The Journal of Infectious Diseases

BRIEF REPORT

Serum Lipocalin 2 (Neutrophil Gelatinase–Associated Lipocalin) in Relation to Biomarkers of Inflammation and Cardiac Stretch During Activation of the Renin-Angiotensin-Aldosterone System in Human Immunodeficiency Virus

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Purpose: To evaluate the relationship of lipocalin 2 to inflammation and cardiac injury with increased aldosterone in human immunodeficiency virus (HIV).

Methods: A standardized 6-day low-sodium diet was used to stimulate renin-angiotensin-aldosterone system (RAAS) activation, and serum lipocalin 2 and biomarkers of inflammation and cardiac stretch were assessed among persons with or without HIV.

Results: Lipocalin 2 levels increased with RAAS activation compared with suppression in the HIV group (median level [interquartile range], 71.3 [59.2–99.7] vs 67.0 [51.8–86.3] ng/mL; $P = .01$). During RAAS activation, lipocalin 2 was related to biomarkers of inflammation (tumor necrosis factor α [$P = .007$]), monocyte/macrophage activation (soluble CD163 [$P = .005$] and chemokine [C-C motif] ligand 2 [$P = .03$]), and markers of cardiac stretch (brain natriuretic peptide [$P < .001$] and N-terminal fragment of the prohormone brain natriuretic peptide [$P = .001$]) in HIV.

Conclusion: Lipocalin 2 may be important in modulating aldosterone-induced inflammation, monocyte activation, and cardiac stretch during RAAS activation in HIV.

Clinical Trial Registration: NCT01407237

Keywords. HIV; renin-angiotensin-aldosterone system; lipocalin 2; inflammation; BNP.

Subclinical heart disease is prevalent and a leading contributor to morbidity and mortality in human immunodeficiency virus (HIV). We have previously demonstrated increased aldosterone in association with heightened inflammation and monocyte/macrophage activation among persons with HIV (PWH) compared to persons without HIV (PWOH) during a renin-angiotensin-aldosterone system (RAAS)–activated state [1, 2]. Aldosterone, a mineralocorticoid, is involved in physiologic processes related to sodium homeostasis and volume handling. In contrast, inappropriate mineralocorticoid activation may contribute to cardiovascular disease (CVD). Aldosterone may have detrimental effects on cardiac structure and function via mineralocorticoid receptor signaling and downstream inflammation and fibrosis.

Lipocalin 2, also known as *neutrophil gelatinase–associated lipocalin,* is a 25-kDa glycoprotein initially discovered as a secretory protein in neutrophils. Subsequently, lipocalin 2 was identified as being expressed in a variety of other cells, including macrophages, adipocytes, smooth muscle cells, endothelial cells, and cardiomyocytes [3, 4], all critical to cardiovascular function. Studies have also demonstrated a potential association between lipocalin 2 and inflammation in the assessment of CVD risk [5, 6].

Lipocalin 2 may be a target gene of the mineralocorticoid receptor, and thus aldosterone may increase lipocalin 2 levels by way of mineralocorticoid receptor binding on the lipocalin 2 gene promoter site [7]. This suggests that lipocalin 2 may be important to the RAAS pathway and a key contributor to inflammatory-mediated CVD in the setting of RAAS activation. To begin to understand the relationship between lipocalin 2 and aldosterone in HIV, we assessed the response of lipocalin 2 and its association with markers of inflammation, monocyte/macrophage activation, and cardiac stretch during RAAS activation, as compared with RAAS suppression, among both PWH and PWOH.

METHODS

Study Participants

Twenty PWH and 10 PWOH were recruited from the Greater Boston area through medical providers and local advertisements as part of a prospective study to assess RAAS physiology. Study criteria for inclusion and exclusion were identical regardless of serostatus [1]. The 2 groups were selected to be of comparable age (18–65 years) and sex. The PWH included had stable antiretroviral therapy (ART) use for ≥3 months. Individuals were excluded for history of known CVD (including congestive heart failure), current tobacco use, pregnancy, current use of antihypertensive or RAAS-related medications, evidence of renal disease (urine protein >1 g/d or creatinine >1.5 mg/dL), potassium >5.5 mEq/L, or liver disease (alanine aminotransferase level >2.5 times the upper

Received 19 April 2019; editorial decision 1 July 2019; accepted 10 July 2019; published online July 11, 2019.

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The Journal of Infectious Diseases® 2019;220:1420–4

DOI: 10.1093/infdis/jiz346

limit of normal). Individuals were excluded for the use of hormone replacement therapy containing estrogen or progesterone within 3 months of participation.

This study was approved by the institutional review board of the Partners Human Research Committee. All individuals provided informed consent for participation.

Standardized Diets to Stimulate RAAS Activation

Participants were asked to consume a standardized 6-day low-sodium diet (mean ± standard error of the mean (SEM) content, 10 ± 2 mEq sodium, 100 ± 2 mEq potassium, and 1000 ± 50 mg calcium) to stimulate RAAS activation. A urine aliquot was collected to measure sodium levels and confirm adherence to the diet, and appropriate conditions were achieved if the aliquot predicted a 24-hour urine sodium level <50 mEq. A formal 24-hour collection for urine sodium was also completed. In contrast, to suppress RAAS, study participants were asked to consume a 6-day liberal sodium diet by supplementing their usual diet with 3 broth packets daily (47.8 mEq sodium per packet) to achieve a dietary sodium intake >200 mEq/d. All low-sodium diets were prepared by the Metabolic Kitchen at Brigham and Women's Hospital Center for Clinical Investigation. To assess the impact of RAAS activation, aldosterone and lipocalin 2 levels were compared during alternate conditions of RAAS simulation and suppression.

Characterization of Lipocalin 2, RAAS, and Biomarkers

Enzyme-linked immunosorbent assay (ELISA) was used to measure serum lipocalin 2 (R&D Systems), high-sensitivity interleukin 6 (R&D Systems), tumor necrosis factor α (TNF-α; R&D Systems), high-sensitivity C-reactive protein (Labcorp), soluble CD163 (sCD163; Trillium Diagnostics), chemokine (C-C motif) ligand 2 (CCL-2; R&D Systems), atrial natriuretic peptide (Ray Biotech), and brain natriuretic peptide (BNP; Ray Biotech). Serum N-terminal fragment of the prohormone BNP (NT-proBNP; sensitivity, 5 pg/mL) was assessed by means of the Cobas electrochemiluminescence immunoassay technique (Roche Diagnostics).

Serum aldosterone was measured using a solid-phase radioimmunoassay with the Coat-A-Count method (Diagnostics Products). Plasma renin activity was assayed using the GammaCoat iodine 125 radioimmunoassay kit (Diasorin). Serum and plasma samples were obtained while participants were in a supine position overnight and had fasted for 12 hours after the 2 consumed diet protocols. Data evaluating RAAS activation in relation to visceral fat, inflammation, and natriuretic peptides among the same participants have been reported elsewhere [1, 2]. The current data assessing lipocalin 2 changes and relationship to inflammatory and cardiac stretch indices during RAAS activation have not previously been analyzed.

HIV-Related Parameters

HIV viral load was measured by ultrasensitive reverse-transcription polymerase chain reaction (Roche Cobas Amplicor system; lower limit of detection, 48 copies/mL). $CD4^+$ T-cell counts were assessed by flow cytometry.

Statistical Analysis

The distribution of variables was evaluated using the Shapiro-Wilk test. Log transformation was applied to nonnormally distributed variables, and these data are reported before log transformation to represent variables in a clinically relevant manner. Data are reported as mean ± SEM or median (interquartile range [IQR]) values. Categorical variables are shown as proportions.

Within-group and between-group comparisons were made using paired and unpaired *t* tests, respectively. Univariate correlations of lipocalin 2 were assessed using Pearson correlation coefficients within each group. Subsequent multivariate regression modeling was performed within the HIV group to elucidate the independent contributions of the low-sodium diet (independent variable 1) and the effects of lipocalin 2 (independent variable 2) on inflammatory and cardiac stretch indices (dependent variables) during RAAS activation. Statistical significance was defined as $P \leq .05$. All statistical analyses were performed using SAS JMP software (version 14.0).

RESULTS

Baseline Demographic and Clinical Characteristics

PWH and PWOH were of similar age (mean ± SEM, 49 ± 2 and 52 ± 2 years, respectively), and similar proportions were male in the 2 groups (65% and 70%). There were more white participants in the PWOH group than in the PWH group (80% vs 45%, respectively). Body mass index was similar in PWH and PWOH (mean ± SEM, 26.2 ± 1.3 vs 25.0 ± 1.1 kg/m^2, respectively). PWH had good immunologic control (mean ± SEM $CD4^+$ T-cell count and log HIV viral load, 571 ± 73 cells/μL and 1.77 ± 0.19 copies/mL, respectively), a long history of HIV, and long-term ART use (Table 1). Eighty percent of PWH had undetectable viral loads. Tenofovir disoproxil fumarate and abacavir use was reported in 50% and 35% of PWH, respectively.

Comparison of Aldosterone and Lipocalin 2 Physiology During RAAS Activation and Suppression by HIV Serostatus

Serum aldosterone was significantly increased during the RAAS-activated state compared with the RAAS-suppressed state in both PWH (median level [IQR], 13.8 [9.7–30.9] vs 2.6 [2.5–3.5] ng/dL) and PWOH (9.2 [7.6–13.6] vs 2.8 [2.5–3.9] ng/dL) (both $P < .001$), demonstrating adequate physiologic conditions to assess change in lipocalin 2 with RAAS activation. In parallel, lipocalin 2 levels were also significantly higher during RAAS activation than in a RAAS-suppressed state among PWH (median [IQR], 71.3 [59.2–99.7] vs 67.0 [51.8–86.3] ng/mL, respectively; $P = .01$). An overall similar pattern of increased lipocalin with RAAS activation was seen in PWOH (median [IQR], 69.2 [46.8–87.2] vs 55.0 [46.8–75.5] ng/mL during RAAS suppression; $P = .10$). The percentage change in lipocalin

Table 1. Demographic and Clinical Characteristics of Persons With or Without Human Immunodeficiency Virus

Characteristic	Persons Without HIV	Persons with HIV
Age, mean ± SEM, y	52 ± 2	49 ± 2
White race, %	80	45
Male sex, %	70	65
Prior tobacco use, %	30	40
BMI, mean ± SEM, kg/m^2	25.0 ± 1.1	26.2 ± 1.3
VAT area, median (IQR), cm^2	140 (84–184)	134 (56–188)
HIV-related parameters		
CD4$^+$ T-cell count, mean ± SEM, cells/μL	NP	571 ± 73
Log HIV RNA viral load, mean + SEM, copies/mL	NP	1.77 ± 0.19
Undetectable viral load, %	NA	80
Duration of HIV infection, mean ± SEM, y	NA	18 ± 1
Duration of ART use, mean ± SEM, y	NA	11 ± 1
Current TDF use, %	NA	50
Current abacavir use, %	NA	35
History of HCV infection, %	0	20

Abbreviations: ART, antiretroviral therapy; BMI, body mass index; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IQR, interquartile range; NA, not applicable; NP, not performed; SEM, standard error of the mean; TDF, tenofovir disoproxil fumarate; VAT, visceral adipose tissue.

2 values from a RAAS-activated to a RAAS-suppressed state did not differ by HIV status (median [IQR], 4.1% [−2.5%–17.0%] for PWH vs 7.8% [−3.4%–28.6%] for PWOH; $P = .95$).

Relationship of Lipocalin 2 to RAAS, Inflammatory and Cardiac Stretch Parameters During RAAS Activation by HIV Serostatus

Among PWH, lipocalin 2 was significantly and positively correlated with markers of inflammation TNF-α ($r = 0.59$; $P = .007$), sCD163 ($r = 0.61$; $P = .005$), and CCL-2 ($r = 0.49$; $P = .03$), as well as markers of cardiac stretch BNP ($r = 0.67$; $P < .001$) and NT-proBNP ($r = 0.68$, $P = .001$) with RAAS activation (Table 2). Stratification of these relationships among PWH by current tenofovir disoproxil fumarate and abacavir use are shown in Supplementary Table 2*A* and 2*B*. In contrast lipocalin 2 was not related to inflammatory or cardiac stretch parameters during RAAS activation among PWOH. There were no significant relationships between lipocalin 2 and RAAS parameters and renal indices in either group.

Independent Effects of Lipocalin 2 on Inflammatory and Cardiac Stretch Parameters During RAAS Activation in HIV

Lipocalin 2 was significantly and independently related to levels of TNF-α (β estimate, 0.0100; $P = .01$), sCD163 (13.9877;

Table 2. Relationship of Lipocalin 2 to Renin-Angiotensin-Aldosterone System (RAAS), Inflammatory and Cardiac Stretch Parameters in Persons With or Without Human Immunodeficiency Virus During RAAS Activation

	Relationship to Log Lipocalin 2 (ng/mL)[a]			
	Persons Without HIV		Persons With HIV	
Parameter	*r*	*P* Value	*r*	*P* Value
Log plasma renin activity (ng/mL/h)	0.18	.63	−0.31	.19
Log serum aldosterone (ng/dL)	0.30	.39	−0.36	.12
Urine sodium (mmol/24 h)	−0.27	.46	0.05	.83
Serum creatinine (mg/dL)	−0.11	.77	0.19	.42
eGFR (mL/min/1.73)	0.24	.50	−0.15	.54
Log IL-6 (pg/mL)	0.14	.71	0.36	.12
Log TNF-α (pg/mL)	−0.21	.56	0.59	.007
Log hsCRP (mg/L)	−0.01	.97	0.24	.32
Log sCD163 (ng/mL)	−0.14	.69	0.61	.005
Log CCL-2 (pg/mL)	−0.37	.29	0.49	.03
Log ANP (pg/mL)	0.10	.80	−0.01	.96
Log BNP (pg/mL)	0.20	.58	0.69	<.001
Log NT-proBNP (pg/mL)	−0.15	.68	0.68	.001

Abbreviations: ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide; CCL-2, chemokine (C-C motif) ligand 2; eGFR, estimated glomerular filtration rate; HIV, human immunodeficiency virus; hsCRP, high-sensitivity C-reactive protein; IL-6, interleukin 6; NT-proBNP, N-terminal fragment of the prohormone BNP; sCD163, soluble CD163; TNF-α, tumor necrosis factor α.

[a]Relationships were assessed based on Pearson correlation coefficients.

$P = .002$), CCL-2 (0.9772; $P = .008$), BNP (1.2326; $P = .01$), and NT-proBNP (0.6858; $P = .004$) among PWH after controlling for 24-hour urine sodium during the RAAS-activated state (Supplementary Table 3). Urinary sodium was not independently related to these markers of inflammation and cardiac stretch.

DISCUSSION

Our results demonstrate for the first time in PWH that lipocalin 2 is increased during RAAS activation, assessed under strictly controlled physiologic conditions, in association with critical markers of inflammation (TNF-α), monocyte/macrophage activation (sCD163 and CCL-2), and cardiac stretch (BNP and NT-proBNP). These data begin to inform us about a potential cascade in which RAAS activation may contribute to heart disease through mineralocorticoid receptor signaling and downstream activation of lipocalin 2 among the HIV population.

Few studies have evaluated lipocalin 2 in PWH, and these studies have demonstrated elevated levels in PWH compared with PWOH [8, 9]. Given compelling evidence for an interaction between RAAS and lipocalin 2, our well-controlled protocol assessing dynamic changes to dietary sodium manipulation was important in evaluating the link between aldosterone, mineralocorticoid receptor activation, lipocalin 2, and cardiac inflammation and injury. Importantly, the relationships between lipocalin 2, inflammation, and cardiac injury remained after controlling for urinary sodium. The relationships between lipocalin 2 and inflammation, monocyte/macrophage activation, and cardiac stretch were distinct to the PWH group and were not demonstrated among the PWOH group, suggesting a unique physiology linking mineralocorticoid receptor activation to lipocalin 2 among PWH, who demonstrate increased aldosterone.

Studies have shown that secretion of lipocalin 2 from immune cells is integral to mediating aldosterone-mediated changes in cardiac remodeling and inflammation. Cardiac levels of CCL-2 and TNF-α were increased after aldosterone stimulation, and those increases in aldosterone-induced cardiac inflammation were prevented after lipocalin 2 inactivation in immune cells [10]. Similarly, in the current study, we demonstrated that circulating lipocalin 2 is positively correlated with TNF-α and CCL-2 levels during an aldosterone-activated state among PWH. Lipocalin 2 may also function as part of a proinflammatory loop, both stimulating cytokine production and undergoing stimulation by cytokines. In this way, aldosterone could be the inciting factor for this cyclic lipocalin-related inflammatory process.

Animal studies have demonstrated that the mineralocorticoid receptor may control the transcription of lipocalin 2 on binding to the promoter site of lipocalin 2 [7]. Moreover, up-regulation of lipocalin 2 has been implicated in multiple pathologic CVD conditions, including atherosclerosis and myocardial dysfunction, and may be a predictive biomarker of heart failure prognosis [11], adverse CVD events [12], and deaths from cardiovascular causes [13]. Mineralocorticoid receptor blockade is effective in preclinical experiments at blunting aldosterone-induced increases in lipocalin 2 [14].

Lipocalin 2 is relatively increased after ischemic-induced left ventricular dysfunction. Furthermore, compared with wild-type mice, lipocalin 2–knockout mice after myocardial infarction have better preserved cardiac structure and function, demonstrating reduced left ventricular inflammation and fibrosis, greater left ventricular contractility and compliance, and higher stroke volume and cardiac output [14]. Although we were unable to assess cardiac structure and function in the current study, we did see an important positive correlation among the HIV group between lipocalin 2 and BNP, as well as NT-proBNP, which are well-established surrogates of cardiac injury. In addition, studies have demonstrated that lipocalin 2 mediates vascular fibrosis, and loss of lipocalin 2 in knockout mice prevents increases in blood pressure, blunts extracellular matrix remodeling, and may be protective of the profibrotic vascular phenotype [15].

Our study was exploratory and has some limitations. We studied a small group of individuals in a cross-sectional study. Causality cannot be inferred from these associations, and future studies that test mineralocorticoid receptor blockade may enhance our understanding of whether lipocalin 2 has beneficial effects on inflammation and specific indices of cardiac structure and function in HIV. Data regarding ART use are self-reported in the current study, and it may be important to formally assess the interaction between ART, RAAS, and lipocalin 2.

As the risk of heart disease continues to rise in the HIV population, additional pathophysiologic insight can help direct targeted treatment strategies to reduce CVD risk. Lipocalin 2 may be important for modulating aldosterone-induced inflammation, monocyte activation, and cardiac stretch among PWH, in whom we have demonstrated excess mineralocorticoid activation. Reducing lipocalin 2 levels could decrease cardiovascular injury in HIV.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Acknowledgments. The authors thank the nursing staff at the Massachusetts General Hospital Translational and Clinical Research Center and the Brigham and Women's Hospital Center for Clinical Investigation for their dedicated patient care and also thank the volunteers who participated in this study.

Disclaimer. Funding sources had no role in the design of the study, data analysis, or writing of the manuscript.

Financial support. This work was supported by the National Institutes of Health (grant R01DK49302 to G. K. A. and S. K. G. and K24 HL103845 to G. K. A.; Harvard KL2/Catalyst Medical Research Investigator Training (cMeRIT) award to S. S.; grant K23 HL136262 to S. S.; grants UL1 TR000170, UL1 RR025758, and UL1 TR001102 to the Harvard Catalyst/Harvard Clinical and Translational Science Center from the National Center for Research Resources and National Center for Advancing Translational Sciences; and grant P30 DK040561, a pilot and feasibility grant to the Nutrition and Obesity Research Center at Harvard University).

Potential conflicts of interest. K. V. F. and S. S. have been supported by an educational grant from Gilead Sciences and Merck to participate in a continuing medical education activity. G. K. A. has been a consultant for Pfizer and has received nonfinancial support from Valeant Pharmaceuticals. S. K. G. has received research funding from Gilead, KOWA, and Theratechnologies and has served as a consultant for Theratechnologies, all unrelated to the current work. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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