Harpreet Kaur, Ph.D. | Genomic Medicine Institute, Lerner Research Institute, Cleveland Clinic | Cleveland, OH 44195 | (PH) (216) 444-8801 | kaurh2@ccf.org

00691

Ferritin And Transferrin Independently Reflect Renal Function In Virologically Suppressed Adults With HIV

Harpreet Kaur[1], Ronald J. Ellis[2], Donald R. Franklin, Jr.[3], Oluwakemi Okwuegbuna[4], Scott L. Letendre[5], Asha R. Kallianpur[1,6]

[1]Genomic Medicine Institute, Cleveland Clinic/Lerner Research Institute, Cleveland, OH; [2]Departments of Neurology & Psychiatry, University of California-San Diego, San Diego, CA; [3]Department of Psychiatry, University of California-San Diego, San Diego, CA; [4]Altman Clinical and Translational Research Institute, University of California-San Diego, San Diego, CA; [5]Departments of Medicine & Psychiatry, University of California-San Diego, San Diego, CA; [6]Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH.

CHARTER — CNS HIV Anti-Retroviral Therapy Effects Research

CNS HIV ANTI-RETROVIRAL THERAPY EFFECTS RESEARCH

OBJECTIVE

- To investigate plausible links between levels of iron-storage/iron-delivery proteins and chronic kidney disease (CKD) among adults with HIV (AWH) on suppressive antiretroviral therapy (ART).

BACKGROUND & SIGNIFICANCE

- HIV disrupts iron homeostasis (*e.g.*, ↑ intracellular iron), promoting viral replication and potentially inducing iron-mediated renal injury due to oxidative stress.[1, 2]
- Renal iron dyshomeostasis is an emerging factor in CKD.[2]
- Declining renal function and CKD are disorders of aging, which often co-occur with neurocognitive impairment (NCI)[3], suggesting a shared mechanism.
- AWH of African ancestry on ART experience a heightened risk of renal injury and 2-20-fold increased rates of end-stage renal disease requiring hemodialysis.[3]
- Previously, we associated higher cerebrospinal fluid (CSF) levels of the iron-binding, antioxidant proteins H-ferritin and transferrin (TF) with better neurocognitive function over time in AWH.[4]
- The purpose of this study was to investigate the role of iron-related proteins in renal function in AWH.

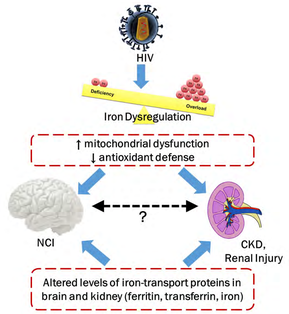


Figure 1: Possible shared mechanisms of CKD and NCI pathogenesis in AWH.

HYPOTHESIS

Iron-regulatory proteins are potential markers of renal function and/or renal injury in AWH.

METHODS

Study Participants

- Parent HIV study (CHARTER): >1500 AWH, who had comprehensive neuropsychiatric testing, assignment of a Global Deficit Score (GDS)[5], evaluation of comorbid conditions, and routine serum chemistries [blood urea nitrogen (BUN), creatinine, serum albumin]
- 94 virologically suppressed AWH (<50 HIV RNA copies/mL) without neuro-confounding comorbidities, ongoing drug abuse, or opportunistic infections

Biomarker Quantification

- Blood was obtained by venipuncture for serum assays.
- **Iron** - QuantiChrom™ colorimetric assay; **TF, soluble TF receptor (sTFR), ferritin, β2-microglobulin,** & **neopterin** - Enzyme-linked Immunosorbent Assays (ELISA)

Statistical Methods

- Outcome: estimated Glomerular Filtration Rate **(eGFR)** from the CKD-EPI equation[3]
- Exposure: serum iron, TF, ferritin, or sTFR level
- *Univariate Analyses:* Pearson's correlations (continuous variables); Wilcoxon Rank Sum tests (non-normal continuous variables), all non-normal continuous variables were log-transformed
- *Multivariable Linear Regression Analyses* of eGFR, covarying for **age**, **race**, **hemoglobin**, **tenofovir** use, **β2-microglobulin**, **systolic/diastolic blood pressures**, and **comorbidity** including **diabetes** (± race-stratification)
- Removed 2 participants with biomarkers >2.5 SD from the mean

References:
1) Kallianpur AR *et al. The Journal of Infectious Disease* 2016; 213(7): 1065–1073. PMID: 26690344
2) van Swelm RPL, *et al. Nature Reviews. Nephrology* 2020; 16(2):77-98. PMID: 31554933
3) Alfano G, *et al. Journal of Clinical Medicine* 2019; 8(8): E1254. PMID: 31430930
4) Kaur H, *et al.* 2020 *(Manuscript under review)*
5) Heaton RK, *et al. Neurology* 2010; 75(23): 2087-2096. PMID: 21135382

RESULTS

Table 1. Demographic and clinical characteristics of study participants

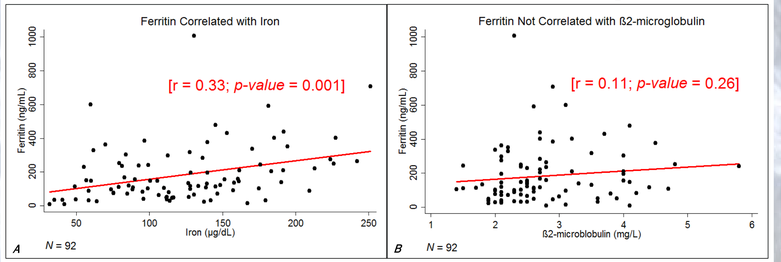
Study participant characteristics (N=92)			
Women, N (%)	18 (19.5)	Nadir CD4, median (IQR), cells/μL	158.0 (28.0, 264.0)
African Ancestry, N (%)	27 (29.3)	Hemoglobin, mean±SD, g/dL	14.4±1.5
Diabetes, N (%)	8 (8.7)	On Tenofovir, N (%)	58 (63.0)
Age, mean±SD years	47.5±9.3	Mild/Moderate-severity comorbidity, N (%)	15 (16.3)

Table 2. Distribution of serum iron indices by racial ancestry

Serum iron biomarkers	European ancestry (N=65)	African ancestry (N=27)	*p*-value
Transferrin (mg/dL)	314.0 (274.0, 364.0)	323.0 (265.0, 372.0)	0.79
Iron (μg/dL)	127.0 (88.8, 160.5)	112.1 (81.4, 145.1)	0.29
Ferritin (ng/mL)	118.6 (65.3, 240.5)	140.4 (89.1, 304.1)	0.42
Soluble Transferrin Receptor (nmol/L)	31.5 (24.0, 40.9)	37.0 (28.3, 46.5)	0.04

Median and interquartile range (IQR) values are presented in Table 2.

Ferritin is correlated with iron but not with inflammation/immune activation (e.g., β2-microglobulin).



Transferrin is correlated with the serum Creatinine and eGFR, especially in AWH of African ancestry.

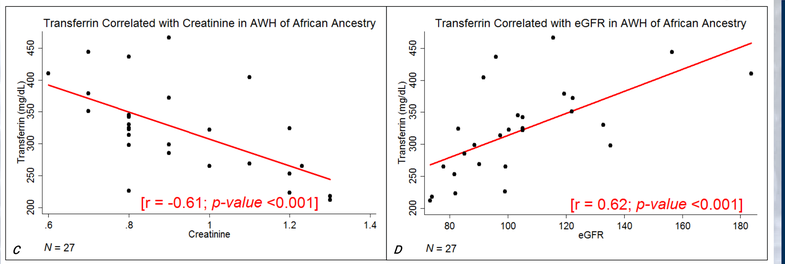


Figure 2 (A-D): Selected correlation results for serum iron biomarkers (ferritin, TF, and sTfR) and biomarkers of renal function (Creatinine, eGFR) and renal injury/inflammation (β_2-microglobulin).

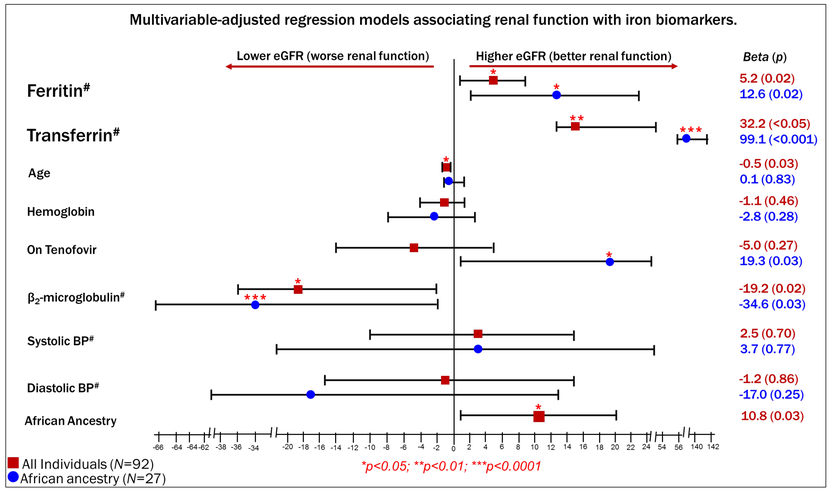


Figure 3: Higher ferritin and TF are associated with higher *(better)* Glomerular Filtration Rate in AWH (■), particularly in individuals of African ancestry (●).

#Log-transformed variables. Additional adjustment for diabetes diagnosis had minimal effect on these associations.
Abbreviations: eGFR, Glomerular Filtration Rate; *Beta*, *Beta*-coefficient (estimate of effect); *p, p-value*; *BP*, blood pressure.

SUMMARY & DISCUSSION

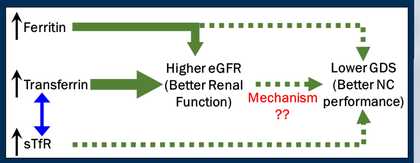
- Higher serum TF and ferritin are associated with better renal function (higher eGFR) in AWH, independent of inflammation/immune activation, particularly in individuals of African ancestry, suggesting that these proteins protect the kidney from iron-mediated oxidative injury.
- Since iron homeostasis and renal function are linked to neurocognitive (NC) performance, these findings suggest that iron dysregulation is part of a shared mechanism underlying CKD and NCI pathogenesis in AWH on ART.

LIMITATIONS:

- Relatively small sample size; cross-sectional design

FUTURE DIRECTIONS:

- A larger longitudinal study of iron biomarkers in AWH and HIV(-) persons with renal outcome measures, to confirm these results and determine HIV-specific effects
- Ferritin and TF formulations might be an effective means of restoring renal iron homeostasis and limiting renal injury.



National NeuroAIDS Tissue Consortium (NNTC)/CHARTER NeuroAIDS Data Resource

WWW.NNTC.ORG

Funding: Cleveland Clinic Catalyst Award to AK; N01 MH22005, HSN271201000036C, HHSN271201000030C to SL (CHARTER Study).

Cleveland Clinic

Conference on Retroviruses and Opportunistic Infections | March 8-11, 2020 | Boston, Massachusetts, USA