Association between osteogenesis and inflammation evaluated by 18F-NaF and 18F-FDG PET/CT in HIV infected patients

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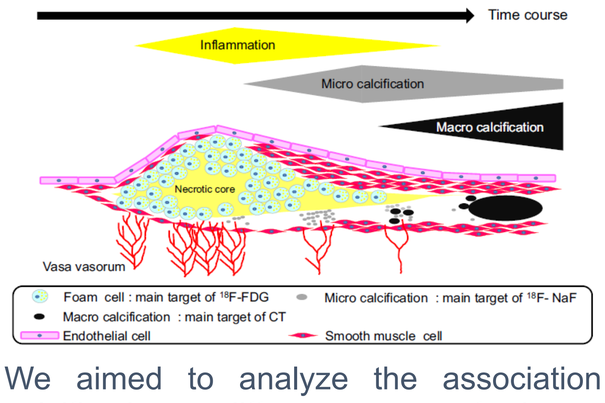
Background

Initiation and progression of atherosclerotic plaque is a dynamic and complex process involving various pathophysiologic steps including inflammation and calcification.



Formation and progression of atherosclerotic plaque is a complex process involving both inflammation and calcification that may be detected by ^{18}F-FDG and ^{18}F-NaF PET/CT, respectively.

Figure 1. *Pathogenesis of atherosclerosis*

We aimed to analyze the association between inflammation and vascular calcification at different stages of atherosclerosis, as well as the interrelationship between these two processes during HIV disease progression.

Methods

Eighty-two HIV-positive patients with undetectable viral load who underwent two coronary CT at least 2 years apart for evaluation of coronary artery calcium (CAC) progression were enrolled. 50 patients were examined by whole-body^{18}F-sodium fluoride (^{18}F-NaF) PET, and 32 with ^{18}F-FDG PET.

Tracer uptake in various arterial segments was analyzed both qualitatively and semi-quantitatively by measuring the blood-pool–corrected standardized uptake value (target-to-background ratio [TBR]) using 1.6 cut-off value for both ^{18}F-NaF PET and ^{18}F-FDG PET.

The Fisher exact test and the Spearman correlation coefficient were used for statistical correlation of tracer uptake with CAC=0, progression and non-progression of CAC. CAC progression was defined as: initial CAC=0 followed by CAC≥ 30, or initial CAC ≥ 30 followed by>15%increase yearly.

Results

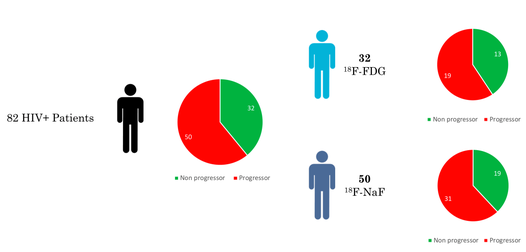
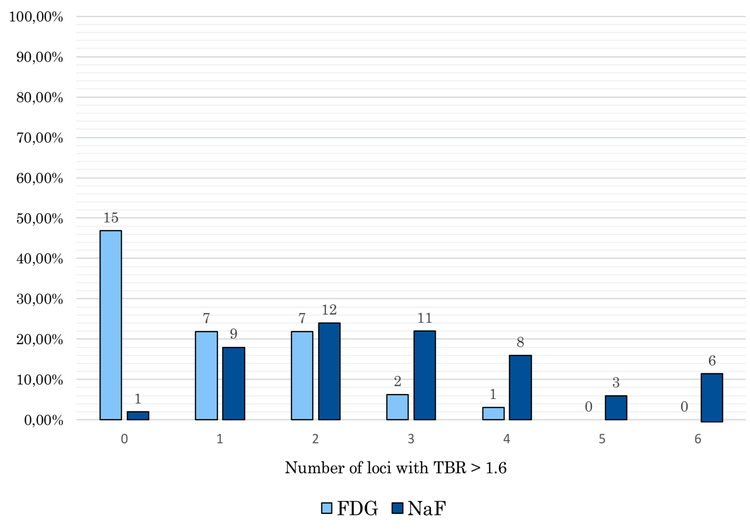


Figure 2. *Study population and distribution according to CAC score.*

- Median age of 56 years
- 71 (86%) males, 11 (14%) females
- ASCVD mean value of 10.29
- Mean duration of infection - 283 months and excellent viro-immunological control (100% presented HIV-RNA < 40 c/mL)



	Area	TBR_{mean}
FDG	Aortic arc	1,42 ± 0,32
	Innominate artery	1,18 ± 0,29
	Right coronary	1,20 ± 0,24
	Left coronary	1,26 ± 0,22
	Right carotid	1,38 ± 0,34
	Left carotid	1,39 ± 0,40
		1.35 ± 0.36
NaF	Aortic arc	1,65 ± 0,52
	Innominate artery	1,66 ± 0,49
	Right coronary	1,65 ± 0,41
	Left coronary	2,08 ± 0,66
	Right carotid	1,69 ± 0,80
	Left carotid	1,64 ± 0,66
		1.75 ± 0.62

Figure 3. *Distribution uptake of 18F-FDG and 18F-NaF PET/CT based on the number of loci with a TBR > 1.6.*

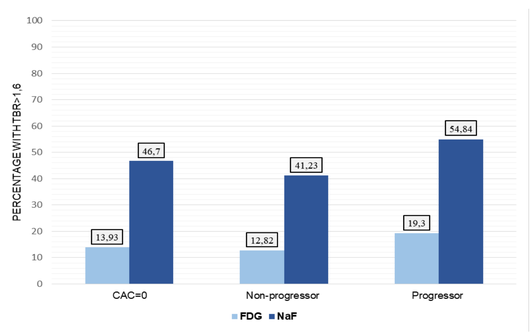


Figure 4. *Distribution in progressor, non-progressor and CAC=0 of the population performing ^{18}F-FDG or ^{18}F-NaF PET/CT stratified by each analysed area TBR > 1.6*

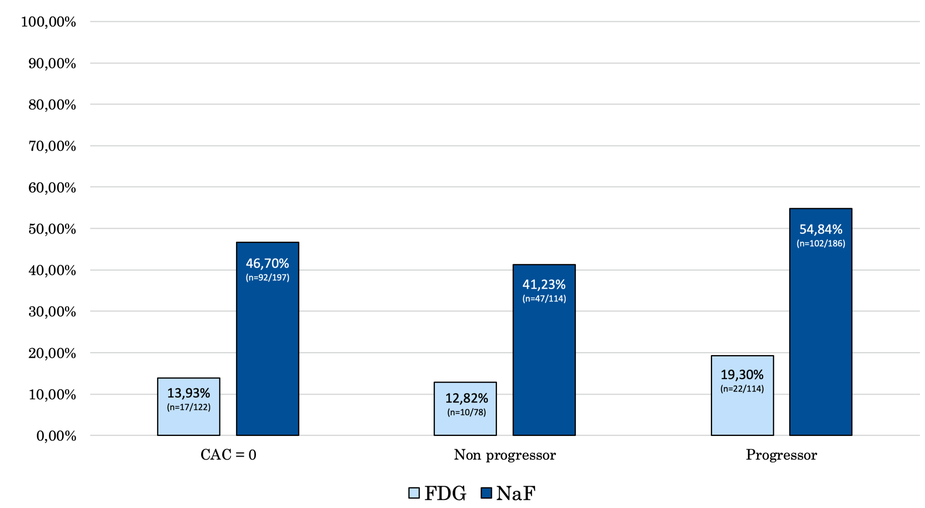
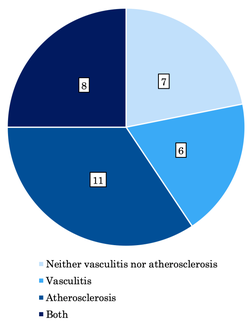


Figure 5. *Uptake percentage of ^{18}F-FDG and ^{18}F-NaF by analysed areas stratified for CAC=0, non-progressor and progressor.*

Table 1. *Prevalence and predictors of CAC non-progressor and progressor in all vascular sites.*

Both ^{18}F-FDG ^{18}F-NaF	Total	Non- progressor	Progressor	p
Patients	82	32 (39.02%)	50 (60.98%)	
	32	13	19	
	50	19	31	
Age, years, (SD), [N]	56.52 (7.1) [82]	52.5 (4.54) [32]	59.1 (7.28) [50]	<0.00001
	55.62 (5.81) [32]	52.46 (4.59) [13]	57.79 (5.64) [19]	0.00842
	57.1 (7.82) [50]	52.53 (4.64) [19]	59.9 (8.1) [31]	0.00017
Male gender (%)	71 (86.59%)	25 (78.12%)	46 (92%)	0.14259
	29 (90.6%)	12 (92.3%)	17 (89.5%)	0.99
	42 (84%)	13 (68.4%)	29 (93.5%)	0.05057
ASCVD risk score, (SD), [N]	10.29 (9.57) [35]	7.28 (6.08) [17]	13.13 (11.43) [18]	0.07471
	10.28 (9.53) [18]	7.16 (5.26) [8]	12.77 (11.6) [10]	0.32838
	10.31 (9.9) [17]	7.39 (7.05) [9]	13.59 (11.99) [8]	0.21096
Previous CVD (%)	11 (13.41%)	4 (12.5%)	7 (14%)	0.99
	4 (12.5%)	3 (23.1%)	1 (5.26%)	0.34094
	7 (14%)	1 (5.26%)	6 (19.3%)	0.33004
Type 2 diabetes (%)	30 (36.59%)	11 (34.38%)	19 (38%)	0.92238
	16 (50%)	6 (46.1%)	10 (52.6%)	0.99
	14 (28%)	5 (26.3%)	9 (29%)	0.99
BMI, kg/m^2, (SD), [N]	25.37 (3.98) [78]	25.8 (4.1) [29]	25.12 (3.94) [49]	0.46882
	24.41 (3.59) [31]	26 (4.12) [12]	23.4 (2.89) [19]	0.0475
	26.01 (4.14) [47]	25.66 (4.2) [17]	26.2 (4.16) [30]	0.6678
Chronic kidney disease (%)	31 (37.8%)	8 (25%)	23 (46%)	0.09304
	12 (37.5%)	3 (23.1%)	9 (47.4%)	0.30664
	19 (38%)	5 (26.3%)	14 (45.2%)	0.30186
Multimorbidity (%)	50 (60.98%)	12 (37.5%)	38 (76%)	0.00114
	18 (56.2%)	5 (38.5%)	13 (68.4%)	0.18848
	32 (64%)	7 (36.8%)	25 (80.6%)	0.00468
Nadir CD4, c/μL, median, (IQR), [N]	189.5 (96.5 - 304.75) [76]	198.5 (134.25 - 423.5) [28]	167.5 (56.5 - 289.5) [48]	0.06959
	161 (78 - 252) [29]	175 (120 - 198.75) [10]	136 (61 - 276) [19]	0.73069
	200 (107.5 - 324) [47]	249.5 (142.75 - 430.5) [18]	170 (59 - 286) [29]	0.01734
CD4/CD8 ratio, (SD), [N]	0.94 (0.43) [76]	0.99 (0.43) [28]	0.91 (0.43) [48]	0.29122
	0.89 (0.46) [27]	0.97 (0.55) [10]	0.85 (0.42) [17]	0.40734
	0.97 (0.41) [49]	1.01 (0.37) [18]	0.94 (0.44) [31]	0.6012
HIV duration, months, median, (IQR), [N]	283 (212.75 - 365.5) [82]	281 (154.75 - 335.75) [32]	283 (252.5 - 374.5) [50]	0.0981
	290.5 (228.2 - 376.2) [32]	302 (166 - 329) [13]	279 (264.5 - 376.5) [19]	0.33735
	277.5 (191.25 - 354) [50]	267 (113 - 340) [19]	287 (239.5 - 358.5) [31]	0.18708



Qualitative radiological interpretation of PET FDG included description of several vasculitis areas thus, we have hypothesized a correlation between vasculitis, which is considered by some authors a risk factor for the developing of cardiovascular diseases and atherosclerosis.

Figure 6. *Prevalence of vasculitis, atherosclerosis or both*

Table 2. *Predictors of of vasculitis, atherosclerosis or both.*

	Total	Atherosclerosis	Both	Vasculitis	p
Patients	25	11 (44%)	8 (32%)	6 (24%)	
Age, years, (SD), [N]	56.36 (6.13) [25]	57.55 (6.58) [11]	58.12 (4.45) [8]	51.83 (5.78) [6]	0.11103
Male gender (%)	22 (88%)	10 (90.91%)	7 (87.5%)	5 (83.33%)	0.89862
ASCVD risk score (SD), [N]	11.5 (10.66) [13]	13.51 (14.02) [7]	11.05 (3.13) [3]	7.25 (6.47) [3]	0.82053
Hypertension (%)	20 (80%)	9 (81.82%)	7 (87.5%)	4 (66.67%)	0.6155
Previous CVD (%)	2 (8%)	1 (9.09%)	0 (0%)	1 (16.67%)	0.51537
Statine therapy (%)	6 (24%)	1 (9.09%)	2 (25%)	3 (50%)	0.16792
Triglycerides, mg/dl, (SD), [N]	173.14 (157) [21]	174.91 (210.37) [11]	157 (48.32) [6]	192.5 (109.05) [4]	0.12231
Type 2 diabetes (%)	13 (52%)	6 (54.55%)	4 (50%)	3 (50%)	0.97483
BMI, kg/m^2, (SD), [N]	24.54 (3.72) [25]	23.56 (2.27) [11]	23.18 (3.73) [8]	28.15 (4.01) [6]	0.01673
Nadir CD4, c/μL, median, (IQR), [N]	163.5 (84 -264) [24]	100 (69 -316.5) [11]	209 (59.25 -224.25) [8]	189 (138 -199) [5]	0.75382
CD4/CD8 ratio, (SD), [N]	0.85 (0.39) [22]	1.01 (0.44) [11]	0.56 (0.16) [6]	0.87 (0.32) [5]	0.04932
Current CD4 %, (SD), [N]	31.82 (8.83) [23]	35.25 (9.36) [11]	24.6 (4.25) [6]	32.75 (7.75) [6]	0.04856
Current CD8 %, (SD), [N]	41.04 (9.36) [23]	38.01 (9.6) [11]	45.38 (9.16) [6]	42.25 (8.52) [6]	0.29243
HIV duration, months, median, (IQR). [N]	302 (264 - 377) [25]	270 (264.5 -318.5) [11]	382 (315 -390) [8]	312.5 (245 -369.5) [6]	0.21161
Multimorbidity (%)	16 (64%)	6 (54.55%)	7 (87.5%)	3 (50%)	0.23994

Conclusions

- This study did not find a strong positive correlation between ^{18}F-FDG or ^{18}F-NaF TBR and the CAC progression in HIV-infected patients.
- ^{18}F-FDG and ^{18}F-NaF PET are not useful for cardiovascular risk stratification in clinical practice but may play a role in the interpretation of specific pathogenesis of cardiovascular disease.
- ^{18}F-FDG and ^{18}F-NaF PET do not identify classic cardiovascular risk factors; these methods can recognize unknown cardiovascular risk factors that do not correlate with the traditional characteristics that describe HIV disease.
- Challenge for PET diagnostic is to identify new tracers that can better correlate with the pathogenesis of CVD and provide new insight mechanism of disease progression.

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