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PLASMA RENALASE AND ALL-CAUSE MORTALITY IN PEOPLE WITH AND WITHOUT HIV

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BACKGROUND

Renalase is a recently discovered secretory flavoprotein that promotes cell survival and growth, reduces inflammation and modulates immune cells. Growing evidence indicate that immune cells are the target of renalase signaling. Increased levels of renalase in tissue and plasma have been associated with advanced tumor characteristics and increased mortality in patients with pancreatic cancers. Renalase modulates immune recognition of and autoimmunity against murine beta cells by CD8+ T cells. Our objective was to examine plasma renalase in patients with HIV and determine its association with HIV viremia and mortality.

METHODS

We measured plasma renalase levels from participants in the Veterans Aging Cohort Study (VACS) Biomarker Cohort (2,361 participants with 1,532 with HIV and 829 without HIV), a subset of the VACS survey cohort of more than 7,200 (half with HIV, half without HIV matched by age, race/ethnicity, sex and enrollment site) enrolled between 2002 and 2006 from VA primary care and infectious disease clinics. In 2005 and 2006, patients in VACS were asked to donate a sample of blood for further testing. Plasma samples were pretreated with acid to expose an epitope of renalase that promotes cell survival and growth. Renalase levels were measured using enzyme-linked immunosorbent assay (ELISA). We performed a cross-sectional comparison of renalase by HIV status and HIV-1 RNA level using robust linear regression models. In Cox models, renalase levels were divided into quintiles with the lowest quintile used as reference. Both models were adjusted for age, renal function, hemoglobin, diabetes, liver fibrosis, hepatitis C, alcohol use, cardiovascular disease, lipids and soluble CD14.

Main findings:

- The plasma level of renalase, a recently discovered flavoprotein that promotes cell survival and growth, reduces inflammation and modifies immune cells, was significantly associated with HIV viremia and higher all-cause mortality among people with HIV.
- The higher plasma renalase may be an anti-inflammatory response to uncontrolled HIV viremia. Conversely, uncontrolled HIV viremia may be the result of suppression by renalase of the immune response to HIV.

RESULTS

Of 2,361 VACS Biomarker Cohort participants, mean (SD) age was 52 (9) years and 67% were Black and 5% were female. Median (interquartile range) plasma renalase was 9,307 [6,756 (Q1), 12,238 (Q3)] ng/ml among people with HIV and 8,716 [6,198 (Q1), 11,879 (Q3)] ng/ml among those without HIV. We did not detect a significant association of renalase and HIV status until HIV status was stratified by HIV-1 RNA which revealed a stepwise increase in renalase with HIV-1 RNA (Figure). In adjusted regression models, we found evidence that the association of renalase and mortality differed by HIV status (interaction p-value 0.08). The highest quintile (vs. lowest quintile) of renalase was associated with an increased risk of all-cause mortality in people with HIV (adjusted hazard ratio 1.70; 95% CI 1.18 - 2.27). The lower quintiles (vs. lowest quintile) of renalase in people with HIV and renalase in people without HIV were not significantly associated with mortality.

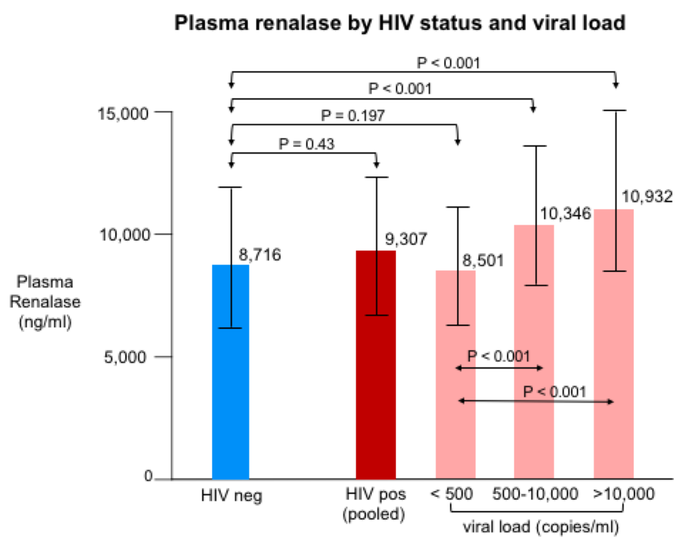

Figure. Results from robust linear regression models adjusting for covariates. Median (with interquartile ranges) of renalase levels shown.

Cox regression for mortality in people with HIV with renalase as predictor

Quintile	Renalase levels in each quintile (min, max) ng/ml	Hazard Ratio (95% CI)	P
1st	(436, 7,385)	reference	-
2nd	(7,386, 9,847)	1.21 (0.87, 1.68)	0.268
3rd	(9,849, 12,276)	1.38 (0.98, 1.93)	0.062
4th	(12,280, 15,820)	1.18 (0.84, 1.66)	0.347
5th	(15,822, 232,819)	1.70 (1.22, 2.37)	0.002

CONCLUSIONS

- Plasma renalase was significantly associated with HIV viremia and higher all-cause mortality among people with HIV.
- These novel findings suggest that renalase may modulate disease responses in HIV as in preclinical disease models.
- The higher plasma renalase may be an anti-inflammatory response to uncontrolled HIV viremia. Conversely, uncontrolled HIV viremia may be the result of suppression by renalase of the immune response to HIV.
- Further investigation should focus on understanding the role of renalase in HIV viral suppression and mortality

ADDITIONAL KEY INFORMATION

Additional Resources

1. Thomas Pointer, Fred Gorelick, Gary V. Desir. Renalase: A Multi-Functional Signaling Molecule with Roles in Gastrointestinal Disease. *Cells* 2021; 10, 2006
2. Erica P. Cai, Yuki Ishikawa, Wei Zhang, Nayara C. Leite, Jian Li, Shurong Hou, Badr Kiaf, Jennifer Hollister-Lock, Nese Kurt Yilmaz, Celia A. Schiffer, Douglas A. Melton, Stephan Kissler, Peng Yi. Genome scale *in vivo* CRISPR screen identifies *RNLS* as a target for beta cell protection in type 1 diabetes. *Nature Metabolism* 2020; 2(9): 934-945

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