INFLAMMATORY BIOMARKERS RELATED WITH SUBLINICAL ATHEROSCLEROSIS IN SUPPRESSED HIV-INFECTED PATIENTS.

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BACKGROUND

Inflammation and immune activation persist in HIV-patients despite an optimal virological control and can accelerate atherosclerosis. The objective of the study was to assess associations of risk factors and inflammatory biomarkers with subclinical atherosclerosis (SA) in virologically suppressed HIV-patients.

OBJECTIVE

- To determine the prevalence of SA in virologically suppressed HIV-infected patients
- To assess HIV, traditional cardiovascular risk (CVR) factors and inflammatory biomarkers that could predict SA.

METHODOLOGY

Obsevational cross sectional cohort study. Participants were randomly selected from our HIV and STD Unit.
Inclusion criteria: Clinically stable HIV-patients >18 years old, on c-ART, with virological suppression (plasma HIV-RNA <40 copies/mL) for the last 6 months, that signed the informed consent form. **Exclusion criteria:** Active infection or inflammatory disease, neoplasia requiring systemic treatment, cardiovascular disease (myocardial infarction, angina, coronary angioplasty or coronary bypass) or prior cerebrovascular disease (stroke, transient ischemic stroke or carotid endarterectomy).
Variables analyzed:
- Demographic and HIV related data; CVR assessment using SCORE and Regicor (Framingham validate to Spanish population(Marrugat, J Epidemiol Com 2007;61:40)).
- Laboratory: HIV viral load, CD4 cell count, creatinine, insulin and lipid profile. Plasma biomarkers were measured: sCD163, sCD14, Interleukin-6 (IL-6), D-dimer and sVCAM by ELISA, high-sensitivity C-reactive protein (hs-CRP) by immunocolorimetry and lipoprotein-phospholipase A2 (Lp-PLA2) by 2-thio-PAF.
-Carotid ultrasound: measurement of carotid intima-media thickness (c-IMT) of far wall of left and right common carotid using a semi-automatic software and presence of plaque (focal structure into the arterial lumen of at least 0.5 mm or 50% of the surrounding IMT value or c-IMT ≥=1.5 mm) in common, bulb and internal carotid. Subclinical atherosclerosis was defined as the presence of a plaque or common c-IMT > 75th percentile of a reference population (Grau M,Rev Esp Cardiol 2012;65:1086).
Sample size: in order to obtain a precision of 2.5%, with a finite population of 1.500 patients and assuming an expected proportion of 28% of patients with SA, 680 patients were required. As we found a higher proportion of SA we could reduce the number of participants to 450.
Statisitics: Multivariable logistic regression included all variables with p≤0.1 in univariate analyse was used.

RESULTS

1.Demographical, antiretroviral and laboratory characteristics of participants

Variable	Total N=441	No Subclinical atherosclerosis N= 224	Subclinical atherosclerosis N=217	P-value
Age, years	50.4 (10.1)	47.5 (9.1)	53.1 (10.1)	<0.001
< 35	25 (5.6)	18 (8)	7 (3.2)	
35-44	104 (23.6)	74 (33)	30 (13.8)	
44-54	203 (46)	98 (44)	105 (48.4)	<0.001
54-64	69 (15.6)	22 (9.8)	47 (21.7)	
>65	40 (9.1)	12 (5.4)	28 (12.9)	
Sex, Male	356 (80.7)	178 (79.5)	178 (82)	0.495
Risk group,				
Intravenous drug user	157 (35.6)	68 (30.4)	89 (41)	
Heterosexual	137 (31.1)	73 (32.6)	64 (29.5)	0.125
MSM	131 (29.7)	74 (33)	57 (26.3)	
Other/unknown	16 (3.6)	9 (4)	7 (3.2)	
Ilicit drugs				
Ever cocaine use	101 (22.9)	52 (23.2)	49 (22.6)	0.874
Ever heroin use	88 (19.9)	47 (21.0)	41 (18.9)	0.583
AIDS-Cstage	137 (31)	58 (25.9)	79 (36.4)	0.017
CD4 cell count(cel/mm3)				
Nadir	339 (216)	340 (211)	339 (222)	0.832
Current	716 (336)	743 (319)	958 (495)	0.309
HIV viral load zenit(log copies/mL)	4.7 (0.9)	4.8 (0,9)	4.6 (1.1)	0.037
Hepatitis C virus	180 (40.7)	78 (35)	102 (47)	0.009
Duration of HIV infection, y	16.4 (7.9)	14.7 (8.1)	18.1 (7.4)	<0.001
Antiretroviral therapy				
- Duration of treatment, years	14.7 (6,6)	13.07 (6.7)	16.4 (6.2)	<0.001
- Current antiretroviral therapy				
NNRTI	280 (63.5)	140 (62.5)	140 (64.5)	0.66
PI	132 (29.9)	60 (26.8)	72 (33.1)	0.143
Integrase inhibitor	96 (21.8)	41 (18.3)	55 (25.3)	0.073
- Abacavir use, yes	261 (59.1)	122 (54)	139 (64.1)	0.04
- Duration of abacavir use, years	5.4 (4.2)	4.9 (4)	5.9 (4.3)	0.049
- PI use, yes	318 (72.1)	150 (66.9)	168 (77.4)	0.014
- Duration of PI, years	7 (5.5)	6.1 (5.1)	7.6 (5.7)	0.013

Variable	Total N=441	No Subclinical atherosclerosis N= 224	Subclinical atherosclerosis N=217	P-value
Cardiovascular risk factors				
Hypertension	107 (24.3)	27 (12)	80 (36.9)	<0.001
Diabetes	32 (.27)	8 (3.6)	24 (11.1)	0.002
Smoking (past or current)	352 (78)	167 (74.5)	177 (81.6)	0.075
Family history of CV disease	66 (14.9)	35 (15.6)	31 (14.3)	0.693
Anthropometric variables				
Body mass index, Kg/m2	25.5 (5)	25.1 (4.4)	25.8 (5.5)	0.106
Waist-to-hip ratio	1 (0.1)	1 (0.1)	1 (0.1)	<0.001
SCORE, mean	2 (2.9)	1.2 (1.6)	2.8 (3.6)	<0.001
Regicor, mean	3.5 (2.8)	2.7 (1.9)	4.3 (3.3)	<0.001
Concomitants drugs				
Lipid lowering therapy	106 (24)	33 (15)	73 (34)	<0.001
Antihipertensive therapy	89 (20)	22 (9.8)	67 (61)	<0.001
Antidiabetic therapy	26 (5.8)	7 (3.1)	19 (8.8)	0.012
Antiaggregant therapy	10 (2.2)	5 (2.2)	5 (2.3)	0.96
Laboratory measurements				
Total cholesterol, mmol/L	4.7 (1)	4.6 (1)	4.9 (1)	0.005
LDL-c, mmol/L	2.7 (0.8)	2.8 (0.8)	2.7 (0.8)	0.289
HDL-c, mmol/L	1.3 (0.5)	1.4 (0.5)	1.3 (0.5)	0.244
Trygicerides, mmol/L	1.7 (1.4)	1.5 (1.1)	1.8 (1.7)	0.004
Glucose, mmol/L	5.4 (1.4)	5.2 (0.9)	5.6 (1.8)	0.003
Insulin, pmol/L	105.3 (96.8)	94.6 (73.1)	116.1 (115.4)	0.11
Creatinin Clearance, mL/min	96.1 (26.6)	92.3 (20.7)	94.9 (29)	0.216
Biomarkers				
Hs-CRP, mg/L	1.6 (0.8-3.8)	(1.6 (0.7-3.9)	1.8 (0.8-3.4)	0.303
sCD163, ng/mL	304.7 (200-443)	284.7 (176-384)	342.6 (226-512)	<0.001
sCD14, ug/mL	1.34 (0.93-1.71)	1.34 (0.94-1.68)	1.32 (0.91-1.72)	0.974
Interleukin-6, pg/mL	1.11 (0.43-2)	0.89 (0.43-1.76)	1.19 (0.53-2.19)	0.043
D-dimer, ng/mL	14.65 (9.9-24.1)	14 (9.5-20.6)	15.4 (10.2-28.3)	0.036
sVCAM, ng/mL	8.5 (6.8-10.6)	8.3 (6.7-10.2)	9 (7.2-11.4)	0.041
Lp-PLA2 activity, umol/min*mL	20.6 (17.6-24.2)	20.3 (17.2-23.9)	21.2 (18.2-25)	0.027

CV: cardiovascular; HDL-c: high density lipoprotein cholesterol; hs-CRP: high-sensitivity C-reactive protein; LDL-c: low density lipoprotein cholesterol; MSM: men who have sex with men; NNRTI: non-nucleoside reverse transcriptase inhibitor; PI: protease inhibitor; s-VCAM: soluble vascular cell adhesion molecule-1 ; Lp-PLA2: lipoprotein-phospholipase A2.
Continuous variable: mean (standar desviation), except biomarkers: median (Interquartile range); qualitative variables: n (percentage).
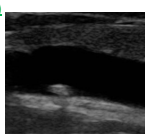
2. Carotid measurements

Mean **common carotid intim-media thickness** : 0.63 (SD 0.13) mm

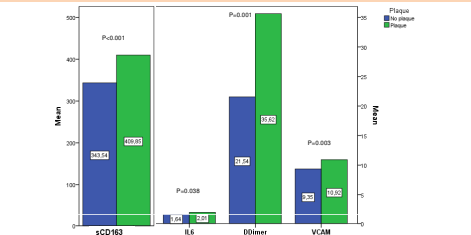Percentage of patients with **CC-IMT > 75th percentile** 134 (30.5%)

Percentage of patients with **carotid plaque**: 151 (34.1%)

Plaque location:
Common carotid: 21 (4.7%)
Bulb: 146 (96%)
Internal carotid: 37 (8.4%)

Percentage of patients with **subclinical atherosclerosis**: 217 (49.2%)

3. Plasma biomarker levels and carotid plaque

3. Multivariate logistic regression analysis

	CC c-IMT		Presence of plaque		Subclinical atherosclerosis	
	Beta coefficient (95%CI)	p	Odds ratio (95% IC)	p	Odds ratio (95% IC)	p
Age	0.007 (0.005;0.008)	<0.001	1.08 (1.04; 1.11)	<0.001	1.04 (1.01; 1.07)	0.014
Gender (female)	-0.031 (-0.059;-0.003)	0.031	0.76 (0.39; 1.48)	0.418	1.28 (0,71; 2,34)	0.413
Baseline HIV RNA viral load	-0.015 (-0.027;-0.004)	0.01				
Body mass index	0.003 (3.47×10⁻⁴; 0.005)	0.023				
Hypertension	0.032 (0.004; 0.059)	0.026	3.54 (2.01; 6.23)	<0.001	2.66 (1.46; 4.85)	<0.001
Cholesterol non-HDL					1.52 (1.17; 1.97)	0.001
Ever smoker			2.22 (1.52; 3.23)	<0.001	1.41 (1.04; 1.92)	0.027
Lipid lowering therapy			1.89 (1.05; 3.38)	0.032		
ART duration			1 (1;1.01)	0.042		
Total cholesterol			1.01 (1;1.02)	0.002		
Systolic blood pressure					1.01 (1;1.03)	0.092
Thymidine analogue use					1.76 (1.05; 2.95)	0.032
sCD163			1 (1;1)	0.085	1.001 (1;1.002)	0.028
D-dimer			1.01 (1;1.02)	0.082		
Constant	0.287 (0.176; 0.399)	<0.001	1.35×10⁻³	<0.001	2.69×10⁻³	<0,001

Multivariate logistic regression model using variables associated in the univariate analyses (p<0.1) adjusted by age and sex.
Cc-IMT: common carotid intima-media thickness. Subclinical atherosclerosis: plaque or cc-IMT> 75th percentile

4. Correlation between CD4 and biomarkers
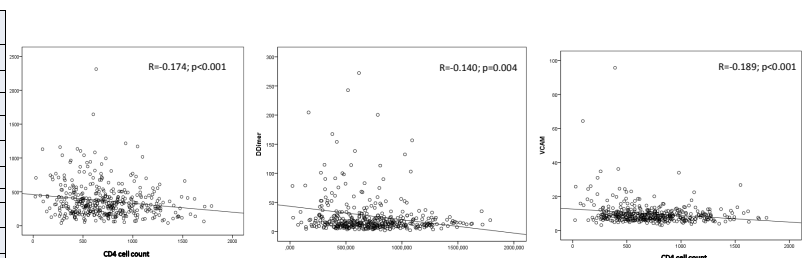
Only a weak correlation was found between cc-IMT and some biomarkers: IL-6 (r=0.109; p=0.029 and D-Dimer (r=1.06; p=0.034)

CONCLUSIONS

We have found a high prevalence of subclinical atherosclerosis (SA) associated with traditional CVR factors and HIV. SCD163 was associated with SA independently of traditional CVR factors. In our study, inflammatory biomarkers were more strongly associated with carotid plaque and SA than with cc-IMT.
Strategies to decrease inflammatory biomarkers, mainly those related with macrophage activation (sCD163), may be useful to prevent atherogenesis in HIV patients, besides an optimal control of CVR factors.