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ORIGINAL ARTICLE

Observational Study

Matrix metalloproteases and their tissue inhibitors in non-alcoholic liver fibrosis of human immunodeficiency virus-infected patients

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Abstract

AIM

To investigate the relationships among diverse metalloproteases (MMPs) and their tissue inhibitors (TIMPs) and non-alcoholic liver fibrosis in human immunodeficiency virus (HIV)-infected patients.

METHODS

Single nucleotide polymorphisms (SNPs) in *MMPs*, *TNF-α* and *CCR5* genes, and serum levels of MMPs and TIMPs were determined in HIV-infected individuals with/out hepatitis C virus (HCV) coinfection. A total of 158 patients were included, 57 of whom were HCV-coinfected. All patients drank < 50 g ethanol/day. Diverse SNPs (*MMP-1 -1607 1G/2G*, *MMP-8 -799C/T*, *MMP-9 -1562 C/T*, *MMP-13 -77A/G*, *TNF-α -308 G/A*,

CCR5-Δ32), and serum levels of MMPs (2, 3, 8, 9 and 10) and TIMPs (1, 2 and 4) were assessed. Liver fibrosis was determined by transient elastometry, although other non-invasive markers of fibrosis were also considered. Significant liver fibrosis (F ⩾ 2) was defined by a transient elastometry value ⩾ 7.1 kPa.

RESULTS

A total of 34 patients (21.5%) had liver fibrosis ⩾ F2. MMP-2 and TIMP-2 serum levels were higher in patients with liver fibrosis ⩾ F2 (P = 0.02 and P = 0.03, respectively) and correlated positively with transient elastometry values (P = 0.02 and P = 0.0009, respectively), whereas MMP-9 values were negatively correlated with transient elastometry measurements (P = 0.01). Multivariate analyses showed that high levels of MMP-2 (OR = 2.397; 95%CI: 1.191-4.827, P = 0.014) were independently associated with liver fibrosis ⩾ F2 in the patients as a whole. MMP-2 (OR = 7.179; 95%CI: 1.210-42.581, P = 0.03) and male gender (OR = 10.040; 95%CI: 1.621-62.11, P = 0.013) were also independent predictors of fibrosis ⩾ F2 in the HCV-infected subgroup. Likewise, MMP-2, TIMP-2 and MMP-9 were independently associated with transient elastometry values and other non-invasive markers of liver fibrosis. None of the six SNPs evaluated had any significant association with liver fibrosis ⩾ F2.

CONCLUSION

Certain MMPs and TIMPs, particularly MMP-2, seems to be associated with non-alcoholic liver fibrosis in HIV-infected patients with/without HCV coinfection.

Key words: Human immunodeficiency virus; Hepatitis C virus; Liver fibrosis; Transient elastometry; Non-invasive fibrosis markers; Metalloproteases; Their tissue inhibitors; Genetic polymorphisms

Core tip: The role of matrix metalloproteases (MMPs) and their tissue inhibitors (TIMPs) in the development of liver fibrosis is uncertain. We determined some single nucleotide polymorphisms (SNPs), as well as the serum levels of diverse MMPs and TIMPs, in non-alcoholic, human immunodeficiency virus-infected patients with/out hepatitis C virus coinfection, to evaluate their possible relationship with liver fibrosis as assessed by transient elastometry. MMP-2 was independently associated with significant fibrosis. Likewise, MMP-2, TIMP-2 and MMP-9 were independent predictors of transient elastometry values and of other non-invasive tests of fibrosis. No SNP was significantly associated with liver fibrosis. Our findings support the value of these markers in the evaluation of fibrosis.

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INTRODUCTION

Liver fibrosis is characterized by a pathological accumulation of extracellular matrix (ECM), reflecting an imbalance between enhanced matrix synthesis and reduced breakdown of connective tissue proteins. ECM degradation is mediated by matrix metalloproteases (MMPs), a large family of zinc-dependent endopeptidases. Different levels of MMP regulation ensure the constant remodeling of the ECM, including regulation at the gene expression level, cleavage of the pro-enzyme to an active form, and specific inhibition of activated forms by tissue inhibitors (TIMPs)[1,2]. The relevance of MMPs for liver ECM remodeling is shown by the fact that pro-MMP-2 and pro-MMP-9 are activated during rat liver regeneration following hepatectomy and both MMPs contribute to priming hepatocyte proliferation[3]. Different genetic polymorphisms (SNPs) of MMPs and TIMPs have been described. Some of them such as the *MMP-1 -1607 1G/2G , MMP-3 -1612 5A/6A, MMP-9-1562 C/T* and *MMP-13 -77 A/G* are located in the MMPs genes promoter region and induce changes in MMPs genes mRNA and protein expression. These functional *MMPs* SNPs are associated mostly with cardiovascular diseases, but also with cancer and osteomyelitis susceptibility[4,5]. *MMP-1*, *MMP-3* and *MMP-9* SNPs have been associated with progression of liver disease in hepatitis C virus (HCV)-mono-infected Japanese patients[6]. Carriage of the *MMP-3 -1612 5A/6* SNP *6A* allele has been associated with increased albumin-globulin ratios in HCV-infected Mexican patients with advanced LF[7]. A *MMP14* SNP has also been associated with hepatocellular carcinoma[8].

Different studies have shown a correlation between TIMP-1, MMP-2 and MMP-9 serum levels and increased LF in HCV-monoinfected and human immunodeficiency virus (HIV)-HCV-coinfected individuals[9-13]. The Fibrocheck, a combination of direct and indirect markers for LF stages in chronic hepatitis C, is constructed combining collagen Ⅲ and its degrading enzyme MMP-1[14].

The aim of this study was to investigate the relationships among diverse *MMPs* SNPs, MMPs and TIMPs serum levels and non-alcoholic LF, evaluated by means of different non-invasive markers, in HIV-infected patients with and without HCV coinfection.

MATERIALS AND METHODS

Study patients and data collection

A total of 158 patients from the Infectious Diseases Outpatient Clinic of the Hospital Universitario Central de Asturias, a third-level 1500-bed University Hospital at Oviedo, Northwestern Spain, were included in the study. Patients older than 18 years with active HIV or HIV-HCV

coinfection, demonstrated by positive serology and viral RNA plasma detection, were enrolled. Demographic, analytical and clinical data, including ethanol and drug consumption, were obtained from patients and their medical charts at enrollment. In addition, we did transient elastometry (TE) to determine the degree of LF. Patients with alcohol abuse, defined as an ethanol intake of ⩾ 50 g/d for > 5 years, were excluded. Many patients were not aware of how long they were HCV infected. In such cases, it was assumed that the patients acquired HCV-infection one year after starting intravenous drugs, as previously reported[15]. All patients were receiving antiretroviral therapy (ART) at the time of inclusion. All patients underwent standard care, including routine non-invasive procedures. Patients were members of a homogeneous Caucasian population, and were residents in the same region (Asturias, Northern Spain) that has a small foreign immigrant population (less than 5%).

Exclusion criteria

Pregnant women and those individuals in whom there were technical difficulties for obtaining reliable TE readings were excluded from the study. In addition, patients with an acute episode of cytolysis or cholestasis, ascitis or spontaneous bacterial peritonitis were excluded because TE reading could be altered by these factors[15]. We also excluded patients who currently or previously were treated with anti-HCV therapy and those who had resolved their HCV infections spontaneously (defined as positive serology but with undetectable HCV RNA). Patients with ART adherence < 75% were also excluded. To avoid other confounding factors, patients with HBV coinfection with/out delta virus coinfection, ethanol consumption ⩾ 50 g/d for > 5 years, alcoholic hepatopathy, other liver diseases, or treatment with immunosuppressant drugs, were excluded from the study as well.

Laboratory methods

HIV and HCV serologies were determined by enzyme immunoassay (MEIA AxSYM; Abbott Diagnostics, Abbott Park, IL, United States). HIV and HCV RNA by quantitative PCR (Cobas TaqMan; Roche Diagnostics, Branchburg, NJ, United States) and HCV genotypes by a line probe assay (Versant HCV, Siemens). Routine laboratory methods were used to calculate LF indexes: AST and platelets for APRI index[16], age, platelet counts, total cholesterol and GGT for calculating the Forns index[17], and age, AST, ALT and platelet counts for FIB-4[18]. In addition, the Yearly Fibrosis Progression Index (YFPI) was also calculated in HCV-infected patients as follows: YFPI = TE value/years of estimated HCV infection.

Transient elastometry

LF was assessed by TE using Fibroscan (EchoSens, Paris, France) following pre-established methods[15,19]. Patients were divided into four groups according to TE measurements, reflecting the progressive stage of LF and analogous to the F0-1, F2, F3 and F4 histological stages of the Metavir scoring system. The TE cut-offs used for this purpose were those described by Castéra *et al*[20]: F0-1: < 7.1 kPa, F = 2: 7.1-9.4 kPa, F = 3: 9.5-12.4 kPa and F = 4 ⩾ 12.5 kPa.

MMPs and TIMPs serum levels assessment

Ten millilitres of whole blood were drawn in siliconized glass tubes, and centrifuged at 1800 × g for 5 min. The obtained serum was aliquoted in Eppendorf tubes and stored at -70 ℃ until further use. MMPs (-2, -3, -8, -9, -10) and TIMPs (-1,-2,-4) were measured by the Quantibody™ Human MMP Array 1 (RayBiotech, Parkway Lane, Norcross, GA, United States), according to the manufacturer's instructions and as previously published by our group[21].

MMPs SNPs genotyping

DNA was obtained from peripheral white blood cells and stored at -20 ℃ before use. The following SNPs of MMPs were genotyped by PCR: *MMP-1 (-1607 1G/2G,* rs 11292517), *MMP-8 (-799 C/T*, rs 11225395), *MMP-9 (-1562 C/T,* rs 34016235), and *MMP-13 (-77 A/G,* rs 2252070). In addition the *TNF-α* (*-308 G/A*, rs 1800629) and the *CCR5 Δ32* (rs 333) SNPs were also genotyped. Oligonucleotide primer sequences, PCR conditions and restriction enzymes used for genotyping and sequencing of the different SNPs studied have been described elsewhere[5,21-23].

Statistical analysis

As MMPs and TIMPs serum levels presented a markedly non-Gaussian distribution, original values were logarithmically transformed for analysis. The reported values are the result of back-transformation into the original units (ng/mL). Continuous variables are presented as mean (95%CI). Proportions were compared with the χ^2 test, whereas *t* test and one-way analysis of variance were used for the comparison of continuous variables in two or more than two groups, respectively. Correlations between MMPs, TIMPs and LF indexes were assessed with the Pearson's correlation coefficient. Stepwise logistic regression analyses were carried out to find the factors independently associated with significant LF, and stepwise multiple regressions were performed to detect the parameters independently predictive of the different LF indexes. SPSS v.22 software was used for statistical calculations. A *P* value < 0.05 for a two-tailed test was considered statistically significant.

RESULTS

The study population was composed of 158 HIV-infected patients, 57 (36.1%) of whom were coinfected with HCV. The mean age was 44.6 years, 65.8% were

male, the mean CD4 counts were 581.5 cells/μL and 85.4% of them had undetectable HIV viral load. Thirty-four patients (21.5%) had significant LF (⩾ F2).

Table 1 shows the demographic, clinical and laboratory data of the patients with and without LF ⩾ F2, as well as the comparison between the two groups. As expected, HCV infection and IDU were associated with LF, but the estimated duration of HCV infection was not. Regarding the HIV-related parameters, both nadir and current CD4 counts were lower, and the duration of HIV infection and time on ART higher in patients with LF ⩾ F2 than in patients without LF. There were no statistically significant differences in HIV or HCV viral loads between the two groups, although there was a trend towards higher HCV viral load and lower rates of undetectable HIV viral load in the patients with LF. The different HCV genotypes were similarly represented in the two groups and there were no significant associations between TE values and HCV genotypes (P = 0.5).

Not surprisingly, the laboratory parameters used for the calculations of the LF indexes, such as platelet count, cholesterol, AST, and GGT, differed significantly between the LF groups. Regarding MMPs and TIMPs, MMP-2 and TIMP-2 serum levels were significantly higher in LF than in patients without LF.

Table 2 shows the genotypic frequencies of the SNPs evaluated according to LF and HCV status. No genotype or SNPs was significantly associated with any of the two conditions.

The relationships of the SNPs and the LF markers are detailed in Table 3. No statistically significant association was found between the different SNPs and the LF indexes, including TE, although patients carrying the heterozygous *CT* genotype of the *MMP-9 -1562 C/T* SNP had consistently higher values of all LF indexes than those with the homozygous *CC* genotype. Table 4 shows the comparisons of the MMPs and TIMPs serum levels according to the different SNPs. Statistically significant differences were observed only between *MMP-8 -799C/T* SNP and TIMP-2 (P = 0.01), *MMP-9-77A/G* SNP and MMP-2 (P = 0.02) and *TNF-α-308 G/A* SNP and TIMP-4 levels (P = 0.02).

Table 5 summarizes the correlations between the different MMPs, TIMPs and LF indexes. There was a good positive correlation among the different LF indexes (P < 0.0001 for all comparisons). Likewise, the diverse fibrosis indexes correlated positively with MMP-2 (P = 0.02 to P = 0.06) and TIMP-2 (P = 0.08 to P < 0.0001) and negatively with MMP-9 (P = 0.2 to P = 0.01). Also, the different MMPs and TIMPs correlated among them. There were strong correlations between MMP-8 levels and levels of MMP-9 and TIMP-1, and between MMP-9 and TIMP-1 levels (P < 0.0001 for each comparison), which explained about a half of the variability of their values.

Multivariate analyses

The variables with a P ⩽ 0.2 significance level in the univariate analyses were entered into the different multivariate models for LF evaluation, excluding the parameters directly indicative of LF and the laboratory tests used for their calculations.

Stepwise logistic regression analyses revealed that high serum levels of MMP-2 (OR = 7.179; 95%CI: 1.210-42.581, P = 0.03) and male gender (OR = 10.040; 95%CI: 1.621-62.11, P = 0.013) were independent predictors of fibrosis ⩾ F2 in the HCV-infected subgroup. In the patients as a whole, only MMP-2 (OR = 2.397, 95%CI: 1.191-4.827, P = 0.014) was independently associated with LF ⩾ F2, whereas gender was close to the significance level (P = 0.08).

Multiple regression analyses were also carried out to evaluate the factors independently associated with each of the five LF indexes (TE, APRI, Forns, FIB-4, and YFPI). Among the different variables considered, only five factors (MMP-2, TIMP-2, MMP-9, CD4 counts and age) explained the diverse markers evaluated. MMP-2 was the parameter most consistently predictive of these indexes. Table 6 shows the P values corresponding to these associations, as well as the adjusted percentage of variability of each LF index accounted for by the model.

The SNPs we evaluated did not have any significant association in the multivariate analyses with either LF ⩾ F2 or any of the different LF indexes analyzed.

DISCUSSION

We found that serum MMP-2 was an independent predictor of non-alcoholic LF ⩾ F2 in HIV-infected patients, as evaluated by TE. In addition, higher serum levels of MMP-2 and TIMP-2, as well as lower levels of MMP-9, were also predictive of higher scores of the diverse laboratory-derived indexes commonly used to measure the degree of LF. Taking into account that these LF indexes are calculated by means of different parameters, the consistent association of these MMPs and TIMPs with each of them reinforces our findings and the value of these MMPs and TIMPs as additional markers of LF. Our results agree with those of Macías *et al*[13] that found an association of serum MMP-2 with LF measured by liver biopsy in 90 HIV-HCV-coinfected Spanish patients. These authors suggested that the combination of AST, platelet count and serum MMP-2 levels is a biochemical surrogate marker for LF ⩾ F2.

We did not observe any association between serum TIMP-1 and LF, or any of the multiple fibrosis indexes studied, as was reported by others studying heterogeneous aspects related to fibrosis in HCV-monoinfected or HIV-HCV-coinfected individuals[9-12]. On the contrary, we found an independent association of serum MMP-2, MMP-9 and TIMP-2 with diverse LF indexes. We did not measured serum MMP-1, which was associated with LF in HCV-mono-infected individuals in another study and was included in the Fibro-check[14].

We did not find any statistically significant association between LF and the different SNPs evaluated,

Table 1 Demographic, clinical and laboratory characteristics of the patients, according to the existence or not of significant liver fibrosis (≥ F2)

	All patients (*n* = 158)	No fibrosis (*n* = 124)	Fibrosis (*n* = 34)	*P* value
Demography, epidemiology, anthropometry and habits				
Age (yr)	44.56 (43.20-45.92)	44.50 (42.93-46.07)	44.79 (41.96-47.63)	0.9
Male, *n* (%)	104 (65.8)	78 (62.9)	26 (76.5)	0.14
Weight (kg)	65.17 (62.88-67.46)	64.46 (61.72-67.20)	67.76 (64.03-71.50)	0.24
Height (cm)	164.4 (160.6-168.2)	163.4 (158.5-168.2)	168.2 (166.2-170.2)	0.3
Body mass index (kg/m^2)	23.58 (23.10-24.05)	23.48 (22.95-24.01)	23.90 (22.75-25.0.6)	0.5
Tobacco smokers, *n* (%)	105 (66.5)	78 (62.9)	27 (79.4)	0.07
Cannabis use, *n* (%)	38 (24.1)	22 (17.7)	16 (47.1)	0.0004
Alcohol intake, *n* (%)[1]	55 (35.0)	43 (34.7)	12 (36.4)	0.9
IDU, *n* (%)	58 (36.9)	29 (23.6)	29 (85.6)	< 0.0001
Men who have sex with men, *n* (%)	28 (17.8)	27 (22.0)	1 (2.9)	0.01
Heterosexual, *n* (%)	67 (42.7)	63 (51.2)	4 (11.8)	< 0.0001
Transfusion, *n* (%)	4 (2.5)	4 (3.3)	0 (0.0)	0.3
HIV-related parameters				
Current CD4 counts (cells/μL)	581.5 (533.0-630.1)	612.3 (555.8-668.8)	469.6 (383.7-555.4)	0.017
Nadir CD4 counts (cells/μL)	201.8 (176.5-227.1)	213.4 (183.4-243.4)	159.7 (116.7-202.6)	0.04
CD4 gain (cells/μL)	379.7 (334.4-425.0)	399.0 (345.4-452.6)	309.9 (231.4-388.4)	0.11
Undetectable HIV viral load, *n* (%)	135 (85.4)	109 (87.9)	26 (76.5)	0.09
HIV viral load (log copies/mL)[2]	2.996 (2.556-3.434)	2.991 (2.407-3.575)	3.006 (2.173-3.840)	0.97
Years of HIV infection	11.93 (11.12-12.73)	11.31 (10.39-12.22)	14.19 (12.70-15.68)	0.003
Months on antiretroviral therapy	114.3 (106.8-121.8)	109.9 (101.3-118.5)	130.2 (115.0-145.3)	0.03
CDC clinical stage, *n* (%)				
A	84 (53.5)	65 (52.8)	19 (55.9)	0.07
B	23 (14.6)	22 (17.9)	1 (2.9)	
C	50 (31.8)	36 (29.3)	14 (41.2)	
HCV-related parameters				
HCV infection, *n* (%)	57 (36.1)	25 (20.2)	32 (94.1)	< 0.0001
HCV viral load (log copies/mL)	5.745 (5.504-5.985)	5.524 (5.085-5.964)	5.915 (5.649-6.181)	0.11
Years of HCV infection	22.46 (20.71-24.21)	21.84 (18.96-24.72)	22.94 (20.65-25.23)	0.5
HCV genotype, *n* (%)				
1	31 (54.4)	14 (56.0)	17 (53.1)	0.7
2	2 (1.3)	1 (4.0)	1 (3.1)	
3	15 (23.6)	5 (20.0)	10 (31.3)	
4	9 (15.8)	5 (20.0)	4 (12.5)	
Liver fibrosis parameters				
Transient elastometry (kPa)	7.53 (5.99-9.06)	4.65 (4.45-4.85)	18.02 (11.93-24.10)	< 0.0001
APRI	0.633 (0.511-0.756)	0.385 (0.346-0.423)	1.541 (1.093-1.989)	< 0.0001
Forns	4.412 (4.116-4.707)	3.990 (3.734-4.246)	5.949 (5.095-6.802)	0.0001
FIB-4	1.475 (1.249-1.700)	1.088 (0.985-1.191)	2.884 (2.031-3.736)	0.0002
YFPI[3]	0.584 (0.416-0.752)	0.281 (0.222-0.340)	0.821 (0.548-1.095)	0.0004
Degree of liver fibrosis, *n* (%)				
F0-F1	124 (78.5)	124 (100)	0 (0.0)	< 0.0001
F2	15 (9.5)	0 (0.0)	15 (44.1)	
F3	10 (6.3)	0 (0.0)	10 (29.4)	
F4	9 (5.7)	0 (0.0)	9 (26.5)	
Laboratory parameters				
Platelet count (/μL)	222570 (211690-233450)	236750 (225410-248090)	169270 (147220-191330)	< 0.0001
Glucose (mg/dL)	98.54 (95.25-101.84)	98.00 (94.62-101.38)	100.66 (90.92-110.39)	0.5
Total cholesterol (mg/dL)	195.01 (188.51-201.51)	201.0 (193.8-208.3)	173.0 (160.6-185.4)	0.0004
HDL cholesterol (mg/dL)	49.33 (46.88-51.78)	49.42 (46.95-52.29)	48.25 (42.02-54.48)	0.7
LDL cholesterol (mg/dL)	110.73 (104.68-116.77)	116.97 (110.22-123.72)	87.53 (76.91-98.16)	0.0001
Triglycerides (mg/dL)	199.79 (170.08-229.50)	189.0 (157.5-220.5)	241.7 (161.4-322.0)	0.22
AST (UI/mL)	40.89 (36.01-45.78)	30.72 (28.30-33.13)	78.00 (62.01-93.99)	< 0.0001
ALT (UI/mL)	47.82 (40.54-55.09)	36.91 (32.03-41.79)	87.59 (62.16-113.02)	0.0003
AST/ALT ratio	1.011 (0.949-1.074)	0.993 (0.927-1.059)	1.079 (0.913-1.246)	0.3
GGT (UI/mL)	83.95 (66.61-101.29)	59.73 (48.40-71.07)	174.21 (110.61-237.81)	0.001
Alkaline phosphatase (UI/mL)	91.87 (85.09-98.65)	90.72 (83.22-98.23)	98.31 (81.46-115.17)	0.4
MMP-2 (ng/mL)	0.538 (0.442-0.654)	0.482 (0.387-0.600)	0.867 (0.579-1.300)	0.02
MMP-3 (ng/mL)	15.00 (13.24-17.01)	14.36 (12.47-16.54)	17.77 (14.45-23.49)	0.18
MMP-8 (ng/mL)	0.031 (0.023-0.041)	0.029 (0.021-0.039)	0.040 (0.020-0.078)	0.4
MMP-9 (ng/mL)	22.49 (18.81-26.90)	23.19 (19.00-28.31)	19.94 (13.01-30.58)	0.5
MMP-10 (ng/mL)	2.50 (1.66-3.75)	2.163 (1.487-3.145)	5.077 (0.938-27.469)	0.12
TIMP-1 (ng/mL)	50.56 (45.58-56.08)	50.84 (45.43-56.88)	49.49 (37.71-64.94)	0.8
TIMP-2 (ng/mL)	8.23 (7.16-9.46)	7.62 (6.59-8.80)	11.15 (7.55-16.45)	0.03
TIMP-4 (ng/mL)	0.040 (0.030-0.054)	0.037 (0.027-0.051)	0.054 (0.026-0.110)	0. 3

[1]Less than 50 g/d; [2]Only if detectable; [3]YFPI: Yearly fibrosis progression index (only in HCV-infected patients), calculated as transient elastometry value divided into the years of estimated HCV infection. Values are expressed as mean (95%CI) or *n* (%) as appropriate. IDU: Intravenous drug use. MMP: Matrix metalloprotease; HCV: Hepatitis C virus; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; APRI: AST to Platelet Ratio Index; FIB-4: Fibrosis-4 index; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; GGT: Gamma-glutamyl transpeptidase; TIMP: Tissue inhibitor of metalloprotease.

Table 2 Genotypic frequencies of different single nucleotide polymorphisms according to liver fibrosis ≥ F2 and hepatitis C virus status

SNP	Genotype	No fibrosis *n* (%)	Fibrosis *n* (%)	*P* value	HIV mono-infected *n* (%)	HIV/HCV coinfected *n* (%)	*P* value
MMP-1 -1607 1G/2G	*1G1G*	14 (20.3)	4 (16.7)	0.9	9 (16.1)	9 (24.3)	0.6
	1G2G	13 (18.8)	5 (20.8)		12 (21.4)	6 (16.2)	
	2G2G	42 (60.9)	15 (62.5)		35 (62.5)	22 (59.5)	
MMP-8 -799C/T	*CC*	30 (27.0)	6 (22.2)	0.6	25 (26.3)	11 (25.5)	1
	CT	47 (42.4)	10 (37.0)		39 (41.1)	18 (41.9)	
	TT	34 (30.6)	11 (40.8)		31 (32.6)	14 (32.6)	
MMP-9 -1562 C/T	*CC*	78 (81.2)	28 (84.8)	0.6	61 (83.6)	45 (80.4)	0.6
	CT	18 (18.8)	5 (15.2)		12 (16.4)	11 (19.6)	
	TT	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
MMP-13 -77A/G	*AA*	89 (74.8)	21 (61.8)	0.14	70 (72.9)	40 (70.2)	0.7
	AG	30 (25.2)	13 (38.2)		26 (27.1)	17 (29.8)	
	GG	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
TNF-α -308 G/A	*AA*	11 (11.3)	4 (11.8)	0.5	7 (9.5)	8 (14.0)	0.7
	AG	62 (63.9)	18 (52.9)		46 (62.1)	34 (59.6)	
	GG	24 (24.7)	12 (35.3)		21 (28.4)	15 (26.3)	
CCR5-Δ32	*wt/wt*	96 (80.0)	30 (88.2)	0.27	77 (79.4)	49 (86.0)	0.3
	wt/Δ32	24 (20.0)	4 (11.8)		20 (20.6)	8 (14.0)	
	Δ32/Δ32	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	

SNP: Single nucleotide polymorphisms; HCV: Hepatitis C virus; HIV: Human immunodeficiency virus; MMP: Matrix metalloprotease.

Table 3 Liver fibrosis indexes according to the single nucleotide polymorphisms genotypes

SNP	Genotype	Transient elastometry	YFPI[1]	APRI	Forns	FIB-4
MMP-1 -1607 1G/2G	*1G1G*	5.583 (4.600-6.567)	0.346 (0.215-0.477)	0.693 (0.192-1.195)	3.719 (2.860-4.579)	1.317 (0.723-1.911)
	1G2G	5.911 (4.649-7.174)	0.470 (0.250-0.691)	0.488 (0.307-0.670)	4.253 (3.430-5.077)	1.092 (0.859-1.324)
	2G2G	8.781 (5.585-11.977)	0.689 (0.378-1.001)	0.675 (0.453-0.897)	4.390 (3.914-4.867)	1.479 (1.097-1.862)
	P value	0.3	0.3	0.7	0.4	0.5
MMP-8 -799C/T	*CC*	6.644 (3.736-9.553)	0.633 (0.074-1.193)	0.615 (0.411-0.819)	4.510 (3.920-5.099)	1.461 (1.058-1.864)
	CT	5.628 (5.060-6.196)	0.357 (0.275-0.439)	0.453 (0.347-0.559)	4.126 (3.701-4.551)	1.145 (1.014-1.277)
	TT	7.729 (4.540-10.918)	0.671 (0.376-0.965)	0.768 (0.447-1.088)	4.407 (3.825-4.989)	1.603 (1.081-2.125)
	P value	0.4	0.19	0.1	0.5	0.15
MMP-9 -1562 C/T	*CC*	7.540 (5.810-9.269)	0.527 (0.361-0.694)	0.612 (0.475-0.749)	4.370 (4.024-4.717)	1.404 (1.163-1.645)
	CT	11.178 (4.093-18.264)	0.833 (0.229-1.437)	0.867 (0.412-1.323)	5.083 (4.024-6.142)	2.043 (1.044-3.041)
	TT	-	-	-	-	-
	P value	0.14	0.16	0.16	0.11	0.065
MMP-13 -77A/G	*AA*	7.217 (5.654-8.780)	0.535 (0.358-0.712)	0.623 (0.480-0.766)	4.352 (3.993-4.711)	1.462 (1.185-1.738)
	AG	8.721 (4.646-12.798)	0.700 (0.291-1.109)	0.698 (0.426-0.970)	4.588 (3.998-5.177)	1.553 (1.109-1.998)
	GG	-	-	-	-	-
	P value	0.4	0.4	0.6	0.5	0.7
TNF-α -308 G/A	*AA*	10.073 (1.300-18.849)	0.656 (0.132-1.180)	0.693 (0.135-1.250)	4.331 (3.280-5.383)	1.584 (0.693-2.475)
	AG	8.086 (5.779-10.394)	0.552 (0.336-0.767)	0.675 (0.495-0.855)	4.603 (4.174-5.033)	1.575 (1.210-1.940)
	GG	7.514 (4.623-10.404)	0.620 (0.228-1.012)	0.701 (0.405-0.997)	4.221 (3.513-4.929)	1.466 (1.021-1.910)
	P value	0.7	0.9	0.99	0.6	0.9
CCR5-Δ32	*wt/wt*	7.852 (5.998-9.707)	0.590 (0.399-0.783)	0.664 (0.525-0.803)	4.439 (4.102-4.775)	1.513 (1.264-1.762)
	wt/Δ32	6.521 (4.109-8.934)	0.545 (0.232-0.858)	0.539 (0.230-0.847)	4.391 (3.684-5.098)	1.335 (0.699-1.971)
	Δ32/Δ32	-	-	-	-	-
	P value	0.5	0.9	0.4	0.9	0.6

[1]YFPI: Yearly fibrosis progression index (only for HCV-infected patients); SNP: Single nucleotide polymorphisms; MMP: Matrix metalloprotease. Values are expressed as mean (95%CI) in ng/mL; APRI: AST to Platelet Ratio Index; FIB-4: Fibrosis-4 index.

although patients carrying the heterozygous *CT* genotype of the *MMP-9 -1562 C/T* SNP had consistently higher values of all LF indexes than those with the homozygous *CC* genotype. Okamoto *et al*[6] reported an association of *MMP-1- 1607 1G/2G*, *MMP-3 -1612 5A/6* and *MMP-9 -1562 C/T*, SNPs with LF progression measured by biochemical markers or liver biopsy in HCV-monoinfected Japanese patients. Sánchez-Parada *et al*[7] found that *TGBFB1* +915 C/G (rs 1800471) SNP carriage was associated with severity of hepatic necroinflammation and LF in HCV-mono-infected Mexican patients. In addition, the same authors reported an association between *MMP-3 -1612 5A/6* SNP *6A* allele carriage and an increase in the albumin-globulin ratio, as a surrogate marker of LF. The ethnic background of our patients was different from those of previous reports, and the relatively small sample size of our HIV-HCV-coinfected population could

Table 4 Metalloproteases and their tissue inhibitors according to the single nucleotide polymorphisms genotypes

SNP	Genotype	MMP-2	MMP-3	MMP-8	MMP-9	MMP-10	TIMP-1	TIMP-2	TIMP-4
MMP-1 -1607	*1G1G*	0.379	16.69	0.035	19.93	1.782	41.73	6.79	0.031
1G/2G		(0.195-0.736)	(11.00-25.33)	(0.013-0.095)	(11.59-34.28)	(0.350-9.071)	(30.87-56.42)	(4.52-10.21)	(0.010-0.091)
	1G2G	0.803	19.87	0.041	22.35	1.451	54.07	7.30	0.047
		(0.409-1.575)	(15.13-26.10)	(0.012-0.134)	(13.37-37.36)	(0.417-5.047)	(39.44-74.14)	(4.49-11.87)	(0.020-0.113)
	2G2G	0.609	14.72	0.027	23.65	3.345	50.34	8.39	0.032
		(0.449-0.826)	(11.57-18.73)	(0.017-0.042)	(17.07-32.76)	(1.512-7.399)	(42.16-60.10)	(6.54-10.76)	(0.019-0.053)
	P value	0.18	0.4	0.7	0.9	0.5	0.4	0.6	0.7
MMP-8 799C/T	*CC*	0.655	15.96	0.048	29.93	4.650	61.60	11.67	0.041
		(0.473-0.908)	(12.94-19.68)	(0.025-0.090)	(19.94-44.94)	(1.354-15.97)	(49.94-75.99)	(8.59-15.85)	(0.023-0.073)
	CT	0.568	13.05	0.031	21.30	2.179	47.17	6.71 (5.50-8.18)	0.035
		(0.409-0.787)	(10.22-16.65)	(0.018-0.054)	(15.50-29.28)	(1.201-3.953)	(38.80-57.34)		(0.021-0.058)
	TT	0.432	16.66	0.020	18.86	1.623	47.75	8.12	0.050
		(0.280-0.668)	(13.35-20.81)	(0.015-0.027)	(14.03-25.37)	(0.938-2.808)	(40.75-55.94)	(5.89-11.20)	(0.030-0.084)
	P value	0.3	0.3	0.09	0.17	0.17	0.11	0.01	0.6
MMP-9 1562 C/T	*CC*	0.495	15.42	0.034	22.39	2.405	52.23	8.39 (7.18-9.80)	0.037
		(0.385-0.637)	(13.11-18.14)	(0.024-0.049)	(17.79-28.19)	(1.462-3.957)	(46.17-59.07)		(0.026-0.053)
	CT	1.031	18.15	0.020	22.97	5.960	46.55	8.18	0.058
		(0.853-1.246)	(13.99-23.54)	(0.008-0.047)	(14.77-35.71)	(0.666-53.34)	(33.82-64.07)	(4.40-15.21)	(0.025-0.137)
	TT	-	-	-	-	-	-	-	-
	P value	0.02	0.3	0.2	0.9	0.2	0.4	0.9	0.3
MMP-13 77A/G	*AA*	0.522	15.62	0.030	23.06	2.337	53.30	8.54	0.050
		(0.419-0.650)	(13.47-18.13)	(0.022-0.041)	(18.64-28.54)	(1.380-3.957)	(47.05-60.38)	(7.21-10.12)	(0.036-0.069)
	AG	0.683	14.37	0.037	22.96	2.685	48.10	8.07	0.031
		(0.458-1.017)	(11.10-18.59)	(0.019-0.071)	(16.01-32.93)	(1.215-5.931)	(39.30-58.88)	(6.09-10.68)	(0.016-0.058)
	GG	-	-	-	-	-	-	-	-
	P value	0.22	0.6	0.6	0.98	0.8	0.4	0.7	0.14
TNF-α 308 G/A	*AA*	0.730	21.40	0.039	17.42	0.804	57.25	13.14	0.111
		(0.325-1.639)	(14.72-31.13)	(0.010-0.156)	(8.16-37.21)	(0.369-1.755)	(37.28-87.92)	(8.72-19.80)	(0.054-0.227)
	AG	0.558	14.65	0.031	23.41	4.460	51.62	8.39	0.043
		(0.429-0.727)	(11.96-17.95)	(0.020-0.050)	(17.78-30.83)	(2.097-9.486)	(43.92-60.66)	(6.71-10.48)	(0.028-0.064)
	GG	0.453	16.54	0.027	23.62	1.998	46.63	7.04 (5.36-9.26)	0.023
		(0.281-0.732)	(13.36-20.47)	(0.018-0.040)	(17.25-32.34)	(0.879-4.542)	(39.84-54.59)		(0.012-0.045)
	P value	0.4	0.24	0.8	0.7	0.065	0.6	0.1	0.02
CCR5-Δ32	*wt/wt*	0.601	15.75	0.031	21.55	2.441	50.72	8.10 (6.95-9.45)	0.041
		(0.484-0.747)	(13.71-18.09)	(0.022-0.043)	(17.50-26.53)	(1.482-4.020)	(44.83-57.38)		(0.029-0.057)
	wt/Δ32	0.431	13.64	0.032	27.15	2.662	52.01	9.44	0.043
		(0.286-0.652)	(9.87-18.85))	(0.020-0.051)	(18.55-39.73)	(1.222-5.801)	(42.66-63.42)	(6.49-13.72)	(0.021-0.088)
	Δ32/Δ32	-	-	-	-	-	-	-	-
	P value	0.15	0.4	0.9	0.3	0.9	0.9	0.4	0.9

SNP: Single nucleotide polymorphisms; MMP: Matrix metalloprotease. Values are expressed as mean (95%CI) in ng/mL. APRI: AST to Platelet Ratio Index; FIB-4: Fibrosis-4 index; TIMP: Tissue inhibitor of metalloprotease.

perhaps explain these discrepant findings. We did not genotype the *TGBFB1* +915 C/G nor the *MMP14* [-1658 (rs100349), +7096 (rs2236307) and + 8153 (rs3751489)] SNPs that have been associated with LF and hepatocellular carcinoma in HCV-monoinfected patients of Mexican and Chinese extraction[7,8].

We found that male gender was independently associated with LF in HIV-HCV coinfection. This association was already described by our group in another cohort of patients[24], and appears to be at least partially due to hormonal issues. In this regard, experimental studies in rats have shown the beneficial effects of estradiol administration on LF through diverse mechanisms[25-28].

Limitations to our study include those inherent to cross-sectional studies and the relatively small number of patients with LF ⩾ F2. The relatively small sample size might affect especially the genetic testing results. However, the sample size was large enough to find significant associations between LF and MMPs, TIMPs and other factors, and our findings on the independent relationships of MMPs and TIMPs with the diverse LF markers evaluated were highly consistent and support the reliability of our results.

A possible reason for the small numbers of patients with LF ⩾ 2 is the exclusion of alcoholics from this study. We used a definition of alcohol abuse based on an ethanol exposition ⩾ 50 g/d for > 5 years previously used by others and us[29,30]. This alcohol consumption equates to approximately 3.5 drinks per day using standard drinks in the United States. Other authors reduced the alcohol abuse to ⩾ 40 g/d for > 5 years[12]. We consider that this discrepancy might play a minor role in our study considering that only 34 patients (21.5% of the total) had LF ⩾ F2 and 32 of them had HIV-HCV coinfection.

We conclude that some MMPs and TIMPs, such as MMP-9, TIMP-2 and especially MMP-2, are associated

Table 5 Correlations among metalloproteases, their tissue inhibitors and liver fibrosis parameters

	MMP-3	MMP-8	MMP-9	MMP-10	TIMP-1	TIMP-2	TIMP-4	TE	YFPI	APRI	Forns	FIB-4
MMP-2	0.19 (0.04)	0.21 (0.02)	0.21 (0.02)	0.20 (0.09)	0.29 (0.002)	0.29 (0.002)	0.35 (0.0002)	0.23 (0.016)	0.30 (0.058)	0.20 (0.03)	0.19 (0.04)	0.20 (0.03)
MMP-3		0.29 (0.0006)	0.30 (0.0006)	0.15 (0.19)	0.33 (0.0001)	0.27 (0.002)	0.38 (< 0.0001)	0.09 (0.3)	0.001 (0.99)	0.16 (0.06)	0.16 (0.06)	0.10 (0.24)
MMP-8			0.69 (< 0.0001)	0.25 (0.02)	0.71 (< 0.0001)	0.40 (< 0.0001)	0.24 (0.005)	-0.02 (0.8)	-0.15 (0.3)	-0.01 (0.9)	0.03 (0.8)	-0.03 (0.7)
MMP-9				0.21 (0.06)	0.71 (< 0.0001)	0.16 (0.06)	0.21 (0.01)	-0.21 (0.01)	-0.32 (0.02)	-0.17 (0.047)	-0.11 (0.2)	-0.20 (0.02)
MMP-10					0.12 (0.3)	0.22 (0.051)	0.11 (0.3)	0.01 (0.9)	-0.09 (0.7)	0.12 (0.3)	-0.08 (0.5)	-0.03 (0.8)
TIMP-1						0.40 (< 0.0001)	0.39 (< 0.0001)	0.02 (0.8)	-0.04 (0.8)	-0.02 (0.8)	0.07 (0.4)	0.01 (0.9)
TIMP-2							0.33 (0.0001)	0.28 (0.0009)	0.25 (0.08)	0.35 (< 0.0001)	0.20 (0.018)	0.36 (< 0.0001)
TIMP-4								0.11 (0.2)	0.03 (0.8)	0.14 (0.12)	0.06 (0.5)	0.19 (0.03)
TE									0.94 (< 0.0001)	0.75 (< 0.0001)	0.59 (< 0.0001)	0.82 (< 0.0001)
YFPI										0.63 (< 0.0001)	0.51 (0.0001)	0.74 (< 0.0001)
APRI											0.55 (< 0.0001)	0.90 (< 0.0001)
Forns												0.67 (< 0.0001)

Values are expressed as *r* (*P* value). MMP: Matrix metalloprotease; HCV: Hepatitis C virus; TE: Transient elastometry; YFPI: Yearly fibrosis progression index (only for HCV-infected patients); TIMP: Tissue inhibitor of metalloprotease.

Table 6 Independent predictors of different fibrosis indexes

	TE	APRI	Forns	FIB-4	YFPI
Higher MMP-2 levels	0.001	0.0001	0.03	0.0009	0.004
Higher TIMP-2 levels	0.016	0.0001	0.024	0.0002	-
Lower MMP-9 levels	0.023	0.016	-	0.03	0.043
Lower current CD4 counts	-	0.032	0.037	0.043	-
Older age	-	-	0.004	0.05	-
% of the index accounted for by the model	20.00%	35.30%	23.30%	33.50%	20.70%

Numbers represent *P* values. HCV: Hepatitis C virus; MMP: Matrix metalloprotease; TE: Transient elastometry; YFPI: Yearly fibrosis progression index (only for HCV-infected patients); APRI: AST to Platelet Ratio Index; TIMP: Tissue inhibitor of metalloprotease.

with non-alcoholic LF and diverse fibrosis markers in HIV-infected patients with and without HCV coinfection. The determination of these parameters could be useful for the development of other laboratory-derived indexes of LF in order to improve the accuracy of the current non-invasive tests. On the contrary, the SNPs evaluated did not significantly associate with LF in our Caucasian cohort, although this aspect needs to be confirmed by other studies with larger sample sizes and, perhaps, with patients of different ethnic extraction, taking into account the trend that we observed with the *MMP-9 1562* SNP.

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COMMENTS

Background

Liver fibrosis reflects an imbalance between extracellular matrix synthesis and reduced breakdown of connective tissue proteins, which is regulated by matrix metalloproteases (MMPs) and their tissue inhibitors (TIMPs). Genetic polymorphisms (SNPs) of MMPs and TIMPs induce changes in *MMPs* genes mRNA and protein expression. However, the role of MMPs, TIMPs and their SNPs in the development of liver fibrosis and their usefulness for the evaluation of fibrosis in clinical practice are uncertain.

Research frontiers

Some studies have inconsistently found a relationship between liver fibrosis and certain MMPs, TIMPs and SNPs in hepatitis C virus (HCV)-monoinfected and human immunodeficiency virus (HIV)-HCV-coinfected individuals, although the issue is far from clear. The topic is important, not only to support a possible pathogenic role of these substances and their genetic polymorphisms in the generation of fibrosis, but also to define the possible value of these determinations in the evaluation of the degree of fibrosis, which could be useful

to clinicians involved in the care of these patients.

Innovations and breakthroughs

Excessive alcohol intake, a common habit among intravenous drug users, most of whom are also coinfected with HCV, is a cause of liver disease, and the influence of MMPs, TIMPs and their SNPs might vary according to the etiology of liver fibrosis. Consequently, the authors excluded patients with excessive alcohol intake, to minimize the possible confounding factor of multiple etiologies of fibrosis. On the other hand, non-invasive methods of measurement of liver fibrosis, mainly transient elastometry, are replacing liver biopsy in the evaluation of the degree of fibrosis. Therefore, the authors have also analyzed the relationships of these substances with multiple fibrosis indexes, in order to verify the consistence of such relationships from the perspective of different fibrosis markers. The authors found that high levels of MMP-2 were independently associated with liver fibrosis ≥ F2. Likewise, MMP-2, TIMP-2 and MMP-9 were independent and consistent predictors of transient elastometry values and of other non-invasive markers of fibrosis. On the contrary, they did not find any significant association between liver fibrosis ≥ F2 and the diverse SNPs evaluated.

Applications

This study supports the implication of these substances in the development of liver fibrosis, and their value as predictors of the degree of fibrosis in HIV-infected patients with non-alcoholic liver disease. The determination of these parameters could be useful for the development of laboratory-derived indexes of fibrosis, in order to improve the accuracy of the current non-invasive tests.

Terminology

MMPs, a family of zinc-dependent endoproteases, and their tissue inhibitors TIMPs are involved in the remodeling and degradation of the extracellular matrix and, therefore, may influence the development of liver fibrosis.

Peer-review

The results presented in this reviewed manuscript are of scientific merit and interest.

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