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Kidney Function Impacts Plasma Alzheimer's Biomarkers In A Cognitively Normal Multi-Ethnic Cohort

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Abstract

Background: Plasma biomarkers of Alzheimer's disease (AD) can be cost-effective, non-invasive, scalable measures for screening into clinical research and trials. Little research has examined the impact of medical comorbidities on these biomarkers especially among underserved communities. The current study examined the impact of kidney functioning on plasma AD biomarkers among a multi-ethnic cohort.

Methods: 1,328 cognitively unimpaired Mexican American (659) and non-Hispanic white (669) participants were examined. eGFR levels were categorized into eGFR1>=90 (normal kidney function), eGFR2 61-89 (mild kidney function loss) and eGFR3 ≤60 (moderate to severe kidney function loss). Aβ40, Aβ42, total tau and NfL were assayed using Simoa.

Results: Mild and moderate/severe eGFR levels, were associated with all plasma biomarkers. For Mexican Americans, mild and moderate/severe kidney function loss was associated with Aβ40, Aβ42, total tau and NfL. Among non-Hispanic whites, mild kidney function loss was associated with Aβ40 and Aβ42 whereas moderate/severe kidney function loss was associated with all biomarkers.

Conclusion: Among cognitively normal adults, even mild kidney loss is associated with alterations in the plasma AD biomarkers. Additional work to determine how to consider eGFR levels best to avoid misdiagnosis and inappropriate referrals for more invasive, and costly, procedures based on plasma biomarker findings is needed.

Introduction

Alzheimer's disease (AD) is the most common neurodegenerative dementia [1,2] and it disproportionately impacts underserved populations. In fact, U.S Hispanics/Latinos are expected to experience the greatest increase in AD and AD related dementias (ADRS) by 2060 [3]. Despite these issues, Hispanic/Latino populations remain severely underrepresented in AD research [2,4,5] and clinical trials [6]. Our group has proposed that blood-based biomarkers may offer a means of increasing access to clinical research and clinical trials for underserved communities [7].

In our prior work, we have demonstrated that AD biomarkers [7–10], and risk factors [8,11–13], are different among Mexican Americans (65% of the **U.S**. Hispanic/Latino population) as compared to non-Hispanic whites. In fact, Mexican Americans have an earlier age of onset of cognitive loss [8,12,13] and neurodegeneration [9] yet lower rates of amyloid positivity [8] and APOE4 genotype presence [12,13]. Additionally, Mexican Americans have higher rates of medical comorbidities [8,11–13], such as diabetes, that have

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well-established links to AD risk. If blood-based biomarkers are to be useful in increasing access to all communities to AD research and clinical trials, a comprehensive understanding of the factors impacting these biomarkers is required.

There has been a tremendous growth in the examination of plasma biomarkers of AD in the last few years with a significant amount of that focusing on plasma-based biomarkers of amyloid (A) [14–16], tau (T) [17–19] and neurodegeneration (N) [10,17,20] to identify cost-effective, non-invasive and scalable measures to detect fundamental AD biomarkers as defined in the 2018 AT(N) biomarker framework of AD [21]. While the current data does not support blood-based biomarkers as "diagnostic" of cerebral markers, these markers likely have tremendous potential to aid in increasing access to AD clinical research and trials in underserved communities [7] by establishing a multi-tiered screening system that begins by ruling out those who have a low likelihood of needing more expensive and invasive procedures [7,22–24]. Another substantial benefit of such an approach is that this method would yield tremendous cost savings [7,23]. In fact, the ongoing AHEAD clinical trial is launching an examination of plasma amyloid as a potential screening tool for this prevention trial.

Chronic Kidney Disease (CKD) has well-established links with cognitive aging [25–27]. In our prior work, lower eGFR (estimated glomerular filtration rate) was associated with poorer neuropsychological functioning among community-dwelling Mexican Americans [27]. However, plasma amyloid also is elevated in a stage-dependent manner with CKD. Gronewold et al [28] examined 106 CKD patients (stages 3-5) along with 53 controls with comparable vascular risk profiles and found that plasma amyloid was elevated in a stage-dependent manner [28]. eGFR levels remained significantly associated with plasma amyloid after controlling for a broad range of vascular risk factors [28]. We are unaware of any work specifically examining the link between eGFR levels and plasma markers of AD in community-based, multi-ethnic study, which was the focus of this study.

Methodology

Participants & Assessment

The Health & Aging Brain Study – Health Disparities (HABS-HD; formally the Health & Aging Brain study among Latino Elders, HABLE study) study is an ongoing, longitudinal, community-based project examining health disparities in Mild Cognitive Impairment (MCI) and AD among Mexican Americans as compared to non-Hispanic whites with recent expansion to enroll African Americans. HABS-HD methods have been published [8] and are briefly outlined below. The data included in this study encompass Mexican American and non-Hispanic white participants since the recruitment of the African American participants is ongoing. Inclusion criteria for the study includes

1. self-reported ethnicity of African American, Mexican American or non-Hispanic white
2. willingness to provide blood samples
3. capable of undergoing neuroimaging studies
4. age 50 and above
5. fluent in English or Spanish.

Exclusion criteria includes

1. Type 1 diabetes
2. presence of active infection
3. current/recent (12 months) cancer (other than skin cancer)
4. current severe mental illness that could impact cognition (other than depression)
5. recent (12 months) traumatic brain injury with loss of consciousness
6. current/recent alcohol/substance abuse
7. active severe medical condition that could impact cognition (e.g., end stage renal failure, chronic heart failure, chronic obstructive pulmonary disease) and current diagnosis of dementia other than AD.

Participant recruitment for HABS-HD includes a community-based participatory research (CBPR) approach [29].

The CBPR approach has been used successfully as a recruitment modality for reaching underserved and minority populations. It involves collaborating with local communities through outreach (holding community events, seminars), word of mouth, marketing modalities (newspaper, television, radio), and providing back information (clinical lab work, MRI clinical reads, neuropsychological test results) to the participants and their health care providers. All aspects of the study protocol can be conducted in Spanish or English. The HABS-HD study is conducted under IRB approved protocols, and each participant (or his/her legal representative) signs written informed consent. The study was performed in accordance with all relevant guidelines and regulations. All HABS-HD data is available to the scientific community through the UNTHSC Institute for Translational Research (ITR) website [30].

Clinical Assessment

A clinical assessment is conducted as part of the HABS-HD protocol which includes an interview and neuropsychological testing with the following battery: Mini Mental Status Exam (MMSE) [31], Wechsler Memory Scale- Third Edition (WMS-III) Digit Span and Logical Memory [32], Digit Symbol Substitution, Trail Making Test Parts A and B [33], Spanish-English Verbal Learning Test (SEVLT) [34], Animal Naming (semantic fluency) [34], FAS (phonemic fluency) [34], the

American National Adult Reading Test (English-speakers) [35], and Word Accentuation Test (Spanish-speakers) [36]. An informant interview is also conducted for completion of the Clinical Dementia Rating (CDR) Scale [37] by clinicians with expertise in dementia to evaluate for functional declines.

Blood Biomarkers

eGFR levels were conducted by Quest Laboratories. For analyses, eGFR levels were grouped into three levels ml/min/1.732: eGFR1 = ≥90 ml/min/1.73 [2] (normal, Stage 1), eGFR2: 61-89 ml/min/1.73 [2] (mild loss, Stage 2) and eGFR3 ≤60 ml/min/1.732 (moderate to severe loss, Stages 3 and 4). Blood samples were collected, processed, and stored per previously published international guidelines [38]. Assay preparation was completed using a custom automated StarPlus system from Hamilton Robotics. Plasma markers of amyloid (Aβ40, Aβ40), tau (total tau), and neurodegeneration (neurofilament light [NfL]) were assayed using the ultra-sensitive Simoa (single molecule array technology platform HD-X (Quanterix.com) [7,8,10].

Diagnostic Classification

Cognitive diagnoses were assigned algorithmically (decision tree) and verified at consensus review as follows: Unimpaired Cognition = no cognitive complaints, CDR sum of boxes score of 0 [39,40], and cognitive tests scores broadly within normal limits (i.e., performance greater than that defined as meeting diagnostic criteria for MCI [i.e. <=1.5 standard deviations below the normative range]); Mild Cognitive Impairment (MCI): cognitive complaint (self or other), CDR sum of boxes score between 0.5- 2.0 [39,40] and at least one cognitive test score falling <=1.5 standard deviations below normative ranges; Dementia: CDR sum of boxes score >=2.5 [39,40] and at least two cognitive test scores 2 standard deviations below normative ranges.

In order to examine data relevant for novel prevention trials, only data from controls were included in this study.

Statistical Analyses

Statistical Analyses were conducted in SPSS 25 (IBM). Chi-square and ANOVA were utilized to compare groups on demographic variables. ANCOVA models were created to examine differences in all plasma AD biomarkers by eGFR group with follow-up group level comparisons for eGFR1 versus eGFR2 and eGFR3 with age, gender and education entered as covariates in all models. Analyses were run for the entire cohort and then split by ethnicity. Statistical significance was set at $p<0.05$.

Results

Demographics

The demographic characteristics of the cohort are provided in Table 1. Data from 1,328 cognitively unimpaired participants (659 Mexican American and 669 non-Hispanic white) were included in the analyses. The Mexican American participants were significantly younger, achieved fewer years of formal education, and were more likely to be female (all $p<0.001$).

Table 1: Descriptive Statistics of the Sample

	Total Cohort n=1328	Mexican American n=659	Non-Hispanic White n=669	Statistics (p-value)
Age- Years	M= 66.10 SD= 16.38	M= 63.23 SD= 7.70	M= 68.93 SD= 8.34	F=166.95 (<0.001)
Education- Years	M= 12.68 SD= 4.71	M= 9.72 SD= 4.52	M= 15.59 SD= 2.58	F=847.59 (<0.001)
Gender (% male)	36%	31%	42%	χ^2=18.52 (<0.001)
eGFR ml/min/1.73^2	M= 80.68 SD= 16.38	M= 86.10 SD= 15.83	M= 75.32 SD= 15.12	F=157.17 (<0.001)
eGFR 1 >=90	36%	52%	21%	χ^2=35.52 (<0.001)
eGFR 2 60-89	53%	40%	65%	χ^2=29.03 (<0.001)
eGFR 3 <=59	11%	8%	14%	χ^2=31.51 (<0.001)
MMSE	M= 28.07 SD= 2.30	M= 26.94 SD= 10.41	M= 29.19 SD= 1.02	F=419.06 (<0.001)
$A\beta_{40}$ pg/mL	M= 250.81 SD= 65.93	M= 236.42 SD= 64.42	M= 264.98 SD= 64.37	F=62.63 (<0.001)
$A\beta_{42}$ pg/mL	M= 11.99 SD= 3.25	M= 11.77 SD= 3.36	M= 12.22 SD= 3.12	F=6.04 (=0.01)
T-tau pg/mL	M= 2.44 SD= 0.93	M= 2.55 SD= 0.91	M= 2.33 SD= 0.93	F=17.86 (<0.001)
NfL pg/mL	M= 18.18 SD= 11.31	M= 16.46 SD= 11.48	M= 19.87 SD= 11.00	F=29.23 (<0.001)

NOTE: M= Mean SD= Standard Deviation; eGFR = estimated glomerular filtration rate; MMSE = mini mental state examination (range 0-30), Aβ = plasma amyloid, t-tau = plasma total tau; NfL = neurofilament light chain

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Table 2: Ancova Comparing Plasma Alzheimer's Biomarkers By Egfr Groups In The Total Cohort And Split By Ethnicity (Age, Gender, And Education As Covariates)

	Total Cohort	Mexican American	Non-Hispanic White
	Overall ANCOVA Significance		
	(post-hoc comparisons)		
PLASMA AB_{40}	**F=111.26 (<0.001)**	**F=63.76, p<0.001**	**F=48.18, p<0.001**
	eGFR 1 222.22 (47.24)	eGFR 1 217.81 (47.84)	eGFR 1 233.72 (43.78)
	eGFR 2 253.81 (59.78)	eGFR 2 242.64 (61.50)	eGFR 1 260.45 (57.79)
	1vs2 23.35, p<0.001	**1vs2 21.68, p<0.001**	**1vs2 20.41, p=0.001**
	eGFR 3 327.86 (74.85)	eGFR 3 331.85 (79.14)	eGFR 3 325.78 (72.88)
	1vs3 92.73, p<0.001	**1vs3 108.25, p<0.001**	**1vs3 80.72, p<0.001**
PLASMA AB_{42}	**F=120.08, p<0.001**	**F=94.09, p<0.001**	**F=42.85, p<0.001**
	eGFR 1 10.66 (2.34)	eGFR 1 10.67 (2.38)	eGFR 1 10.63 (2.21)
	eGFR 2 12.05 (2.77)	eGFR 2 11.96 (2.86)	eGFR 2 12.11 (2.71)
	1vs2 1.26, p<0.001	**1vs2 1.00, p<0.001**	**1vs2 1.36, p<0.001**
	eGFR 3 15.77 (4.46)	eGFR 3 17.68 (4.71)	eGFR 3 14.78 (4.00)
	1vs3 4.83, p<0.001	**1vs3 6.48, p<0.001**	**1vs3 3.95, p<0.001**
PLASMA TAU	**F=38.48, p<0.001**	**F=24.22, p<0.001**	**F=16.62, p<0.001**
	eGFR 1 2.35 (0.87)	eGFR 1 2.38 (0.79)	eGFR 1 2.29 (1.04)
	eGFR 2 2.38 (0.87)	eGFR 2 2.60 (0.88)	eGFR 2 2.25 (0.83)
	1vs2 0.15, p=0.02	**1vs2 0.224, p=0.005**	eGFR 3 2.80 (1.07)
	eGFR 3 3.00 (1.14)	eGFR 3 3.38 (1.17)	**1vs3 0.64, p<0.001**
	1vs3 0.82, p<0.001	**1vs3 1.00, p<0.001**	
PLASMA NFL	**F=48.46, p<0.001**	**F=30.80, p<0.001**	**F=19.92, p<0.001**
	eGFR 1 14.07 (8.06)	eGFR 1 13.69 (8.37)	eGFR 1 15.03 (7.18)
	eGFR 2 18.60 (10.04)	eGFR 2 17.25 (11.63)	eGFR 2 19.41 (8.88)
	1vs2 1.86, p=0.009	**1vs2 1.96, p=0.04**	eGFR 3 28.19 (17.50)
	eGFR 3 28.99 (17.14)	eGFR 3 30.46 (16.54)	**1vs3 8.46, p<0.001**
	1vs3 10.57, p<0.001	**1vs3 13.81, p<0.001**	

NOTE: EGFR 1 = >=90, EGFR2 = 60-89, EGFR3 = <=59 MEAN (STANDARD DEVIATION); AB_{40} PLASMA AMYLOID BETA 40, AB_{42}= PLASMA AMYLOID BETA 42, TAU = PLASMA TOTAL TAU, NFL = NEUROFILAMENT LIGHT CHAIN

Blood Biomarkers

The Mexican American cohort had significantly higher eGFR levels (86.10 sd=15.83) when compared to the non-Hispanic whites (75.32 sd=15.12)(p<0.001). eGFR groupings were also significantly different between Mexican Americans as compared to non-Hispanic whites. Mexican Americans were more likely to be in eGFR1 (p<0.001) and less likely to be in eGFR groups 2 and 3 (p<0.001). Mexican Americans had significantly lower Aβ40 (p<0.001) and Aβ42 (p=0.01) levels as compared to non-Hispanic whites. Mexican Americans had significantly higher **total tau** levels (p<0.001) and significantly lower NfL levels (p<0.001) (See Table 1).

Impact of eGFR on Plasma Biomarkers

After adjusting for age, education and gender in ANCOVA models, there was a significant main effect for eGFR on all plasma AD biomarkers (See Table 2): Aβ40 F=111.26, p<0.001; Aβ42 F=12.08, p<0.001; total tau F=38.48, p<0.001; NfL F=48.46, p<0.001. Of note, there was a significant effect of even mild kidney function loss for all plasma AD biomarkers when comparing eGFR1 versus eGFR2 groups: Aβ40 contrast estimate 23.35, p<0.001; Aβ42 contrast estimate 1.26, p<0.001; total tau contrast estimate 0.15, p=0.02; NfL contrast estimate 1.86, p=0.009. There was also a significant difference between eGFR1 and eGFR3 groups for all plasma AD biomarkers (See Table 2).

Impact of eGFR on Plasma Biomarkers by Ethnicity

When split by ethnicity, the overall main effect for eGFR remained for all plasma AD biomarkers for both Mexican Americans and non-Hispanic whites (See Table 2). Among Mexican Americans, there remained a significant impact for even mild loss of kidney function (i.e., eGRR2 group) on all plasma AD biomarkers. Specifically, when comparing

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eGFR1 vs eGFR2 groups among Mexican Americans, there were significant differences in Aβ40 (contrast estimate 21.68, p<0.001), Aβ42 (contrast estimate 1.00, p<0.001), total tau (contrast estimate 0.224, p=0.005), and NfL (contrast estimate 1.96, p=0.04). Among non-Hispanic whites, there was a significant effect for mild kidney function loss as well when comparing eGFR1 vs eGFR2 groups for Aβ40 (contrast estimate 20.41, p=0.001) and Aβ42 (contrast estimate 1.36, p<0.001), but not for total tau or NfL. However, there were significant differences between eGFR1 versus eGFR3 groups among all plasma AD biomarkers among non-Hispanic whites (See Table 2).

Discussion

The current study reflects, to our knowledge, the first large-scale assessment of the impact of eGFR on plasma biomarkers of AD among a community-dwelling, multi-ethnic cohort. The current findings demonstrate that eGFR levels, even reflective of mild kidney function loss, have a significant impact on all plasma AD biomarkers examined. Additionally, mild kidney functional loss had more effect on plasma AD biomarkers among the Mexican American participants as compared to non-Hispanic whites.

There is substantial literature linking kidney functional loss and CKD to cognitive performance. Chu et al. [41] examined data from the National Health and Nutrition Examination Survey (NHANES, 2011-2014) and found that CKD was associated with lower cognitive functioning among those with low, but not high, physical activity. Mansson and Elmstahl [42] recently found that eGFR<60 was not associated with the incidence of MCI or dementia; however, a decline in processing speed was observed. In our prior work, eGFR levels were found to be associated with cognitive functioning in a community-based sample of Mexican Americans [27]. Lau et al. [43] found that eGFR levels were not associated with brain amyloid levels among a cohort of individuals aged 90 and over, suggesting that cognitive impairment among the oldest adults associated with CKD may be due to cerebrovascular disease rather than AD pathology.

There are weaknesses to the current study. First and foremost, the current results are cross-sectional in nature. However, given the current efforts to apply one-time plasma AD biomarkers as screening tools, the current findings have direct applicability to such efforts. The current study utilized only one marker of kidney function (eGFR). Additionally, the HABS-HD study is longitudinal, and additional work will be conducted to determine the impact of eGFR levels on plasma AD biomarkers over time. A second limitation of the study is the lack of direct comparison with amyloid and tau brain measures. However, the HABS-HD study is currently capturing cross-sectional and longitudinal amyloid, and tau PET scans in the cohort, which will facilitate such future work. Additionally, the lack of representation of African Americans in the current work is a limitation, given that African Americans, Mexican Americans, and "non-Hispanics" whites reflect the three largest racial/ethnic groups in the U.S. The HABS-HD study is currently enrolling 1000 African Americans and, therefore, future work will be conducted examining the impact of eGFR levels on plasma AD biomarkers amongst all three groups. Even with these limitations, the size of the samples and the use of highly sensitive assays of the biomarkers are significant strengths supporting the utility of the findings.

Conclusion

Given the tremendous amount of effort focused on the identification of context of use (COUs) for plasma biomarkers of AD pathology, there is an urgent need to understand how these biomarkers behave among cognitively normal older adults with common medical comorbidities. In our prior work, we demonstrated that medical comorbidities, particularly diabetes, have a significant impact on plasma NfL levels [10]; however, there remains a dearth of science examining the impact of common medical comorbidities on plasma AD biomarkers with a near absence of work examining these biomarkers among underserved communities. If plasma AD biomarkers are to be implemented as front-line screening measures for clinical trials (e.g., AHEAD trial) or in clinical practice, a comprehensive understanding of these factors is required. The current results demonstrate that eGFR levels must be considered when interpreting plasma AD biomarkers, even in the context of mild kidney function loss rather than CKD. Therefore, eGFR levels could impact the accuracy of ongoing efforts for implementation of plasma AD biomarkers in clinical practice and clinical trial recruitment.

Lists of abbreviations

AD – Alzheimer's Disease

eGFR – estimated glomerular filtration rate

CKD – chronic kidney disease

Ab40 – plasma amyloid beta 40

Ab42 – plasma amyloid beta 42

Tau – plasma total tau

NfL – plasma neurofilament light chain

PET – positron emission tomography

NC – cognitively normal control

MCI – mild cognitive impairment

DECLARATIONS

Ethics Approval and Consent to Participate

This study protocol was reviewed and approved by the UNTHSC IRB protocols UNTHSC 2016-128 & 2020-125.

Each participant (or his/her legal representative) signed written informed consent to participate in the study.

Consent for Publication

Not applicable

Data Availability Statement

The data is available to the scientific community through the UNTHSC Institute for Translational Research (ITR) website - https://apps.unthsc.edu/itr/

Competing Interests

SEO has multiple patents on precision medicine for neurodegenerative*diseases and is the founding scientist of Cx Precision Medicine. No other authors reported any potential conflicts of interest.

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Author Contributions

JRH = conceptualization and design of study; acquisition and interpretation of data; drafting and revising manuscript; final approval of version to be published; agreement to be accountable for the accuracy and integrity of the work. SEO = conceptualization and design of study; acquisition, analysis and interpretation of data; drafting and revising manuscript; final approval of version to be published; agreement to be accountable for the accuracy and integrity of the work. LAJ = conceptualization and design of study; acquisition, analysis and interpretation of data; drafting and revising manuscript; final approval of version to be published; agreement to be accountable for the accuracy and integrity of the work. MP = design of study; acquisition and interpretation of data; drafting and revising manuscript; final approval of version to be published; agreement to be accountable for the accuracy and integrity of the work.

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