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INSULIN RESISTANCE AND LIVER STIFFNESS IN HIV/HCV COINFECTED PATIENTS: A NEW GUEST IN LIVER DISEASE PROGRESSION?

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ABSTRACT

BACKGROUND: The factors that influence liver fibrosis progression in HIV/HCV-coinfected patients are not completely understood. In this sense, it is not known if insulin resistance (IR), a condition that promotes liver fibrosis in HCV-monoinfected individuals, is one of these factors.

METHODS: The objective of this study was to evaluate the association between IR and liver stiffness (LS) in a multicenter prospective cohort of HIV/HCV-coinfected patients. LS was assessed by transient elastography, a technique has shown a high accuracy to predict significant fibrosis in HIV/HCV-coinfected patients. The outcome variable of the study was a LS ≥ 9 kPa. IR was calculated using the homeostasis model assessment (HOMA) method.

RESULTS: Three hundred and thirty-four patients were included in the study. One hundred and forty-seven (44%) patients showed a LS ≥ 9 kPa. HOMA levels were correlated with LS (Spearman's rho correlation coefficient: 0.36; p<0.0001). The median (Q1-Q3) value of HOMA in patients with LS ≥ 9 kPa was 3.31 (2.11-5.19) while it was 2.13 (1.39-3.23) in patients with a LS < 9 kPa (p<0.0001). Ninety-three (37.7%) individuals with a HOMA < 4 and 54 (62.1%) with a HOMA > 4 showed a LS ≥ 9 kPa (p<0.0001). As cirrhosis may cause hyperinsulinemia due to reduced hepatic insulin extraction, we performed analyses after excluding patients with cirrhosis that yielded similar results. After multivariate analyses, a CD4 cell count below 200 cells/mL [Adjusted Odds Ratio (AOR) 3.45; 95% Confidence Interval (CI) 1.7-7.01; p=0.001], hepatitis B virus coinfection [AOR 6.13; 95% CI 1.90-19.69; p=0.002], age ≥ 40 years [AOR 2.52; 95% CI 1.43-4.45] and a HOMA ≥ 4 [AOR 2.43; 95% CI 1.40-4.24; p=0.002] were the independent predictors of a LS ≥ 9 kPa.

CONCLUSION: IR is associated with LS in HIV/HCV-coinfected patients.

BACKGROUND

- Insulin resistance (IR) is a frequent condition in chronic hepatitis C (CHC). Several studies have shown that IR is associated with liver fibrosis in hepatitis C virus (HCV)-monoinfected patients.
- However, it is not known wether IR, which is frequently seen in patients receiving antiretroviral therapy (ART), influences liver fibrosis progression in HIV/HCV-coinfected patients.
- Transient elastography (TE), a non-invasive technique that assesses liver fibrosis by measuring liver stiffness (LS), has shown a high accuracy to predict significant fibrosis in HIV/HCV-coinfected patients.
- TE has some advantages when compared to liver biopsy. First, TE measures LS in a more representative volume of hepatic parenchyma than usual biopsy samples. Second, the values of LS obtained by TE are expressed in a continuous scale. This avoids the problems of classifying liver fibrosis in a ordinal scale and allows to detect subtle changes in liver damage. Finally, TE is non invasive, rapid and painless, and therefore well accepted by the patient. Thus, it may be performed in a larger number of patients than liver biopsy. For these reasons, TE is a very appropiate tool to explore potential factors involved in liver fibrosis evolution.

OBJECTIVE

- To evaluate the association between IR and LS in a cohort of HIV/HCV-coinfected patients.

PATIENTS AND METHODS

Study design

- Multicenter cross-sectional study.

Patients

- All consecutive HIV-infected patients with CHC who underwent a TE evaluation in seven tertiary care hospitals in Spain between December 2005 and September 2008 were included.
- HCV infection was diagnosed by the presence of serum antibodies against HCV and detectable serum HCV RNA in all patients.
- Patients with a previous diagnosis of diabetes were excluded

TE evaluations

- LS was determined using TE according to the standard technique. We obtained at least ten valid measures of LS in each patient before ending the examination.
- To guarantee the validity of TE results, we considered for the analysis only the examinations with an interquartile range (IQR) below 30% of the median value and a success rate of acquisitions above 60%.

IR assessment

- IR was determined by the homeostasis model assessment method (HOMA) by using the following equation: fasting insulin (mU/mL) x fasting glucose (mmol/L) / 22.5.
- IR was defined as a HOMA ≥ 4.

Statistical analysis

- The outcome variable of the study was LS.
- A possible correlation between LS and HOMA was evaluated using the Spearman rank correlation method.
- Univariate analyses were performed to identify factors associated with the presence of a LS ≥ 9 kiloPascals (kPa), including IR.
- Those variables associated with the presence of a LS ≥ 9 kPa with a p < 0.2 in the univariate analysis were entered in multiple logistic regression models. Associations with p values < 0.05 were considered significant. The adjusted odds ratio (AOR) and the respective 95% confidence intervals (CI) were also calculated.

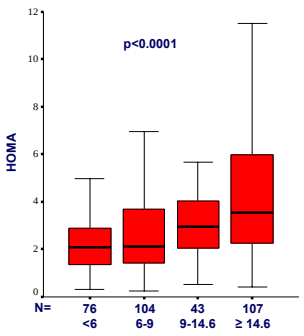
RESULTS

Characteristics of the study population

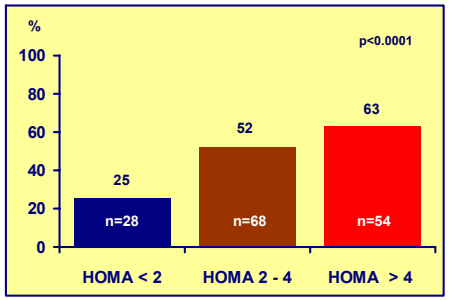
Characteristics	Patients n=330
Age (years)[1]	42 (39-46)
Male gender, no (%)	265 (80)
Daily alcohol intake ≥ 50 grs/day, no (%)[2]	43 (13)
Body-mass index (Kg/m²)[3]	22.7 (21.1-24.8)
Previous intravenous drug users, no (%)	282 (85)
HCV genotype, no (%)[4]	
1	178 (61)
2	3 (1)
3	61 (21)
4	51 (17)
HCV RNA load (log_{10} IU/mL)[1]	6.05 (5.47-6.61)
Hepatitis B virus infection, no (%)[5]	17(5)
Serum alanine-aminotransferase (IU/L)[1]	58 (37-92)
HIV RNA load < 50 copies/mL, no (%)	262 (80)
CD4 cells/mL[1]	406 (289-603)
Current ART[7] regimen, no (%)	
No ART	33 (10)
Protease inhibitors-based ART[7]	151 (46)
NNRTI[8]-based ART[7]	106 (32)
Other	40 (12)
HOMA[1]	2.53 (1.66-4.12)
Liver stiffness (kPa)[1]	8.13 (6.1-17.7)

[1]Median (Q1-Q3). Available in [2]277, [3]266, [4]293 and [5]314 patients. [7]ART: Antiretroviral therapy. [8]NNRTI: Non-nucleoside retrotranscriptase inverse analogues.

Median (Q1-Q3) values of HOMA in the population according to different cut-off points of LS



Proportion of patients with a LS ≥ 9 kPa according to HOMA



Factors associated with a LS ≥ 9 kPa

Variable	N	LS > 9 kPa [n (%)]	*P* univariate	Adjusted Odds Ratio (95% CI)	*P* multivariate
Sex					
Male	265	128 (48)	0.03		0.17
Female	65	22 (34)			
Age (years)					
< 40	97	33 (34)			
≥ 40	233	117 (50)	0.01	1.85 (1.03-3.29)	0.03
Body mass index					
< 25	201	88 (44)			-
≥ 25	60	30 (50)	0.39		
Daily alcohol intake					
< 100 grs/day	261	125 (48)			-
≥ 100 grs/day	16	10 (62)	0.25		
Hepatitis B surface antigen					
Negative	297	130 (44)			
Positive	17	14 (82)	0.002	9.25 (2.42-35.31)	0.001
HCV RNA load (IU/mL)					
< 600.000	121	54 (45)			-
≥ 600.000	209	96 (46)	0.8		
HCV genotype					
1 or 4	229	106 (46)			-
2 or 3	64	31 (48)	0.76		
CD4 cell count/mL					
< 200	49	33 (67)	0.001	3.45 (1.67-7.11)	0.001
≥ 200	281	117 (41)			
HIV RNA load (copies/mL)					
< 50	262	124 (47)	0.18		0.27
≥ 50	68	26 (38)			
Previous ART[1] strategy					
No ART	33	10 (30)			
Only PI[2]-based ART	70	31 (44)			
Only NNRTI[3]-based ART	44	9 (43)	0.36		-
PI to NNRTI-based ART	44	21 (48)			
NNRTI to PI-based ART	25	9 (36)			
Other	114	60 (52)			
Current ART strategy					
No ART	33	10 (30)			
PI-based ART	151	73 (48)	0.2		0.86[5]
NNRTI-based ART	106	51 (48)			
Other	40	16 (38)			
HOMA[4]					
< 2	114	28 (25)			
2 - 4	130	68 (52)	< 0.0001	3.46 (1.90-6.29)	<0.0001
≥ 4	86	54 (63)		5.33 (2.70-10.49)	<0.0001

[1]ART: Antiretroviral therapy; [2]PI: Protease inhibitor; [3]NNRTI: Non-nucleoside retrotranscriptase inverse analogue; [4]HOMA: homeostasis model assessment; [5]For multivariate analysis current ART strategy was categorized as No ART vs Yes.

CONCLUSIONS

- IR is an independent predictor of LS in HIV/HCV-coinfected patients.
- Further research should evaluate if therapies that modify IR may have an impact on liver damage in these individuals.

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