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RESEARCH ARTICLE

Prevalence and Factors Associated with Hepatic Steatosis and Fibrosis Using Fibroscan in HIV-positive Patients Treated with Anti-retroviral (ARV) Medicines Referred to the Biggest Hospital in Tehran, 2018 to 2019

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Abstract:

Background:

Liver injury is a characteristic feature of HIV infection, which is the second most common cause of mortality among HIV positive patients. Non-alcoholic fatty liver disease (NAFLD) has become a new concern in the management of people living with HIV (PLWH). The condition encompasses a spectrum of diseases from non-alcoholic steatohepatitis (NASH) to fibrosis and cirrhosis. The current study was to evaluate hepatic steatosis and fibrosis using fibroscan among PLWH treated with anti-retroviral (ARV) medicines.

Methods:

The present research was designed as a cross-sectional study and 100 HIV positive patients under antiretroviral treatment (ART) were enrolled in the study. All PLWH, including 49 men (49%) and 51 women (51%) (Mean age of 39.9 years), were evaluated by Transient Elastography (TE) in Imam Khomeini Hospital during 2018 and 2019.

Results:

The mean CD4 count was 610 cells/ μ l, 4% with CD4 < 200 cells/ μ l, 30% between 201 and 500 cells/ μ l, and 66% with CD4 > 500 cells/ μ l. Based on the TE result, 10% of patients had significant fibrosis (F2:6% and F3:4%) and most of the patients had mild fibrosis (F1:77%). A significant, direct relationship was found between HIV infection duration and fibrosis, especially in the duration of more than five years of the disease. There was no significant association between liver fibrosis and other factors ($P > 0.05$).

Conclusion:

The presence of hepatic fibrosis and steatosis demonstrates the main health concern for PLWH mono-infection, and mainly transient elastography is recommended for HIV mono-infected patients, especially if their infection period is over five years.

Keywords: AIDS, HIV, ART, Liver fibrosis, Steatosis, Fibroscan.

Article History

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1. INTRODUCTION

HIV infection remains an important public health issue. Globally, there were approximately 37.9 million people living with HIV (PLWH), with 1.7 million people becoming newly

infected with HIV by the end of 2018 [1, 2].

Introduction and the widespread use of anti-retroviral therapy (ART) and improvements in the management of patients with AIDS have led to a significant reduction in morbidity and mortality rate of PLWH and resulted in increased life expectancy. AIDS-related diseases account for less than 50% of deaths. Liver disease has become a growing

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concern in HIV/AIDS and is the significant cause of death in PLWH [3, 4].

HIV-infection is the cause of many hepatobiliary disorders, including increased liver enzymes, hepatomegaly and liver steatosis [5]. The potential mechanisms responsible for HIV-related liver damage include the direct interaction between HIV and multiple cell types of liver and an effect of HIV glycoproteins on hepatic stellate cells thus, stimulating collagen production [5, 6]. Prior to ART, opportunistic infections and AIDS-related neoplasms were the most common causes of liver damage in PLWH [6 - 8]. After the extensive implementation of ART, the spectrum of liver disease in PLWH has changed to drug-induced liver disease, concomitant infections with HCV and HBV hepatitis, Non-Alcoholic Fatty Liver Disease (NAFLD), and alcohol abuse [9, 10].

Vibration-controlled Transient Elastography (VCTE) by Fibroscan measures shear wave velocity of a low frequency shear wave (50 Hz) transmitted *via* an ultrasound probe in the liver tissue and liver stiffness. Conceptually, with increased liver stiffness, shear wave velocity increases correspondingly. In addition to the non-invasive nature of evaluation, VCTE is very useful having excellent inter and intra-operator reproducibility and is disputable ability of this method to assess a larger area of liver parenchyma (approximately 1cm*4 cm), the volume of which is about 100 times that of a liver biopsy, which samples only 1/50,000 of the liver volume [11 - 13]. The normal Fibro Scan range is between 2 and 7 kPa. The average normal result is 5.3 kPa [14].

Because transient elastography is a valid tool for the diagnosis of liver fibrosis in HIV-positive and HIV-negative patients, this study was conducted to evaluate liver fibrosis and potential risk factors for PLWH under an ART intervention.

2. MATERIALS AND METHODS

2.1. Study Design

It was a descriptive cross-sectional study conducted between 2018 and 2019 on 100 HIV-positive patients using ART at the Tehran Imam Khomeini Hospital, Iran, and affiliated with Tehran University of Medical Sciences (TUMS).

2.2. Participants

HIV patients undergoing ART treatment were enrolled to this study and referred for fibro scan after completing the necessary information by completing the questionnaire and lab tests. The exclusion criteria were alcohol consumption, hepatitis B and C co-infection.

2.3. Measurements

In this study, the following data were collected for all the patients from the available reports registered in the healthcare center and their periodic tests before fibroscan: demographic characteristics (age, gender, body mass index), HIV-related information (CD4 count, duration of HIV diagnosis, duration and type of ART drugs, and types of medications), a history of smoking and injecting substances, records of diseases such as diabetes mellitus, hyperlipidemia (HLP) (hyper cholesterolemia, and hypertriglyceridemia), liver function tests (AST, and ALT), hepatitis B (HbsAg, HbsAb, and HbcAb) and hepatitis C (HCV Ab). All candidates, who were blind to the condition of the experiment, were evaluated by transient elastography (TE) and their liver steatosis and fibrosis were measured.

2.4. Ethical Considerations

Written informed consent was obtained from all the participants, and all the procedures were performed in confidence. The patients were not made liable for any cost.

2.5. Statistical Analysis

Having collected, reviewed and modified, the information was analyzed by using the SPSS software version 22.0. The authors calculated the values of mean, median and proportional variables such as age, paraclinical parameters (Hb, WBC, platelet, triglyceride, cholesterol, fasting blood sugar, AST, ALT, CD4 count, and viral load), and also the association between these variables and hepatic fibrosis. The analytic analysis was performed using the Pearson correlation chi-square test and Fisher's Exact Test.

3. RESULTS

In the present study, 100 PLWH, including 49 men (49%) and 51 women (51%), were assessed by lab tests and TE. The mean age of patients was 39.9 (SD=9.5) years and the mean time after diagnosis was 71.1 (SD=54.4) months. The mean CD4 count was 610 cells/ μ l, 4% with CD4 < 200 cells/ μ l, 30% between 201 and 500 cells/ μ l, and 66% with CD4 > 500 cells/ μ l. Table 1 shows the demographic profile of the patients who participated in the study.

The main combination for ART intervention consisted of two Nucleoside Reverse Transcriptase Inhibitors (NRTIs) and one Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI). The most frequently used medication taken by 40% of patients was tenofovir/emtricitabine/efavirenz (Vonavir).

Table 1. Demographic characteristics of the PLWH and their association with hepatic fibrosis.

Variable	Patient with Significant Hepatic Fibrosis F (%)	Patient with Mild Hepatic Fibrosis F (%)	Patient with no Hepatic Fibrosis	P Value*
Gender				
Male	4 (40)	40(52)	5(39)	0.65
Female	6 (60)	37(48)	8(61)	

(Table 1) contd....

Variable	Patient with Significant Hepatic Fibrosis F (%)	Patient with Mild Hepatic Fibrosis F (%)	Patient with no Hepatic Fibrosis	P Value*
Age (yrs)				
17-35	3 (30)	26 (34)	6 (46)	0.74
36-50	4 (40)	40 (52)	6 (46)	
>50	3 (30)	11 (14)	1 (8)	
BMI (kg/m²)				
<19.9	1 (10)	8 (10.5)	3 (23)	0.66
20-24.9	5 (50)	31 (40)	7 (54)	
25-29.9	3 (30)	30 (39)	3 (23)	
>30	1 (10)	8 (10.5)	0 (0)	
Smoking				
Never	8 (80)	67 (87)	13 (100)	0.37
Previous	1 (10)	6 (8)	0 (0)	
Now	1 (10)	4 (5)	0 (0)	
Addiction				
Yes	2 (20)	9 (12)	2 (15)	0.62
No	8 (80)	68(88)	11 (85)	
Diet				
Yes	6 (60)	21(27)	4(31)	0.18
No	4 (40)	56(73)	9(69)	
Diabetes				
Yes	1 (10)	0 (0)	0 (0)	0.11
No	9 (90)	77 (100)	13 (100)	
Disease duration (yrs)				
<5	2 (20)	42 (54)	7 (54)	0.008
5-10	3 (30)	19 (25)	6 (46)	
>10	5 (50)	16 (21)	0 (0)	
CD4 (cell/μl)				
<200	2 (20)	2 (3)	0 (0)	0.10
201-350	1 (10)	14 (18)	0(0)	
351-500	1 (10)	10 (13)	4 (31)	
>500	6 (60)	51 (66)	9 (69)	
Viral load (copy/ml)				
<47	8 (80)	68 (88)	10 (77)	0.10
48-200	1 (10)	3 (4)	0 (0)	
201-1000	0 (0)	4 (5)	0 (0)	
>1000	1 (10)	2 (3)	3 (23)	
Triglyceride				
Normal	7 (70)	62 (80)	12 (92)	0.46
High	3 (3)	15 (20)	1 (8)	
LDL				
Normal	4 (40)	38 (49)	9 (70)	0.14
High	6 (60)	39 (51)	4 (30)	
AST				
Normal	9 (90)	71 (92)	12 (92)	0.44
High	1 (10)	6 (8)	1 (8)	
ALT				
Normal	9 (90)	68 (88)	12 (92)	0.65
High	1 (10)	9 (12)	1 (8)	
Steatosis				
S0	3(30)	33(43)	8(61)	0.30
S1	3(30)	28(36)	3(23)	
S2	3(30)	12(16)	1(8)	
S3	1(10)	4(5)	1(8)	

* Fisher's Exact Test

Based on the TE result, 10% of patients had significant fibrosis (F2:6% and F3:4%) and most of the patients had mild fibrosis (F1:77%).

In this study, we considered F0 as no fibrosis, F1 as mild fibrosis, F2 and F3 as significant fibrosis. Then, the relationship between the severity of liver fibrosis and variables was investigated.

In the current study, a significant direct relationship was found between HIV infection duration and fibrosis especially in the duration of the disease more than five years. There was no significant association between the liver fibrosis and age, gender, smoking, addiction, diet, body mass index (BMI), CD4 counts, viral load, none of the drug regimens, and other laboratory parameters such as FBS, TG, LDL, AST, ALT

($P > 0.05$). Also, hepatic steatosis was not associated with fibrosis ($P > 0.05$).

4. DISCUSSION

The primary purpose of this study was to evaluate the prevalence of and factors associated with hepatic fibrosis among HIV-positive patients. All the patients in this study had HIV mono-infection, and co-infected patients with hepatitis B and C and alcohol users were excluded.

In the present research, 10% of the patients had significant hepatic fibrosis (F2, F3) and 22% of the patients had considerable hepatic steatosis. In addition, hepatic fibrosis was associated with disease duration, especially over five years. However, in the current study, no association between liver fibrosis and other risk factors such as age, gender, smoking, addiction, BMI, CD4 count, viral load, drug regimen and laboratory parameters was observed.

Progressive liver injury is a rising concern in PLWH [15]. While life expectancy has increased in recent decades, liver involvement in HIV-positive patients is an emerging concern in this group, where comorbidities have become the major cause of death in recent years [16] (Table 1).

Common organisms, which usually infect the liver in immunocompetent patients, are observed to infect HIV⁺ patients to a greater extent. In addition, these patients are prone to liver infections with unusual organisms such as fungi, parasites, and bacteria. Older studies have demonstrated opportunistic infections (OIs) in 40% of livers of AIDS patients after death [17]. In the current era of ART, the incidence of OIs is on the downward trend [3].

Approximately NAFLD is seen in 30% of PLWH without any evidence of any other co-infection with hepatitis B or C virus [18]. The spectrum of NAFLD in HIV patients varies from mild steatosis and steatohepatitis on the one hand, and cirrhosis and end-stage liver disease on the other hand. Risk factors for NAFLD in HIV⁺ patients may be divided into two groups: namely, patient-related and treatment-related factors. The most prevalent risk factors associated with patients include: high BMI, diabetes mellitus, hyperlipidemia, and physical inactivity [3, 19]. However, PLWH having NAFLD appear to have lower body weight and are physically more active than non-HIV infected individuals [20]. This difference may be due to the direct effect of HIV and role of ART in the development of NAFLD. Various ART medicines (primarily PIs and NRTIs) cause undesirable lipid profiles and therefore, increase the risk of NAFLD. Didanosine and Stavudine are usually involved in the causation of NAFLD [21].

Even in the absence of other common causes of liver disease, such as HBV or HCV co-infections, drugs use, alcohol abuse, metabolic diseases, and immunosuppression, significant risk of liver fibrosis (LF) has been described in PLWH [22, 23], as a result, this potentially indicates HIV as a cause of liver damage in vivo. In contrast, the control of HIV RNA levels induced by ART appears to decrease this process [24].

Our results showed hepatic steatosis in 22% of HIV-mono-infected patients and liver fibrosis in 10% of them. In a similar study conducted by Lombardi *et al.*, (2016), hepatic steatosis

was detected in 55% and significant fibrosis was present in 17.6% of patients [25].

The duration of HIV infection was clearly associated with hepatic fibrosis, which was associated with increased duration of the disease especially over five years. We did not find any study in which this factor was investigated. Liver fibrosis had no association with other factors such as age, gender, smoking, addiction, BMI, and drug regimen in our study, while in the study by Sulyok *et al.*, (2017), age and BMI showed a positive association with liver stiffness [26].

Also, in our study, CD4 count, viral load, and laboratory parameters were not associated with hepatic fibrosis, which was not consistent with other studies. Our explanation is that our country's policies include screening individuals with high-risk behaviors and treating them as soon as patients are diagnosed positive. Therefore, most of the patients we studied had undetectable viral loads and high CD4 count.

In a research study by Perazzo *et al.*, (2018), the prevalence of liver steatosis and fibrosis was 9% and older age, CD4⁺ count < 200 cells/mm³, obesity, type 2 diabetes, dyslipidemia, and metabolic syndrome were associated with steatosis [27].

In a study by Torgersen *et al.*, (2019), only advanced hepatic fibrosis was associated with greater severity of steatosis in HIV⁺ patients, while in our study, hepatic steatosis was not associated with liver fibrosis [28]. In our opinion, the reason was that most of our patients in mild stages of steatosis were identified by ultrasound and therapeutic interventions such as diet control, exercise, and alcohol avoidance prevented the progression to more severe stages of steatosis and eventually fibrosis. In addition, according to a study by Kaspar *et al.*, among the 10 possible mechanisms involved in liver damage in HIV patients, including oxidative stress, mitochondrial injury, lipotoxicity, immune-mediated injury, cytotoxicity, toxic metabolite accumulation, gut microbial translocation, systemic inflammation, senescence and nodular regenerative hyperplasia, some of them, such as immune-mediated injury, cytotoxicity and nodular regenerative hyperplasia could cause liver damage without steatosis [29].

In our research, 60% of patients with liver fibrosis were female and most of them were 36-50 years old. While in a study by Morse *et al.*, (2015), 92% of patients with liver fibrosis were male and the mean age was 50 years [14].

CONCLUSION

In conclusion, liver fibrosis appears to be an important pathological precondition for hepatocellular carcinoma and the rate of liver fibrosis is positively associated with liver cancer. Today, due to advances in the treatment of patients with HIV and the shift in the pattern of liver involvement from opportunistic infections to chronic processes such as steatosis and fibrosis, there is a serious health concern for patients with HIV infection. Therefore, it is recommended that PLWH, especially for more than 5 years, undergo fibroscan. In addition, early prevention and diagnosis of common co-infections such as hepatitis B and C, which exacerbate liver fibrosis, and avoidance of medications that cause liver fibrosis,

along with steatosis control methods, can prevent disease progression.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the ethics committee of Tehran University Of Medical Sciences ,Iran with Ethical code:IR.TUMS.VCR.REC.1397.1120.

HUMAN AND ANIMAL RIGHTS

Not applicable.

CONSENT FOR PUBLICATION

All patients participated on a voluntary basis and gave their informed consent.

AVAILABILITY OF DATA AND MATERIALS

The data supporting the findings of the article is available in the [Research site of Tehran University of Medical Sciences] at [<https://research.tums.ac.ir/index.phtml>], reference number [37264].

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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