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Liver fibrosis is not uncommon in HIV-infected Asian patients without viral or alcoholic hepatitis: the role of diabetes and obesity

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INTRODUCTION

- Liver fibrosis in HIV-infected individuals is mostly attributable to hepatitis B (HBV) or C (HCV) co-infection.
- Liver fibrosis results from accumulation of extracellular matrix protein in the liver, usually as result of chronic liver injury. Ultimately, it may lead to cirrhosis, portal hypertension, liver failure and hepato-cellular carcinoma.
- HIV infected individuals who received long-term combination antiretroviral therapy (cART) may be at high risk of insulin resistance and metabolic syndrome, especially those who have been exposed to stavudine.
- Fatty liver disease is now commonly reported in many high income countries, in the presence and absence of HIV infection. Both insulin resistance and fatty liver disease have been described in HIV infected individuals without HBV or HCV co-infection[1,2]
- An association between significant liver fibrosis and diabetes mellitus (DM) in HIV-uninfected indi-viduals has been reported, but this phenomenon in HIV mono-infected patients has not been well described, and few studies have described liver fibrosis in HIV mono-infected patients from Asia.

OBJECTIVE

- We determined the prevalence and predictors of liver fibrosis measured by transient elastography (TE, Fibroscan®), among participants from our long-term HIV cohort in Bangkok.

METHODOLOGY

- Liver stiffness measurement (LSM) was assessed by TE in 586 (57.5% male) HIV-infected patients without HBV/HCV co-infection, and with no evidence of acute hepatotoxicity.
- LSM values ≥7.2kPa were defined as abnormal.
- Multivariate logistic regression was performed to identify factors associated with abnormal LSM. Predictor covariates included age, sex, metabolic syndrome, cART regimen, duration of cART, alco-hol intake, and smoking. Covariates with a P value of ≤0.1 were adjusted for in a multivariate model.

RESULTS

- Demographic data of all participants is presented in table 1
- The median age was 43 years and 21% were aged >50 years. Median duration on cART was 11 (IQR 6-15) years and only 6% of patients reported alcoholic consumption.
- The percentage of patients with different degrees of liver stiffness is shown in Figure 1.
- Abnormal LSM was observed in 64 (10.9%) patients; 108 (18.4%) patients were diagnosed with DM.
- The proportion of patients with abnormal LSM by DM diagnosis, a BMI indicating obestity, nadir CD4 ≤50 and abnormal ALT (>1.25 ULN) are shown in figure 2.
- 22.2 % (24/108) of DM patients had abnormal LSM versus only 8.4% (40/478) of non-DM patients. In addition, 24.3% and 7.8% of the patients with BMI>25kg/m^2 and BMI≤25kg/m^2 had abnormal LSM, respectively.
- In multivariate analysis (Table 2) BMI>25kg/m^2 (odds ratio[OR] 3.74, 95% confidence interval[CI] 1.62-8.64, P=0.002), diabetes (OR 2.50, 95%CI 1.28-4.86, P=0.007), nadir CD4+T-cell count ≤50 (OR 2.55, 95%CI 1.23-5.28, P=0.012), and ALT≥1.25 ULN (OR 4.07, 95%CI 2.13-7.78, P<0.001) were independently associated with abnormal LSM.

Table 1: Demographic and clinical features of the study participants

Characteristics	Total	TE <7.2kPa	TE >7.2kPa	P-value
Median age, years (IQR)	43 (37-49)	42(37-49)	46(41-53)	**0.015**
Male gender, n(%)	337(58)	291(56)	46(72)	**0.015**
Risk factor for HIV transmission				0.09
Heterosexual, n (%)	356(61)	325(62)	31(48)	
Homosexual, n (%)	184(31)	161(31)	23(36)	
Previous intravenous drug use, n(%)	9(1.5)	7(1)	2(3)	
Other, n (%)	37(6)	29(6)	8(12.6)	
Median BMI, kg/m^2 (IQR)	22(20-24)	22(20-24)	24(21-27)	**<0.001**
Median duration of cART, years (IQR)	11(6-15)	11(5-15)	13(7-16)	0.18
CDC stage C, n(%)	79(13)	70(13)	9(14)	0.89
Median nadir CD4+ count, cells/mm^3 (IQR)	198(116-272)	200(123-275)	170(52-238)	**0.007**
Median CD4+ T-cell count, cells/mm^3 (IQR)	573(447-730)	578(449-733)	553(431-678)	0.25
HIV RNA <50 copies/ml, n(%)	558(95)	498(95)	60(94)	0.56
Current cART regimen				0.29
2 NRTIs and NNRTI	293(50)	265(51)	28(44)	
2NRTIs + boosted PI	260(44)	226(43)	34(53)	
NNRTI + boosted PI	28(5)	27(5)	1(2)	
Other	5(1)	4(1)	1(2)	
Stavudine exposure, n(%)	298(51)	263(50)	35(55)	0.52
Median duration of exposure, years (IQR)	3.0(1.2-5.1)	3.0(1.2-5.1)	2.8(1.4-5.1)	0.872
Didanosine exposure, n(%)	237(40)	206(39)	31(48)	0.17
Median duration of exposure, years (IQR)	2.1(0.9-4.1)	2.1(0.9-4.2)	1.9(0.7-3.3)	0.74
Indinavir exposure, n(%)	107(18)	89(17)	18(28)	**0.033**
Median duration of exposure, years (IQR)	5.1(2.5-7.2)	4.9(2.7-7.1)	5.9(2.4-7.2)	0.79
Median triglycerides, mg/dl (IQR)	138(94-210)	135(93-206)	175(111-274)	**0.003**
Median waist circumference (IQR)	80(74-86)	79(74-85)	85(75-93)	**<0.001**
Metabolic syndrome, n (%)	219(38)	182(36)	37(59)	**<0.001**
Median ALT (IQR)	27 (20-40)	27(19-37)	45(24-74)	**<0.001**
Median liver stiffness, kPa (IQR)	4.8 (4.0-6.1)	4.6(4-5.6)	9(7.6-10.7)	
FIB-4 score >1.45, n(%)	56 (10)	42(8)	14(23)	**<0.001**
APRI score >0.5, n (%)	47 (8)	28(6)	19(32)	**<0.001**

BMI: body mass index; cART: combination antiretroviral therapy; NRTI: nucleoside (t) reverse transcriptase; NNRTI: Non nucleoside reverse transcriptase; boosted PI: boosted protease inhibitor

Figure 1: Percentage of HIV patients with different degrees of liver stiffness assessed by TE

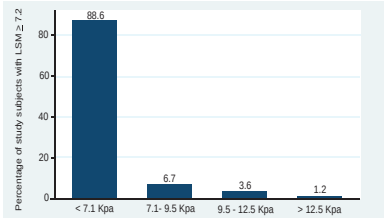
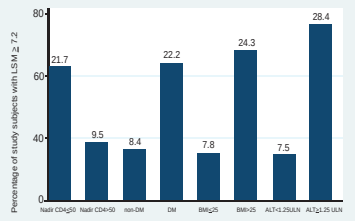


Table 2: Factors associated with an abnormal LSM > 7.2kPa

Characteristic	Abnormal LSM		Univariate		Multivariate	
	No (n=522)	Yes (n=64)	Unadjusted (95%CI)	P-value	Adjusted (95%CI)	P-value
Gender						
Male	291(86.4)	46(13.7)	2.03(1.15-3.59)		1.6(0.68-3.76)	
Female	231(92.8)	18(7.2)	Ref	**0.015**	Ref	0.28
Age						
Age ≥40	325(86.4)	51(13.6)	2.38(1.26-4.48)		1.56(0.75-3.26)	
Age<40	197(93.8)	13(6.2)	Ref	0.007	Ref	0.24
Body mass index (kg/m^2)						
≤25	438(92.2)	37(7.8)	Ref		Ref	
>25	84(75.7)	27(24.3)	3.81(2.20-6.58)	**<0.001**	3.74(1.62-8.64)	0.002
Waist circumference						
Normal	404(91.40)	38(8.60)	Ref	**0.002**	Ref	
Abnormal	118(81.94)	26(18.06)	2.34(1.37-4.02)		2.27(0.25-20.8)	0.47
Duration of cART						
<10 years	239(90.9)	24(9.1)	Ref			
≥10 years	283(87.6)	40(12.4)	1.41(0.82-2.40)	0.21		
Currently drinks alcohol, N (%)						
No	488(89.4)	58(10.6)	Ref			
Yes	27(81.8)	6(18.2)	1.87(0.74-4.72)	0.19		
Current smoker						
No	435(89.7)	50(10.3)	Ref			
Yes	84(86.6)	13(13.4)	1.35(0.70-2.59)	0.37		
Diabetes mellitus						
No	438(91.6)	40(8.4)	Ref		Ref	
Yes	84(77.8)	24(22.2)	3.13(1.79-5.46)	**<0.001**	2.5(1.28-4.86)	**0.007**
Hypertension						
No	488(89.2)	59 (10.8)	Ref			
Yes	34(87.2)	5(12.8)	1.22(0.46-3.23)	0.69		
Lipodytrophy						
No	305(90.8)	31(9.2)	Ref			
Yes	217(86.8)	33(13.2)	1.50(0.89-2.52)	0.13		
Triglyceride, mg/dl						
Normal (<150)	287(92.28)	24(7.72)	Ref		Ref	
Abnormal (≥150)	224(85.17)	39(14.83)	2.08(1.22-3.56)	**0.008**	1.09(0.46-2.56)	0.85
Didanosine exposure						
No	316(90.5)	33(9.5)	Ref			
Yes	206(86.9)	31(13.1)	1.44(0.86-2.43)	0.17		
Indinavir exposure						
No	433(90.4)	46(9.6)	Ref		Ref	
Yes	89(83.2)	18(16.8)	1.90(1.05-3.44)	**0.033**	1.59(0.79-3.23)	0.20
Nadir CD4+ T-cell count, cells/mm^3						
≤50	54(78.3)	15(21.7)	2.65(1.39-5.05)		2.55(1.23-5.28)	
>50	468(90.5)	49(9.5)	Ref	**0.003**	Ref	**0.012**
ALT						
Normal	454(92.5)	37(7.5)	Ref		Ref	
Abnormal	68(71.6)	27(28.4)	4.87(2.79-8.51)	**<0.001**	4.07(2.13-7.78)	**<0.001**

Abnormal Waist Circumference: >90 cm in male and >80 cm in female; ALT Normal: <1.25 ULN; ALT Abnormal: ≥ 1.25 ULN

Figure 2: Proportion of patients with abnormal LSM by DM BMI nadir CD4≤50 and abnormal ALT (>1.25 ULN)



DISCUSSION

- Although the median BMI (22 kg/m^2) of our patients was lower than in other reports (24-25 kg/m^2)[3-5], high BMI was strongly associated with abnormal LSM.
- Metabolic abnormalities may accelerate liver fibrosis and insulin resistance may play a key role in the development of liver fibrosis in HIV-infected patients[5].
- A combination of obesity and insulin resistance which gradually increases in severity, may contribute to the development of both liver damage and diabetes.
- Kotronen et al. found that type 2 diabetic patients have approximately 80% more liver fat compared to non-diabetics matched for age, weight and sex[2].
- Therefore, non alcoholic fatty liver disease (NAFLD) may have a direct causal relationship with the presence of diabetes, probably by promoting insulin resistance[6].
- NAFLD may be an emerging cause of diabetes among Asian HIV mono-infected patients
- Since liver fibrosis can progress to cirrhosis, hepatocellular carcinoma and cardiovascular disease, HIV-infected patients with evidence of insulin resistance or metabolic syndrome should be screened for NAFLD. Early diagnosis will enable interventions for modifiable risk factors, including diet, exer-cise and weight loss.

CONCLUSIONS

- The prevalence of abnormal LSM among our HIV-infected patients without hepatotropic virus infec-tion, in a setting of relatively minimal alcohol consumption and long duration of cART is substantial. Diabetes, being overweight, low nadir CD4 count and abnormal ALT were significantly associated with liver damage in this cohort.

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