Liver Fibrosis and Steatosis in Virally Suppressed HIV-Infected Patients with Cytomegalovirus Seropositivity

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ABSTRACT

Background: *Cytomegalovirus (CMV) is a human herpesvirus common in people with human immunodeficiency virus (HIV). In a patient with immunocompetence, long periodic asymptomatic CMV might affect to develop the abnormal liver function and contribute to non-AIDS defining morbidity, including chronic liver disease. This study aims to know the prevalence of liver fibrosis and steatosis in virally suppressed HIV infected patients with CMV reactive and summarize the correlation of clinical presentation with liver fibrosis and steatosis in these subjects.*

Method: *A cross-sectional study in HIV Integrated Care Unit, Cipto Mangunkusumo Hospital, was conducted from April 2019 until June 2020. Subjects enrolled in this study were suppressed HIV patients aged between 30-40 years with positive IgG CMV and already using stable ART for at least one year. Transient elastography measured the liver stiffness. Patients with liver stiffness above 7 kPa were defined as having significant liver fibrosis. In addition, Spearman correlation was conducted to evaluate the correlation of clinical presentation of subjects related to liver fibrosis and steatosis.*

Results: *A total of subjects was included in this study. Dominantly male (62.5%) with average age 38 ± 4.68 years. The median amount of CMV DNA was 466 (17-21284) copy/mL. Significant Fibrosis was found in 17/80 (21%) subjects. In this study, clinical parameters correlated with liver fibrosis were insulin, glucose fasting, Homa IR, triglyceride, HDL, and platelet. A medium positive correlation was found in insulin, and Homa IR, with coefficient correlation for insulin, was $r = 0.475$, $p < 0.001$; and coefficient correlation for Homa IR was $r = 0 .487$, $p < 0.001$.*

Conclusion: *The prevalence of liver fibrosis was 21% in these subjects. In addition, insulin and Homa IR had a positive correlation with increasing liver fibrosis.*

Keywords: *Liver fibrosis, cytomegalovirus, human immunodeficiency virus (HIV)*

ABSTRAK

Latar belakang: *Cytomegalovirus (CMV) adalah virus herpes manusia yang umum terjadi pada pasien human immunodeficiency virus (HIV). Pada pasien dengan imunokompeten, infeksi CMV dapat terjadi asimtomatik jangka panjang yang dapat menyebabkan gangguan fungsi hati dan menimbulkan morbiditas non-AIDS bersama penyakit hati kronik lainnya. Penelitian ini bertujuan untuk mengetahui prevalensi fibrosis dan steatosis hati pada pasien terinfeksi HIV dengan kadar virus sudah ditekan dengan antivirus, namun kondisi infeksi CMV reaktif, serta mengetahui korelasi berbagai manifestasi klinis dengan fibrosis hati pada subjek tersebut.*

Metode: *Studi potong lintang di Unit Pelayanan Terpadu HIV, Rumah Sakit Cipto Mangunkusumo, dilakukan antara April 2019 hingga Juni 2020. Subyek pada penelitian ini adalah pasien HIV yang kadar virusnya telah ditekan dengan antivirus, berusia antara 30-40 tahun dengan IgG CMV positif dan sudah menggunakan anti-retroviral therapy (ART) stabil setidaknya selama satu tahun. Elastografi transien berfungsi mengukur kekakuan hati. Pasien dengan kekakuan hati di atas 7 kPa didefinisikan memiliki fibrosis hati yang signifikan. Selain itu, korelasi Spearman dilakukan untuk mengevaluasi korelasi presentasi klinis subyek penelitian dengan fibrosis dan steatosis hati.*

Hasil: *Sebanyak 80 pasien dilibatkan dalam penelitian ini. Didominasi laki-laki (62,5%) dengan usia rata-rata 38 ± 4,68 tahun. Jumlah rata-rata DNA CMV adalah 466 (17-21284) copy/mL. Fibrosis signifikan ditemukan pada 17/80 (21%) pasien. Pada penelitian ini, parameter klinis yang berhubungan dengan fibrosis hati adalah insulin, glukosa puasa, Homa IR, trigliserida, HDL, dan trombosit. Korelasi positif sedang ditemukan pada insulin, dan Homa IR, dengan koefisien korelasi untuk insulin, adalah r = 0,475, p-value < 0,001; dan koefisien korelasi untuk Homa IR adalah r = 0,487, p < 0,001.*

Simpulan: *Prevalensi fibrosis hati adalah 21% pada subjek ini. Insulin dan Homa IR memiliki korelasi positif dengan peningkatan fibrosis hati.*

Kata kunci: *Fibrosis hati, cytomegalovirus, human immunodeficiency virus (HIV)*

INTRODUCTION

After introducing antiretroviral treatment (ART) in 1996, the life expectancy of people living with HIV (PLWH) has increased significantly. Non-AIDS diseases are becoming an increasingly important source of morbidity and mortality among HIV-infected people.[1] The opportunistic infections and neoplasms AIDS-related as the leading causes of morbidity and mortality have shifted to cardiovascular and liver disease. It is estimated that liver-related diseases account for 13–18% of all-cause mortality in HIV-infected patients.[1,2] The development of liver fibrosis represents the ultimate common path for the most clinically relevant liver injury. HIV itself can cause liver damage and consequent liver fibrosis (LF) in several ways. Aside from HIV, viral hepatitis, alcoholic and mainly non-alcoholic liver disease have been linked to liver involvement in PLWHA. Another known cause of hepatotoxicity is ART, which raises clinically significant concerns about LF in long-term treatment.[3]

Antiretroviral therapy (ART) has significantly reduced the morbidity and mortality associated with acquired immunodeficiency syndrome (AIDS).[4] Among many comorbidities, cardiovascular disease (CVD) has become a particular concern. Among HIV-infected patients, smoking (38% vs. 18%), hypertension (21% vs. 16%), diabetes (12% vs. 7%), and dyslipidemia (23% vs. 18%) have a higher prevalence.[5] After HIV infection, a decrease in total cholesterol, HDL-cholesterol, and LDL-cholesterol, but an increase in triglycerides is observed in untreated individuals.[6] Nearly half of patients with long-term ART exposure will experience changes in body composition. Lipid metabolism patients with HIV infection may also experience important changes in body fat composition after exposure to antiretroviral therapy.[7] Immune activation leads to chronic inflammation, which varies in severity and is observed in untreated HIV patients and patients receiving combination antiretroviral treatment (cART). In patients treated with antiretroviral drugs, pro-inflammatory cytokines were reduced, but they did not fully return to normal. In patients receiving HIV treatment, the activation of the innate immune system and insulin resistance are like those described in obesity and type 2 diabetes (DM2).[8,9] After the innate immune system is activated, insulin-related protein signals are converted into transcription post-modification results in reduced insulin action.[10,11]

Human cytomegalovirus (CMV) often coexists with HIV and accounts for an excessive proportion of memory T cell responses. Chronic co-infections such as cytomegalovirus (CMV) may lead to a vicious circle of immune activation and reservoir seeding.[12] Hijacking cytokine and chemokine signalling, manipulation of cell development pathways, and transactivation of HIV expression by CMV may aggravate the persistence of HIV. This series of circumstances has allowed HIV to build a larger pool of latently infected cells that can hide in dormant states for decades in the face of virus-suppressive antiretroviral therapy (ART).[13] Cytomegalovirus (CMV) is a human herpesvirus common in people with human immunodeficiency virus (HIV). In patients with immunocompetence, long periodic asymptomatic CMV might affect the development of abnormal liver function and contribute to non-AIDS defining morbidity, including chronic liver disease. In addition, there is accumulated evidence that some infectious agents, such as cytomegalovirus (CMV) and varicella-zoster virus (VZV), may accelerate the course of atherosclerotic disease in HIV-infected patients.[14] This study aims to know the prevalence of liver fibrosis in virally suppressed HIV infected patients with CMV reactive and summarize the correlation of clinical presentation and liver fibrosis in these subjects.

METHOD

A Cross-sectional study in HIV Integrated Care Unit, Cipto Mangunkusumo Hospital, was conducted from April 2019 until June 2020. Patients between the ages of 20 and 45, who had used stable ART for at least one year, were CMV IgG positive and had an HIV RNA viral load < 50 copies/mL, including men and women, were recruited in this study. Patients with the following conditions were excluded from the study: patients undergoing DAA treatment for hepatitis C, decompensated cirrhosis or acute liver failure, history of coronary artery disease, diabetes, brain infection, epilepsy, stroke, rhabdomyolysis or myopathy, severe depression during pregnancy or breastfeeding during the study.

All potential participants received explanations about the purpose and methods of the research and were informed that they had the right to stop or refuse to participate in the research. Viral load, anti-CMV antibody and fasted lipid profile were tested before determining eligibility criteria. Participants with CMV seropositivity, undetectable viral load, and Framingham risk score >10% LDL < 130 or Framingham risk score < 10% LDL < 160 continued the study process. Participants were asked to fast for 10 hours before taking 12 mL of venous blood: for examination of blood glucose, ALT, CMV DNA, soluble CD4 (sCD4), and transient elastography with Controlled Attenuation Parameter (CAP).

Transient elastography (TE) with CAP was done by a trained hepatologist using a Fibro scan (Echosens®) device. The criteria for successful examination are ten shots and an interquartile range (IQR) for liver stiffness of less than 20% of the median value. The cut-off value for steatosis diagnosis using CAP measurement of above 238 dB/m and the value for fibrosis diagnosis if the transient elastography measurement showed higher than 7.1 kPa.14. This study had been approved by Health Research Ethics Committee–Universitas Indonesia and Cipto Mangunkusumo Hospital (HREC-FMUI/CMH).

Table 1. Characteristics of study participant

Variable	Total
Demography	
Age, mean ± SD	38 ± 4.68
Sex, n (%)	
Male	50 (62.5%)
Female	30 (37.5%)
Body mass index (BMI), n (%)	
Obese	15 (18.8%)
Overweight	22 (27.5%)
Normal	33 (41.3%)
Underweight	10 (12.5%)
Alcohol consumption less than one month, n (%)	
Yes	6 (7.5%)
No	74 (92.5%)
Laboratory profile	
CMV amount, median (range)	466 (17-21284)
Hemoglobin, mean ± SD	13.90 ± 1.92
Leukocyte, mean ± SD	6.50 ± 1.86
Platelet, mean ± SD	273 ± 62
Total cholesterol, mean ± SD	296 ± 43.16
HDL, mean ± SD	50 ± 14.10
LDL, mean ± SD	119 ± 35.56
Trygliceride, median (range)	112 (46-1393)
Fasting glucose, mean ± SD	86 ± 11.03
Insulin, median (range)	7.75 (1.7-63.9)
Homa IR	1.69 (0.3-17.99)
HIV diagnosis	
Years of diagnosis, n (%)	
Above five years	60 (75%)
Under-five years	20 (25%)
HIV stage, n (%)	
NA	8 (10%)
4	3 (3.8%)
3	34 (42.5%)
2	5 (6.3%)
1	30 (37.5%)
CD4 absolute when diagnosed, median (range)	113 (2-623)
CD4 recent, median (range)	589 (149-1482)
Years of starting ARV, n (%)	
Above five years	60 (75%)
Under-five years	20 (25%)
Liver profile	
Fibrosis, median (range)	4.85 (2.60-16.30)

CMV: Cytomegalovirus, HDL: high density lipoprotein, LDL: low density lipoprotein, HIV: human immunodeficiency virus, ARV: antiretroviral

Data were analyzed using software SPSS version 24. The mean and standard deviation were used for normally distributed data, and for abnormally distributed data, the median (minimum-maximum) was used. P-value was calculated using the student t-test for normally distributed data and the Mann-Whitney test for abnormally distributed data. The percentages were used to represent categorical data. The $\chi 2$ test was used to calculate the p-value for categorical data. The baseline characteristics of patients have compared significant and non-significant Fibrosis and steatosis. A multivariate linear regression analysis was conducted to identify the predictors of the liver disease, and Spearman correlation coefficients were obtained to evaluate the correlation of insulin level, fasting blood glucose, body mass index (BMI), HOMA IR, triglyceride, HDL, platelet count of subjects related to liver fibrosis. After entering all variables into the model, the variables that showed the least significant associations were subsequently excluded until all variables remained significant ($p < 0.05$). The model fit for the multiple regression was assessed using the R2 - coefficient of determination and the adjusted R2 - coefficient of determination, adjusted for the number of independent variables in the model.

RESULTS

A total of 80 patients was included in this study. Dominantly male (62.5%) with average age 38 ± 4.68 years. The median amount of CMV DNA was 466 (17-21284) copy/mL. Significant fibrosis was found in 17/80 (21%) patients, and significant steatosis were 16/80 (20%) (Table 1). Clinical parameters such as status of smoking, hemoglobin level, triglyceride, insulin, and HOMA-IR, statistically significantly different between significant and non-significant fibrosis and steatosis in bivariate analysis, but not for sex, blood fasting glucose, CD4 absolute when first time diagnosed with HIV, and duration of cART consumption which only statistically significant to differentiate fibrosis group. The level of total cholesterol and LDL seems significant to differentiate the steatosis group (Table 2 and 3).

Table 2. Comparison of baseline characteristic of significant and non-significant fibrosis

	Total	Significant fibrosis* (n = 17)	Non significant fibrosis (n = 63)	p
Demography				
Age, mean ± SD	38 ± 4.68	39 ± 3.20	38 ± 4.98	0.285
Sex, n (%)				
Male	50 (62.5%)	16 (94.1%)	34 (54%)	**0.002**
Female	30 (37.5%)	1 (5.9%)	29 (46%)	
Body mass index (BMI), n (&)				
Obese	15 (18.8%)	6 (35.3%)	9 (14.3%)	0.239
Overweight	22 (27.5%)	4 (23.5%)	18 (28.6%)	
Normal	33 (41.3%)	6 (35.3%)	27 (42.9%)	
Underweight	10 (12.5%)	1 (5.9%)	9 (14.3%)	
Systole blood pressure, mean ± SD	121 ± 16.40	129 ± 24.70	119 ± 12.70	0.101
Diastole blood pressure, mean ± SD	79 ± 11.20	82 ± 12.80	78 ± 10.60	0.138
Smoker, n (%)				
Current	22 (27.5%)	5 (29.4%)	17 (27.0%)	**0.017**
Former	15 (18.8%)	7 (41.2%)	8 (12.7%)	
No	43 (53.8%)	5 (29.4%)	38 (60.3%)	
Alcohol consumption less than one month, n (%)				
Yes	6 (7.5%)	2 (11.8%)	4 (6.3%)	0.815
No	74 (92.5%)	15 (88.2%)	59 (93.7%)	
Hematology and lipid profile				
CMV amount, median (range)	466 (17-21284)	370 (172-1471)	480 (17-21284)	0.332
Hemoglobin, mean ± SD	13.90 ± 1.92	14.72 ± 1.36	13.67 ± 1.99	**0.044**
Hematokrit, mean ± SD	38.81 ± 5.59	40.26 ± 3.20	38.42 ± 6.04	0.097
Leukocyte, mean ± SD	6.50 ± 1.86	6.67 ± 2.46	6.45 ± 1.68	0.678
Platelet, mean ± SD	273 ± 62	249 ± 63	280 ± 61	0.068
Neutrophil, mean ± SD	54.70 ± 9.82	52.41 ± 10.14	55.32 ± 9.73	0.281
Lymphocyte, mean ± SD	34.89 ± 9.34	35.99 ± 10.04	34.60 ± 9.20	0.587
Monocyte, mean ± SD	7.29 ± 2.01	8.02 ± 2.34	7.09 ± 1.88	0.088
Total cholesterol, mean ± SD	296 ± 43.16	202 ± 63.13	195 ± 36.50	0.636
HDL, mean ± SD	50 ± 14.10	45 ± 9.66	52 ± 14.74	0.054
LDL, mean ± SD	119 ± 35.56	112 ± 49.44	121 ± 31.07	0.518
Trygliceride, median (range)	112 (46-1393)	173 (70-1393)	104 (46-332)	**0.004**
Fasting glucose, mean ± SD	86 ± 11.03	92 ± 13.09	84 ± 9.92	**0.029**
Insulin, median (range)	7.75 (1.7-63.9)	12 (7-64)	6.70 (2-34)	**0.001**
Homa IR	1.69 (0.3-17.99)	3.40 (1.54-17.99)	1.30 (0.30-8.41)	**0.001**
HIV diagnosis				
Years of diagnosis, n (%)				
Above 5 years	60 (75%)	16 (94.1%)	44 (69.8%)	0.057
Under 5 years	20 (25%)	1 (5.9%)	19 (30.2%)	

	Total	Significant fibrosis* (n = 17)	Non significant fibrosis (n = 63)	p
HIV stage, n (%)				
NA	8 (10%)	3 (17.6%)	5 (7.9%)	0.440
4	3 (3.8%)	0 (0%)	3 (4.8%)	
3	34 (42.5%)	9 (52.9%)	25 (39.7%)	
2	5 (6.3%)	1 (5.9%)	4 (6.3%)	
1	30 (37.5%)	4 (23.5%)	26 (41.3%)	
CD4 absolute when diagnosed, median (range)	113 (2-623)	42 (2-573)	143 (5-623)	**0.011**
CD4 recent, median (range)	589 (149-1482)	671 (318-1338)	584 (149-1482)	0.651
Years of starting ARV, n (%)				
Above 5 years	60 (75%)	16 (94.1%)	44 (69.8%)	0.057
Under 5 years	20 (25%)	1 (5.9%)	19 (30.2%)	
Years of NRTI, n (%)				
Above 5 years	65 (81.3%)	17 (100%)	48 (76.2%)	**0.032**
Under 5 years	15 (18.8%)	0 (0%)	15 (23.8%)	

* Significant fibrosis ≥ 7 kPa

CMV: Cytomegalovirus, HDL: high density lipoprotein, LDL: low density lipoprotein, HIV: human immunodeficiency virus, ARV: antiretroviral

Table 3. Comparison of baseline characteristic of significant and non-significant steatosis

	Total	S1-S3 significant steatosis (n = 16)	S0 non-significant steatosis (n = 64)	p
Demography				
Age, mean ± SD	38 ± 4.68	38 ± 3.79	38 ± 4.90	0.831
Sex, n (%)				
Male	50 (62.5%)	10 (62.5%)	40 (62.5%)	1.000
Female	30 (37.5%)	6 (37.5%)	24 (37.5%)	
BMI, n (&)				
Obese	15 (18.8%)	6 (37.5%)	9 (14.1%)	0.077
Overweight	22 (27.5%)	5 (31.3%)	17 (26.6%)	
Normal	33 (41.3%)	5 (31.3%)	28 (43.8%)	
Underweight	10 (12.5%)	0 (0%)	10 (15.6%)	
Systole blood pressure, mean ± SD	121 ± 16.40	127 ± 16.77	119 ± 16.13	0.121
Diastole blood pressure, mean ± SD	79 ± 11.20	82 ± 11.78	78 ± 10.95	0.154
Smoker, n (%)				
Current	22 (27.5%)	3 (18.8%)	19 (29.7%)	0.017
Former	15 (18.8%)	7 (43.8%)	8 (12.5%)	
No	43 (53.8%)	6 (37.5%)	37 (57.8%)	
Alcohol consumption, n (%)				
Yes	6 (7.5%)	1 (6.3%)	5 (7.8%)	1.000
No	74 (92.5%)	15 (93.8%)	59 (92.2%)	
Hematology and lipid profile				
CMV amount, median (range)	466 (17-21284)	475 (145-1378)	465 (17-21284)	0.596
Hemoglobin, mean ± SD	13.90 ± 1.92	14.71 ± 1.24	13.69 ± 2.01	0.015
Hematokrit, mean ± SD	38.90 ± 1.92	40.28 ± 3.39	38.45 ± 5.98	0.112
Leukocyte, mean ± SD	6.50 ± 1.86	7.15 ± 2.09	6.34 ± 1.77	0.119
Platelet, mean ± SD	273 ± 62	288 ± 72	268 ± 59.49	0.254
Neutrophil, mean ± SD	55 ± 9.83	57.59 ± 7.90	53.98 ± 10.18	0.190
Lymphocyte, mean ± SD	34.89 ± 9.34	32.43 ± 6.57	35.51 ± 9.86	0.241
Monocyte, mean ± SD	7.29 ± 2.01	7.03 ± 2.31	7.35 ± 1.94	0.566
Total cholesterol, mean ± SD	196 ± 43.16	229 ± 49.52	188 ± 37.47	**0.001**
HDL, mean ± SD	50.95 ± 14.10	47.31 ± 16.20	51.86 ± 13.51	0.251
LDL, mean ± SD	119.36 ± 35.56	139.50 ± 43.43	114.33 ± 31.74	**0.010**
Trygliceride, median (range)	112 (46-1393)	157 (96-1393)	103 (46-448)	**0.002**
Fasting glucose, mean ± SD	86 ± 11.03	82 ± 9.66	87 ± 11.27	0.190
Insulin, median (range)	7.75 (1.7-63.9)	10.6 (5.4-24.4)	7.0 (1.7-63.9)	**0.001**
Homa IR	1.69 (0.3-17.99)	2.19 (1.04-5.78)	1.37 (0.3-17.99)	0.006
HIV diagnosis				
Years of diagnosis, n (%)				
Above 5 years	60 (75%)	13 (81.3%)	47 (73.4%)	0.749
Under 5 years	20 (25%)	3 (18.8%)	17 (26.6%)	
HIV stage, n (%)				
NA	8 (10%)	0 (0%)	8 (12.5%)	0.418
4	3 (3.8%)	1 (6.3%)	2 (3.1%)	
3	34 (42.5%)	6 (37.5%)	28 (43.8%)	
2	5 (6.3%)	2 (12.5%)	3 (4.7%)	
1	30 (37.5%)	7 (43.8%)	23 (35.9%)	
CD4 absolute when diagnosed, median (range)	113 (2-623)	71 (2-579)	135 (11-623)	0.061
CD4 recent, median (range)	589 (149-1482)	685 (268-1338)	576 (149-1482)	0.178
Years of starting ARV, n (%)				
Above five years	60 (75%)	12 (75%)	48 (75%)	1.000
Under 5 years	20 (25%)	4 (25%)	16 (25%)	
Years of NRTI, n (%)				
Above 5 years	15 (18.8%)	13 (81.3%)	52 (81.3%)	1.000
Under 5 years	60 (75%)	3 (18.8%)	12 (18.8%)	

** S0 < 248 db/m, S1= 248-268 db/m, S2= 268-280 db/m, S3 >280 db/m

CMV: Cytomegalovirus, HDL: high density lipoprotein, LDL: low density lipoprotein, HIV: human immunodeficiency virus, ARV: antiretroviral

The clinical parameters which significantly have positive moderate correlation with liver fibrosis were insulin and HOMA-IR ($r = 0.475$; $p < 0.001$ vs. $r = 0.487$; $p < 0.001$), whereas blood glucose fasting, and triglyceride level showed significant positive low correlation with liver fibrosis ($r = 0.247$; $p = 0.027$ vs. $r = 0.241$; $p = 0.031$). The HDL level has significant negative low correlation with liver fibrosis and steatosis ($r = -0.235$; $p = 0.036$ vs. $r = -0.288$; $p = 0.010$) (Table 4).

Table 4. Correlation of fibrosis and steatosis with clinical parameters

Independent Variable	CCoefficient Ccorrelation of Ffibrosis (r)	P-Value***	Coefficien Correlation of Steatosis (r)	P ***
Insulin	0.475	< 0.001	0.374	0.001
Glucose Fasting	0.247	0.027	-	-
Body Mass Index (BMI)	-	-	0.403	0.001
HOMA-IR	0.487	< 0.001	0.311	0.005
Trygliceride	0.241	0.031	0.308	0.005
(High density	-0.235	0.036	-0.288	0.010
lipoprotein)	-0.253	0.024	-	-
HDL				
Platelet				

*** Statistically significant $p < 0.005$

The clinical parameters which significantly have positive moderate correlation with liver steatosis was only body mass index (BMI) ($r = 0.403$; $p = 0.001$), whereas insulin, HOMA-IR, and triglyceride level showed only significant positive low correlation with liver steatosis ($r = 0.374$; $p = 0.001$ vs. $r = 0.311$; $p = 0.005$ vs. $r = 0.308$; $p = 0.005$). (Table 4)

Multivariate linear regression showed that the following factors, sex, HOMA-IR, and platelet count, could predict the liver fibrosis value (kPa), whereas BMI and triglyceride could predict the liver steatosis value (dB/m).

Table 5. Multivariate linear regression related to liver fibrosis

Independent variable	Regression coefficient	Standard error	t value	p
Sex	1.19	0.594	1.995	0.050
HOMA-IR	0.255	0.120	2.130	0.036
Platelet	-0.010	0.005	-2.270	0.026

Prediction Linier Regression Model $\rightarrow Y = \beta o + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3$

Y (Liver Fibrosis) = 7.14+ 1.19(Sex) + 0.26 (HOMA-IR) – 0.01 (Platelet)

Table 6. Multivariate linear regression related to liver steatosis

Independent variable	Regression coefficient	Standard error	t value	p
Body mass index (BMI)	4.718	1.389	3.397	0.001
Triglyceride	0.075	0.029	2.636	0.010

Prediction Linier Regression Model $\rightarrow Y = \beta o + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3$

Y (Liver Steatosis) = 89.28 + 4.72 (BMI) + 0.075 (Triglyceride)

DISCUSSION

This study highlighted the burden of liver fibrosis and steatosis as assessed by TE in patients with HIV mono-infection under condition viral suppressed with long-term ART. Extensive variability remains regarding the prevalence of liver fibrosis and steatosis in patients with HIV mono-infection. In a study of 62 patients with HIV mono-infection during liver biopsy where transaminase levels continued to rise, Morse et al reported the prevalence of steatosis and bridging fibrosis were as high as 70% and 18%, respectively.[14] Lombardi et al followed a limited sample size (n = 125) of patients with persistent HIV infection in European outpatient clinics. The prevalence of steatosis described using abdominal ultrasound and liver stiffness measurement (LSM) (≥ 7.4 kPa) was 55%, and the prevalence of fibrosis was 18%.[14]

Recently, a large Canadian cohort (n = 541) reported a similar prevalence of steatosis (36%) using CAP (≥ 248 dB/m) and higher fibrosis rates (19%) using LSM (≥ 7.2 kPa) in HIV mono-infection.[15] It is almost similar to our data reported the prevalence of fibrosis and steatosis 21% and 20 %, respectively. Among HIV-infected people, central obesity and the duration of HIV infection have been described by previous studies as critical features of liver fibrosis.[15–17]

In the present study, the duration of ART consumption showed a significant difference between significant and non-significant fibrosis but did not differentiate the degree of steatosis. In several studies, cART-induced hepatotoxicity and other risk factors, which might be causal for the development of liver fibrosis in HIV-infected patients, are controversially discussed.[18] While on the one hand, effective control of HIV was associated with slower liver fibrosis progression in HIV/HCV co-infected patients, primarily through the use of Protease Inhibitors (PIs), exposure to Didanosine (ddI), on the other hand, has been associated with liver injury.[18]

The higher prevalence of HIV-suppressed steatosis may be related to the weight gain after the initiation of ART and detectable non-ART compliance in HIV patients, enhancing the potential of antiretroviral drugs for the development of liver steatosis effect. Our study showed that the BMI has a moderate correlation with liver steatosis and, even together with triglyceride, could predict the liver steatosis value (dB/m) based on the multivariate linear regression.

In our study, the triglyceride, LDL, total cholesterol, and HDL levels differed significantly between significant and non-significant steatosis. Some mechanisms could

contribute to the event of dyslipidemia in HIV. Besides activation of the innate immune system and insulin resistance, which contributes to glucose metabolism dysregulation and dyslipidemia, other mechanisms may also explain this dyslipidemia pattern. Some studies suggest that in HIV-infected patients not undergoing cART, there is an increase in fatty acid production that can contribute to the appearance of dyslipidemia and insulin resistance. On the other side, it has been shown that cART not only suppresses HIV infection and reduces inflammation, but it also changes the dyslipidemia pattern, characterized by an increase in TGs and LDL-C, a reduction in HDL-C and maintenance of insulin resistance.[19,20]

So far, the molecular mechanism of the increased severity of CMV-related liver diseases and the viral protein group related to this process are still unclear. Most current studies are listed under the observation category. However, previous reports on the pathogenicity of CMV in other tissues introduced some CMV proteins as inducers of the fibrotic process. Transfection of renal epithelial cells with plasmids encoding human CMV IE1 or IE2 gene products shows their possible role in the process of fibrosis. The latter conclusion can be demonstrated by the potency of the IE1 and IE2 gene products in inducing TGF-β1 activation (a well-known potent fibrotic molecule) and the subsequent potency of the fibrotic phenotype obtained by transfected cells. More importantly, several CMV proteins regulate the mechanism of cell apoptosis. More importantly, several CMV proteins regulate the mechanism of apoptosis.[21,22]

CONCLUSION

Non-AIDS diseases are becoming an increasingly important source of morbidity and mortality among HIV-infected people. HIV itself can cause liver damage and consequent liver fibrosis in several ways. Lipid metabolism patients with HIV infection may also experience essential changes in body fat composition after exposure to antiretroviral therapy. Cytomegalovirus (CMV) is a human herpes virus common in people with human immunodeficiency virus (HIV). In patients with immunocompetence, long periodic asymptomatic CMV might affect the development of an abnormal liver function.

The HDL level has a significant negative low correlation with liver fibrosis and steatosis in patients with HIV mono-infection. Sex, HOMA-IR, and platelet count were the only factors predicting the liver steatosis value (dB/m). The prevalence of HIV-suppressed steatosis may be related to the weight gain after the initiation of ART and detectable non-ART compliance in HIV patients.

Some mechanisms could contribute to the event of dyslipidemia in HIV. It has been shown that cART not only suppresses HIV infection and reduces inflammation but it also changes the dyslipidemia pattern.

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