex had a higher prevalence and in turn, this group (HCV) was the one that reported a higher mortality. On the other hand, we obtained that the greater presentation of metabolic comorbidities, especially those associated with a decrease in HDL, was in the MAFLD group.

Table 2: Demographic table of patients with cirrhosis.

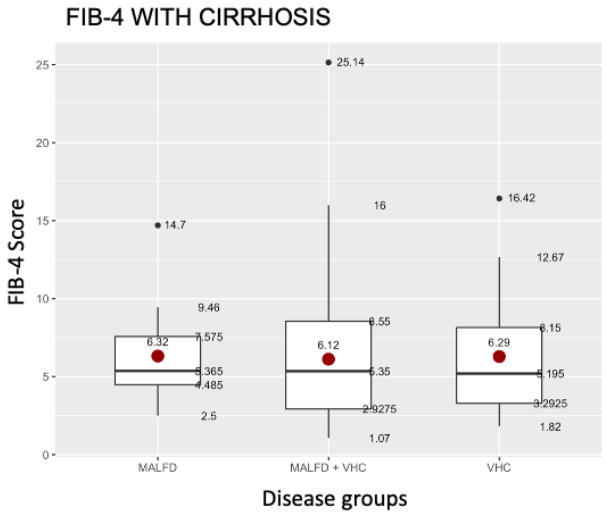
Patients without Cirrhosis	MALFD (n 16)	HCV (n 16)	MALFD + HCV (n 52)
Sex	M 2 W 14	M 11 W 5	M 30 W 22
Age	65 + 8.8	62.8 + 14.4	63.3 + 7.7
BMI	31.1 + 6.1	23.6 + 0.8	29.1 + 3.6
Systemic arterial hypertension	11 (68%)	1 (6%)	33 (63%)
Diabetes	14 (87%)	0	21 (40%)
Low HDL	15 (93%)	3 (18%)	19 (36%)
Hipertriglyceridemia	9 (56%)	1 (6%)	5 (9%)
Descompensations	11 (68%)	4 (25%)	10 (19%)
Mortality	2 (12%)	3 * (18%)	7 * (13%)
• Includes death due to COVID			

Recalling that Fib4 is the score which has the highest correlation to assess the level of fibrosis of non-invasive methods, the score is as follows:<1.45 pts: F0-1 mild fibrosis, 1.45-3.25 pts: F2-3 moderate fibrosis,>3.25 pts: 4-6 severe fibrosis, cirrhosis. In the graph (graph 1) of boxes we can see that in patients without cirrhosis that Fib4 is equal in patients with HCV F2-F3 than in patients with HCV + MAFLD F2-F3 and MAFLD group has a lower F0-1 grade. If there are significant differences p 0.015 in the level of liver fibrosis, with the HCV group having a higher degree of fibrosis (Md 2.02) than the MAFLD group (1.28), however slightly higher than the HCV+ MAFLD group (1.89).



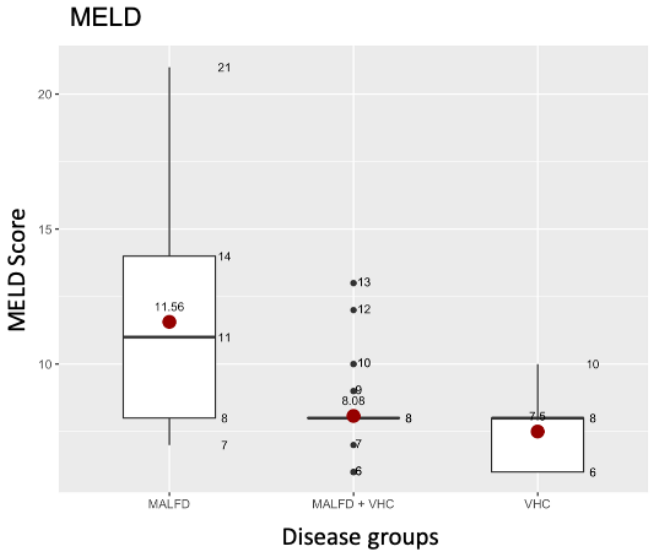
Graph 1: Box plot comparing Fib4 of the three groups evaluated: MAFLD, HCV, MAFLD + HCV in patients without liver cirrhosis.

In the box plot of graph 2, we can notice that in the HCV and MAFLD group is the one who has the highest score, however talking about medians the three groups, HCV, MAFLD and HCV + MAFLD have the same degree of fibrosis F4-F6 without being statistically significant p 0.712.



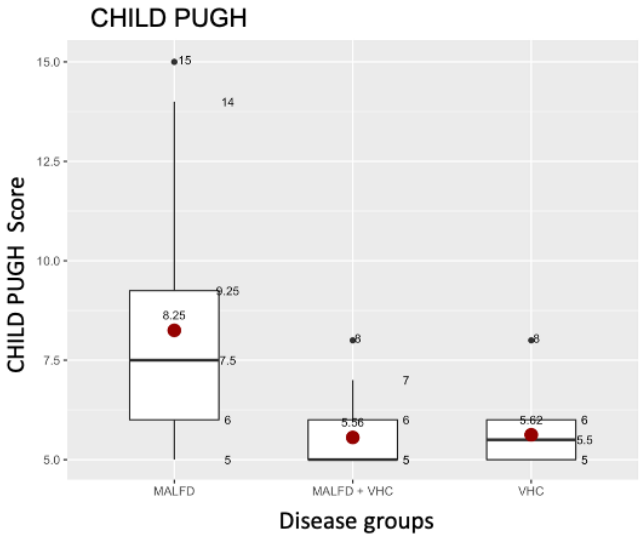
Graph 2: Box plot comparing Fib4 of the three groups evaluated MAFLD, HCV, MAFLD + HCV in patients with liver cirrhosis.

The MELD of patients (graph 3) in the MAFLD group had the highest score as opposed to HCV and MALFD + HCV with a mortality of 6% as opposed to 1.9% for the other two groups. With a higher MELD, with statistical significance (p<0.001).



Graph 3: Box plot comparing the MELD of the three groups evaluated: MAFLD, HCV, MAFLD + HCV in patients with liver cirrhosis.

The Child Pugh of patients (graph 4) in the MAFLD group compatible with MELD is the one with the worst prognosis with a grade B, in contrast to the MAFLD + HCV and HCV group who have a grade A. With statistical significance (p<0.001) (graph 5).



Graph 4: Box plot comparing the Child Pugh of the three groups evaluated: MAFLD, HCV, MAFLD HCV in patients with liver cirrhosis.

Test statistics [a,b]

	ChildPugh	Fib4	MELD	descompensacion
H de Kruskal-Wallis	15.241	.679	14.447	21.960
gl	2	2	2	2
Sig. asin.	<.001	.712	<.001	<.001

a. Prueba de Kruskal Wallis

b. Variable de agrupación: Etiologia

Graph 5: Test statistics.

Discussion

Although, when the concept of MAFLD as a systemic affectation was not known, Lonardo et al. [13], considered that approximately 6% of patients with HCV presented hepatic steatosis that had been associated with other types of metabolic diseases. They assumed that this was secondary to the metabolism of the virus, based on very detailed studies in which they demonstrated that this metabolism was necessary for the virus and therefore presented a greater amount of lipogenic substrates, as well as a decrease in fat oxidation in all genotypes, demonstrating that type III generated greater changes at the microsomal level with greater dyslipidemic risk, however at that time the treatment was based on other types of drugs such as interferon and Ribavirin. It was also mentioned that this condition predisposed to insulin resistance, which in turn was a risk factor for not responding adequately to antiviral treatment. The compilation that this study has about different studies where it tries to correlate steatosis, fibrosis, metabolic diseases, and the response to hepatitis C virus treatment, has studies with different conclusions regarding the association to these variables, however the study concludes that metabolic diseases are hepatotoxic, but that this was a secondary condition to hepatitis C virus infection.

Shortly thereafter, Pavone et al. [14] documented in a study the presence of hypoglycemia in patients with HCV treated with basal hypoglycemic agents due to pre-existing metabolic diseases, contradicting the hypothesis and the results of the previously documented studies, considering that this study was particularly carried out with AAD-based treatment, and therefore concluded that it was secondary to this treatment and that glucose levels had to be monitored to avoid hypoglycemia.

In patients without cirrhosis we were able to document that the degree of fibrosis is statistically significantly higher in patients with HCV compared to patients with MAFLD, and slightly higher in the HCV+ MAFLD group. Contrary to what we would expect from the presence of dyslipidemia in the HCV group, it was higher in the HCV+ MAFLD group, suggesting that in previous studies these two entities may have already coexisted without considering them as two distinct entities.

In patients with cirrhosis, we could see that there is no statistically significant difference in the degrees of fibrosis between the three groups. There is a greater presentation of dyslipidemia in the MAFLD group, with a lower presentation in the HCV group, being an important point in future research to know if it is an effect of AAD or underdiagnosis of the previous studies of these two entities as distinct pathologies, since from previous literature it was expected that this group would present greater dyslipidemia. Likewise, it is demonstrated that there is a statistically significant difference in the prognosis assessed with Child Pugh and MELD, being worse in the MAFLD group. To recapitulate the findings, the moral is very clear: when MAFLD is diagnosed at an early stage, there is time to a certain extent to correct all the metabolic alterations and avoid irreversible liver damage, which can be worse than even having HCV+ MAFLD.

Conclusions

In patients without liver cirrhosis, we could see that the degree of fibrosis is similar in patients with HCV and patients MAFLD + HCV and higher than patients with MAFLD, although it is considered that a variable that influences this result could be the age group since this group was younger compared to the other two, as well as the time of disease, since most patients with MALFD were diagnosed shorter than in the other two groups. It is important to note that the gender with predominance of metabolic diseases is female, a situation that could also be correlated with the postmenopausal status by age group.

In patients with liver cirrhosis, we can see that there is a higher MELD and more advanced disease in patients in the MAFLD group, unlike the other two groups, although the HCV+ MALFD group has two hepatotoxic conditions.

It is noteworthy that in the group of patients with HCV mortality was slightly higher than in the other groups despite the fact that they had less advanced disease than the MAFLD group; however, the causes of mortality were associated with infections by COVID, and not associated with decompensation due to liver cirrhosis.

It is worth mentioning that most of these patients were ambulatory control patients, not severe patients, which could cause a bias in terms of the presentation of decompensations.

What is clear is that MAFLD is a common disease, with a high prevalence, that every clinician should be aware of in order to treat it when it is still reversible and avoid its hepatic affectation since, as we have already seen, in the long run it could increase mortality and morbidity which will condition the increase of health costs, emphasizing that these diseases depend a lot on the habits of the patients and that they are within the reach of anyone in order to prevent irreversible situations.

Consent for Publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Availability of Supporting Data

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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