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N^6-methyladenine DNA and ABCA1 methylation association with coronary atherosclerosis in asymptomatic people with HIV with low-intermediate cardiovascular risk

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Background and aim

- Coronary artery disease (CAD) is more prevalent in people living with HIV (PWH) than in HIV-negative individuals. Asymptomatic PWH have more coronary plaque than asymptomatic HIV negative controls but similar to individuals with stable angina.
- Apolipoprotein A1 and ABCA1 transporter play a role in the reverse cholesterol transport and HIV infection promotes a decrease reverse colesterol transport in macrophages.
- ABCA1 methylation and N6-methyladenine DNA (a prevalent epigenetic base modification) have been identified as epigenetic markers in coronary artery disease in animal models.
- We aim to assess the association between this epigenetic markers with coronary artery plaque in asymptomatic PWH with low-intermediate cardiovascular risk.

Patients and Methods

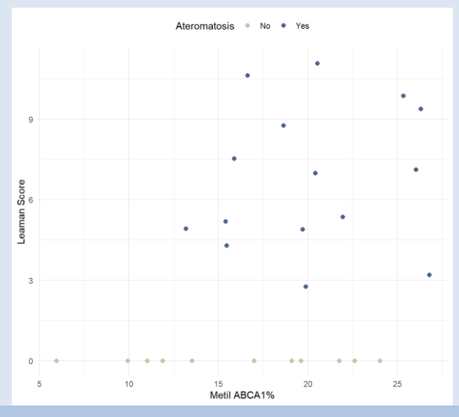
- Cross-sectional exploratory study performed in Hospital Universitario La Paz, and Hospital Universitario Central de la defensa Gómez Ulla in Madrid.
- Selection criteria: Participants ≥ 45 years with two or more cardiovascular risk factors on antiretroviral with a HIV-RNA < 50 copies/mL for at least 6 months. Participants should be asymptomatic regarding cardiac symptoms. We excluded participants with a previous cardiovascular disease and chronic kidney disease.
- 9 hour fast blood test was obtained and PBMCs were isolated by ficoll gradient and freeze in liquid nitrogen until análisis. CT coronary angiogram was performed with a 180 and 320-slice multidetector CT scan were centrally read in La Paz Cardiac Image Unit.
- Analysis of ABCA1 promoter methylation was performed in DNA from monocytes by NGS. N6-methyladenine DNA levels were performed in leukocyte DNA by ELISA.

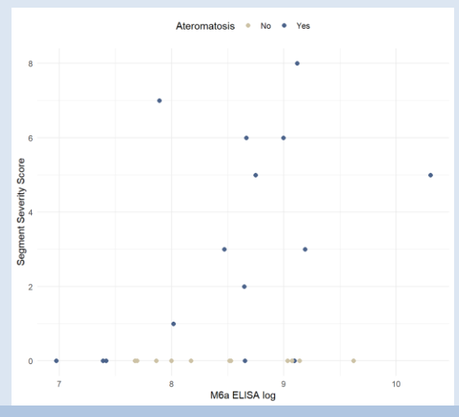
Table 1: Demographic, clinical and epigenetic parameters by presence of plaque

	Overall n=27	Without CAD n=12	CAD n=15	p
Age, median (IQR)	57 (52-64)	56 (52-61)	58 (56-65)	0.31
Male (%)	22 (81.5)	11 (91.7)	11 (73.3)	0.47
Caucasian (%)	23 (85.2)	11 (91.7)	12 (80)	0.59
CD4 count cell/mm³, median (IQR)	659 (480-794)	496 (429-828)	750 (575-794)	0.33
CD4:CD8 ratio, median (IQR)	0.7 (0.5-1.4)	0.6 (0.5-1.3)	0.77 (0.5-1.4)	0.69
ART duration years, median (IQR)	8.04 (5.6-18.9)	7.0 (4.7-10.9)	8.5 (7.0-20.7)	0.33
Cumulative exposure PI months, median (IQR)	0 (0-20)	0 (0-0)	3 (0-54)	0.09
Diabetes (%)	9 (33.3)	2 (16.7)	7 (46.7)	0.29
Hypertension (%)	16 (59.3)	6 (50)	10 (66.7)	0.63
Dyslipemia (%)	23(85.2)	8 (66.7)	15 (100)	0.06
BMI, median (IQR)	25.9 (23.5-27.3)	25.9 (24.6-27.5)	25.5 (23.4-26.7)	0.35
Current smoker (%)	7 (25.9)	3 (25.0)	4 (26.7)	0.24
Prior statin use (%)	20 (74)	6 (50)	14 (93)	0.03
Cardiovascular risk SCORE-2, median (IQR)	6.0 (4.05-8.80)	5.5 (3.3-7.5)	6.75 (5.2-10.75)	0.14
LDL cholesterol mg/dl, median (IQR)	92 (80-115)	111 (83-130)	90 (80-94)	0.26
HDL cholesterol mg/dl, median (IQR)	42 (35-52)	48 (41-58)	37 (32-48)	0.08
M6a ELISA log median (IQR)	8.53 (7.8,9.05)	8.3 (7.8,9.0)	8.65 (7.9,9.0)	0.69
Methyl_ABCA1% median (IQR)	19.6 (15.4-22.2)	18.0 (11.6-21.9)	19.88 (16.2-23.6)	0.15
ABCA1 gene expresión delta Ct, median (IQR)	7.6 (6.8-8.1)	7.6 (6.8-8.0)	7.4 (6.6-8.0)	0.92

Table 2: Characteristics of Coronary CT angiography

Variable	Participants with coronary plaque (n=15)
Calcified plaque score n (%):	
1-2 segments with calcified plaques	6 (40)
≥3 segments with calcified plaques	4 (26.6)
Noncalcified plaque score n (%):	
1-2 segments with noncalcified plaques	10 (66.6)
≥3 segments with noncalcified plaques	1 (6.6)
Participants with vulnerable plaque features n (%)	9 (60)
Stenosis	
Participants with stenosis 50-69%	4 (26.7%)
Participants with stenosis ≥70%	3 (20%)
CAC score n (%)	
1-100	6 (40)
101-400	6 (40)
>400	3 (20)
Segment severity score, mean (SD)	3.07 (2.89)
Segment involvement score, mean (SD)	2.87 (1.85)
Leaman score	
Mean (SD)	6.80 (2.68)
0-5	5 (33.3)
>5	10 (66.7)





Results

- A total of 27 PWH were included: median (P25-75) age 57 years (52-64), 81.5% male, 85% Caucasian, CD4+ T cell count 659 cells/mm^3 (480-794), CD4:CD8 ratio 0.76 (0.52-1.48), 100% HIV-RNA < 50 cp/ml.
- Median SCORE-2 risk score 6% (4.05-8.80). Cardiovascular risk factors: 59.3% had hypertension, 85% dyslipidemia, 33% diabetes, and 26% were active smokers.
- Fifteen (55%) participants had coronary atherosclerosis (defined as the presence of coronary plaque in at least one coronary segment on CCTA).Mean (SD) calcium score (Agatson) was 188.5 (168.2). Plaque burden indexes were: segment severity score 3.07 (2.89), segment involvement score 2.87 (1.85), and Leaman score 6.80 (2.68). Ten participants (67%) had a high coronary plaque burden (Leaman score > 5). Vulnerable high-risk plaque features were observed in 60% of the participants.
- Epigenetic markers were correlated with coronary plaque burden. We found a moderate correlation between ABCA1 methylation and Leaman score (Spearman rho=0.37; p = 0.06), and N6-methyladenine DNA and Segment Severity Score (Spearman rho = 0.33; p = 0.09). ABCA1 methylation was negatively correlated and total plaque volume (Spearman rho= -0.63; p < 0.001). Although we did not found differences in global ABCA1 methylation, there were 6 positions associated with coronary atherosclerosis. In the multivariate analysis methylation in six positions in the ABCA1 gen was independently associated with coronary artery atherosclerosis [OR 1.06 (95% CI 1.01-1.12); p=0.046].

Conclusion

In this small exploratory study, ABCA1 methylation was independently associated with coronary artery disease in PWH. Further research is required to explore the role of epigenetic biomarkers in PWH with coronary artery disease.