Role of Renin-Angiotensin-Aldosterone System Activation in Arterial Inflammation in HIV

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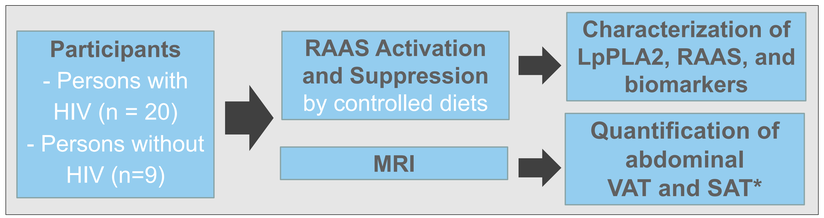
BACKGROUND

- Arterial inflammation is increased in persons with HIV (PWH) compared to persons without HIV (PWOH), even when controlling for traditional risk factors.
- PWH are also at increased risk of atherosclerotic cardiovascular disease (CVD) compared to PWOH, even when well-treated with antiretroviral (ART) medications.
- While there are data demonstrating inflammatory-mediated CVD among PWH, little is known of the mechanistic role of inflammation in CVD.
- We previously demonstrated that PWH have increased aldosterone and markers of generalized inflammation during activation of the renin-angiotensin-aldosterone system (RAAS).
- We assessed whether lipoprotein-associated phospholipase-A2 (LpPLA2), a marker of arterial inflammation, was related to RAAS activation among PWH.

METHODS

i. Study Participants and Design

Figure 1. *Study Schema*



**VAT = visceral adipose tissue, SAT = subcutaneous adipose tissue*

- Inclusion criteria for all participants: age ≥ 18 and ≤ 65 years
- Inclusion criteria for participants with HIV: stable ART regimen ≥ 3 months
- Exclusion criteria for all participants: history of CVD, current tobacco use, current antihypertensive or RAAS-blocking medication use, creatinine >1.5mg/dL, potassium >5.5 mEq/L, ALT >2.5x upper normal limit, estrogen or progesterone use within past 3 months

ii. Metabolic Evaluation

- Participants followed a 6-day low salt diet to simulate RAAS activation. After approximately a month, participants followed a 6-day high salt diet using broth packets to simulate RAAS suppression.
- Serum LpPLA2 was measured by ELISA.

iii. Statistics

- Distribution was evaluated by the Anderson-Darling test.
- The Wilcoxon signed rank and Kruskal-Wallis tests were used to compare within and between serostatus groups, respectively.
- Univariate analysis of LpPLA2 was assessed using Pearson's correlation coefficient within group after log transformation was applied to non-normally distributed variables.
- Statistical significance was defined as P≤0.05.

RESULTS

Table 1. *Baseline Demographic and Clinical Characteristics of Persons with and without HIV*

	Persons without HIV	Persons with HIV	P Value
Demographics			
Age (years)	51.4 ± 2.4	48.9 ± 1.5	0.39
Race (%)			0.22
Caucasian	78	45	
African American	22	35	
Other	0	20	
Male Sex (%)	66.7	65.0	0.93
HIV Parameters			
CD4⁺ T cell count (cells/mL)	--	571.5 ± 72.6	--
Log_{10} HIV RNA Viral Load (copies/mL)	--	1.8 ± 0.2	--
Duration HIV (years)	--	18.4 ± 1.5	--
Duration ART use (years)	--	10.9 ± 1.2	--
Current PI use (%)	--	60	--
Duration PI (years)	--	9.3 ± 1.7	--
Current NRTI use (%)	--	90	--
Duration NRTI (years)	--	10.6 ± 1.3	--
Current NNRTI use (%)	--	25	--
Duration NNRTI (years)	--	9.1 ± 2.1	--
History of HCV infection (%)	0.0	20.0	0.07
Body Composition and Metabolic Parameters			
Iliac Waist Circumference (cm)	90.5 ± 4.3	94.1 ± 3.5	0.53
BMI (kg/m²)	25.8 ± 1.1	26.1 ± 1.3	0.88
VAT (cm²)	140 ± 26	140 ± 20	1.00
SAT (cm²)	222 (130, 287)	209 (107, 342)	1.00
Systolic Blood Pressure (mmHg)	119 (115, 125)	124 (116,138)	0.28
Diastolic Blood Pressure (mmHg)	80 (69, 82)	79 (68, 84)	0.71
Total Cholesterol (mg/dL)	174 ± 13	181 ± 8	0.65
HOMA-IR	1.6 ± 0.6	1.5 ± 0.2	0.88
Creatinine (mg/dL)	0.80 ± 0.04	0.85 ± 0.03	0.37
Potassium (mmol/L)	4.1 (3.9, 4.4)	4.0 (3.9, 4.1)	0.44

Table 2. *Comparison of RAAS Activation between Ad Libitum and Low Sodium Conditions Within and Between Groups of Persons with and without HIV*

	Low Sodium Conditions	Ad Libitum Sodium Conditions	Change Between Ad Libitum and Low Conditions	Within Group Change P Value
LpPLA2 (ng/mL)				
Persons without HIV	179.9 (132.8, 214.8)	171.5 (151.6, 183.8)	14.9 (-7.9, 32.0)	0.30
Persons with HIV	237.3 (190.1, 276.5)	196.5 (173.3, 240.1)	26.1 (-5.2, 51.3)	**0.03**
Between Group Change P Value	**0.01**	**0.01**	0.44	
Serum Aldosterone (ng/dL)				
Persons without HIV	9.1 (7.4, 12.8)	2.5 (2.5, 4.0)	5.4 (4.8, 9.3)	**0.004**
Persons with HIV	13.8 (9.7, 30.9)	2.6 (2.5, 3.5)	10.2 (7.2, 26.4)	**0.0001**
Between Group Change P Value	**0.02**	0.92	**0.005**	

Table 3. *RAAS Parameters During Low Sodium and Ad Libitum Sodium Conditions among Persons with and without HIV*

	Persons without HIV	Persons with HIV	P Value
RAAS Parameters During Low Sodium Conditions			
24 hour Urine Sodium (mmol/24 hour)	18.3 (13.1, 26.1)	14.2 (11.1, 34.0)	0.49
Mean Arterial Pressure (mmHg)	86 (82, 88)	86 (80, 89)	0.87
Potassium (mmol/L)	4.1 (4.0, 4.3)	4.1 (4.0, 4.4)	0.60
RAAS Parameters During Ad Libitum Sodium Conditions			
24 hour Urine Sodium (mmol/24 hour)	264.0 (217.5, 436.5)	270.0 (188.5, 358.3)	0.65
Mean Arterial Pressure (mmHg)	87 (86, 100)	87 (83, 93)	0.38
Potassium (mmol/L)	4.1 (4.0, 4.3)	4.1 (3.9, 4.3)	0.86

Table 4. *Relationship of Body Composition and Metabolic Parameters to LpPLA2 Among Persons with and without HIV During the RAAS Activated State*

	All Participants		Persons without HIV		Persons with HIV	
	r	P Value	r	P Value	r	P Value
Age (years)	-0.21	0.27	0.03	0.94	-0.25	0.29
Iliac Waist Circumference (cm)	0.30	0.11	0.23	0.54	0.32	0.17
BMI (kg/m²)	0.23	0.22	0.09	0.81	0.33	0.15
VAT (cm²)	0.33	0.08	0.24	0.54	0.46	**0.04**
Log SAT (cm²)	0.11	0.56	0.33	0.39	0.04	0.86
Log Systolic Blood Pressure (mmHg)	0.45	**0.01**	0.25	0.51	0.57	**0.009**
Log Diastolic Blood Pressure (mmHg)	0.23	0.23	0.06	0.87	0.39	0.09

SUMMARY

- Both groups demonstrated a significant increase in aldosterone levels in the RAAS-activated state compared to the RAAS-suppressed state, but aldosterone levels were significantly higher among PWH than PWOH in a RAAS-activated state (**Table 2**).
- LpPLA2 levels were significantly higher in PWH than in PWOH during both the RAAS activated and RAAS suppressed states (**Table 2**). The increase in LpPLA2 during RAAS activation compared to RAAS suppression was only significant in PWH (**Table 2**). LpPLA2 levels during the RAAS suppressed state among PWH remained relatively higher than the LpPLA2 levels under both conditions among PWOH.
- Among all participants, log LpPLA2 was significantly related to aldosterone during the RAAS activated state (r=0.39, P=.04).
- Among PWH during RAAS activation and with increased aldosterone, LpPLA2 was significantly correlated to VAT and systolic blood pressure and tended to be related to diastolic blood pressure (**Table 4**).

CONCLUSIONS

- Our results demonstrate that LpPLA2 is increased with RAAS activation and correlates with aldosterone during RAAS activation in PWH, compared to PWOH. These data suggest a unique biologic association between aldosterone and arterial inflammation in PWH.
- While higher sodium levels typically mediate hypertension and contribute to vascular injury, our results show that LpPLA2 increased in relationship to aldosterone and blood pressure during a sodium restrictive state (RAAS activated state). These data suggest that aldosterone, as opposed to sodium, is the mediator of arterial inflammation. Increasing LpPLA2 with RAAS activation may be one mechanism of vascular injury in PWH.
- Our previous studies have demonstrated increased aldosterone during RAAS activation in PWH with increased VAT and also an association between VAT and LpPLA2. Here, we draw a potential relationship connecting all three variables of VAT, aldosterone, and arterial inflammation. The increased and chronic inflammation of the visceral adipose depot may be linked to cytokine production and RAAS activation and promote arterial inflammation.

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