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Vitamin D is Not Associated with HIV-Associated Neurocognitive Disorder in Rakai, Uganda

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Abstract

We investigated whether vitamin D is associated with HIV-associated neurocognitive disorder (HAND). HIV-infected (HIV+) antiretroviral therapy (ART)-naïve adults in rural Uganda underwent a neurocognitive battery for determination of HAND stage at baseline and after two-years. Baseline serum 25-hydroxyvitamin D (25OH-D) and serum and cerebrospinal fluids (CSF) vitamin D binding protein (VDBP) were obtained. Of the 399 participants, 4% (n=16) were vitamin D deficient (25OH-D ≤ 20 ng/mL). There was no association between 25OH-D, serum or CSF VDBP and HAND stage at baseline or follow-up. Future studies in a population with higher levels of vitamin D deficiency may be warranted.

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CONFLICTS OF INTEREST

Dr. Saylor has nothing to disclose.
Dr. Nakigozi has nothing to disclose.
Dr. Pardo has nothing to disclose.
Dr. Batte has nothing to disclose.
Dr. Kisakye has nothing to disclose.
Dr. Kumar has nothing to disclose.
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Dr. Gray has nothing to disclose.
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Keywords

HIV-associated neurocognitive disorder; vitamin D; HIV; Africa; epidemiology

HIV-associated neurocognitive disorder (HAND) occurs in up to 50% of HIV-infected (HIV +) individuals, affects up to 18 million people worldwide, and impairs quality of life.(Saylor et al. 2016) Its pathogenesis is incompletely understood, but increased brain deposition and altered metabolism of amyloid-beta-42 (Aβ42) leading to neuronal dysfunction and cognitive impairment may play a role.(Ortega and Ances 2014; Anthony et al. 2010) Specifically, decreased cerebrospinal fluid Aβ42 levels in the same range as that seen in Alzheimer's Disease have been shown in HIV+ patients with HAND.(Clifford et al. 2009; Rempel and Pulliam 2005; Krut et al. 2013) Furthermore, *in vitro* studies have demonstrated that HIV viral proteins directly alter amyloid metabolism, and several antiretroviral medications have been shown to both increase Aβ42 production and decrease Aβ42 clearance in *in vitro* studies.(Ortega and Ances 2014; Rempel and Pulliam 2005; Giunta et al. 2011)

Vitamin D is increasingly recognized as an immunomodulator. In HIV, vitamin D deficiency has been linked to faster disease progression and increased mortality.(Ezeamama et al. 2015; Mehta et al. 2010; Sudfeld et al. 2012; Klassen et al. 2015) In neurologic disease, vitamin D deficiency has been associated with multiple disorders including multiple sclerosis and Alzheimer's Disease.(Yeshokumar et al. 2015) The link between vitamin D and Alzheimer's Disease, whose pathologic hallmark is deposition of Aβ42, is thought to be related to its role in amyloid metabolism. Aβ42 is known to suppress vitamin D receptor expression, and activation of the vitamin D receptor is known to suppress Aβ42 production.(Berridge 2014) In addition, vitamin D binding protein (VDBP) binds to Aβ42 and has been shown to reduce Aβ42 plaque aggregation *in vitro*, decrease amyloid-mediated cell death and synaptic loss, and prevent memory deficits in a mouse model of Alzheimer's Disease.(Moon et al. 2013; Morley and Farr 2014) Serum vitamin D levels and serum and cerebrospinal fluid (CSF) VDBP levels have been shown to be significantly different in Alzheimer's Disease compared to healthy controls and have been proposed as possible biomarkers for Alzheimer Disease. (Bishnoi, Palmer, and Royall 2015; Johansson et al. 2013; Muenchhoff et al. 2015)

Given the pathologic similarities between Alzheimer's Disease and HAND and the putative pathophysiologic mechanism linking the development of HAND to alterations of Aβ42 production, clearance and deposition, we sought to evaluate whether serum vitamin D levels and serum and CSF VDBP levels were associated with HAND in HIV+ adults in rural Uganda.

METHODS

Study Participants.

Study participants were identified from Rakai HIV clinics and the Rakai Community Cohort Study, an open, community-based cohort of adults residing in 40 communities in Rakai District representative of rural Uganda. Eligible participants were antiretroviral therapy

(ART)-naïve HIV+ adults ≥ 20 years old. Two hundred participants with advanced immunosuppression (CD4 ≤ 200 cells/μL) and 199 participants with moderate immunosuppression (CD4 350–500 cells/μL) were enrolled and offered ART free of charge immediately after enrollment per Ugandan national guidelines. Exclusion criteria included severe systemic illness, inability to provide informed consent, and physical disability restricting travel to the main Rakai Health Sciences Program clinic.

Study Procedures.

Consenting participants were enrolled between August 2013 and July 2015 and were assessed at baseline and after two years. At each visit, participants underwent a sociodemographic survey, depression screen, functional status assessments, and a neurocognitive battery. Peripheral blood draw was performed at baseline for determination of 25-hydroxy vitamin D (25OH-D) and vitamin D binding protein (VDBP) levels. Samples were separated into serum and immediately frozen in a −80C freezer in opaque boxes to ensure protection from light. Additionally, 199 participants consented to an optional lumbar puncture at their baseline visit, and these samples were used to determine CSF VDBP levels.

Laboratory Analyses.

Serum 25OH-D levels were determined by chemiluminescence assays (Diasporin LIAISON XL, Saluggia, Italy at Heartland Assays, Ames, Iowa), and ELISA was used to determine serum VDBP (Heartland Assays, Ames, Iowa) and CSF VDBP (R&D Systems, Minneapolis, MN) in August 2017.

Standard Protocols, Approvals, Registrations and Patient Consents.

Written informed consent was obtained from all study participants. This study was approved by the Western Institutional Review Board, the Uganda Virus Research Institute Research and Ethics Committee, and the Uganda National Council for Science and Technology.

Statistical Analyses.

Participants who had not initiated ART at the time of their follow-up visit (n=21) were excluded from follow-up analyses. Because Rakai District is located in equatorial Uganda, sun exposure does not vary by season, so no seasonal adjustment was made to 25OH-D levels. 25OH-D levels were categorized as deficient (≤ 20 ng/mL), sufficient (21–40 ng/mL), and optimal (>40 ng/mL). HAND stage was determined using normative neurocognitive data locally derived from 400 HIV-negative age- and sex-matched adults from Rakai District and applying the Frascati criteria(Antinori et al. 2007) to classify participants as having either normal cognition, asymptomatic neurocognitive impairment (ANI), minor neurocognitive disorder (MND), or HIV-associated dementia (HAD). HAND stage was then dichotomized as (1) normal versus abnormal (ANI/MND/HAD); (2) symptomatic HAND (MND/HAD) versus normal/ANI; and (3) HAD versus no dementia (normal/ANI/MND).

Mean 25OH-D, serum VDBP and CSF VDBP were compared across HAND stages using ANOVA analyses, and frequencies of vitamin D categories were compared across HAND stages using Fisher’s exact tests. Laboratory markers and vitamin D categories were

compared across dichotomized HAND categories using t-tests for means and Fisher's exact tests for proportions.

RESULTS

Participants were 53% male with a mean age of 35 (SD ±8) years and mean education of 5 (SD ±3) years at baseline (Table 1). 78% of participants (n=312) initiated ART and returned for their two-year follow-up visit. More than half of participants met criteria for HAND at baseline and follow-up with less severe HAND stages predominating at follow-up. Only 4% (n=16) were vitamin D deficient while one-third (n=132) had optimal 25OH-D levels at baseline. Vitamin D levels were higher in men [38.0 ng/mL (SD ± 9.8)] than women [33.9 ng/mL (SD ± 9.3)] ($p<0.001$) but was not correlated with age ($r=0.004$, $p=0.94$).

Mean 25OH-D level at baseline did not vary by baseline or follow-up HAND stage (Table 2). There was no difference in the proportion of participants with baseline vitamin D deficiency or optimal vitamin D by HAND stage at either baseline or follow-up. An alternative cutoff of vitamin D ≥ 30 ng/mL also showed no difference by HAND stage at either baseline or follow-up (data not shown). In addition, there was no difference in baseline serum or CSF VDBP by either baseline or follow-up HAND stage. None of these parameters varied when compared between dichotomous HAND categories (data not shown).

There were no differences in baseline 25OH-D, serum VDBP, CSF VBDP, or vitamin D category between participants whose HAND stage worsened over two years of follow-up compared to participants whose HAND stage remained unchanged or improved over the same duration. There were no differences in any vitamin D parameter in participants whose HAND stage improved over two years compared to those whose remained unchanged or worsened (data not shown).

DISCUSSION

In this study of ART-naïve HIV+ adult patients in rural Uganda who were followed over two years on ART, baseline vitamin D status was not associated with HAND stage at baseline or after two years. Baseline vitamin D status was also not associated with improvement or worsening of HAND stage during follow-up.

Neither baseline serum or CSF VDBP was significantly different by HAND stage at baseline or follow-up. This differs from associations with Alzheimer's Disease which is associated with both higher serum and CSF VDBP levels.(Moon et al. 2013) In addition, our results differ from a prior study in which a proteomics platform for biomarker discovery was used to evaluate CSF from 38 HIV+ persons and found VDBP was upregulated in patients with HAD.(Rozek et al. 2007)

The strengths of this study include its relatively large sample size, prospective nature, and detailed neurocognitive assessment, but its major limitation is the very small number of participants with vitamin D deficiency (4%). This proportion was much lower than expected

as a prior study of vitamin D levels in 398 ART-naïve HIV+ adults in Kampala, Uganda found 17% of participants were deficient in vitamin D.(Ezeamama et al. 2015)

CONCLUSION

In this study of HIV+ Ugandan adults followed over two years, neither 25OH-D, serum VDBP, nor CSF VDBP were associated with HAND stage at baseline or follow-up. However, the small proportion of vitamin D deficient participants in our cohort may have limited our ability to detect an association between vitamin D deficiency and HAND. Given the putative mechanism of amyloid metabolism in the development of HAND and the known role of vitamin D in amyloid regulation, future studies of the association between vitamin D and HAND in cohorts with higher rates of vitamin D deficiency may be warranted especially because vitamin D supplementation may offer a potential therapeutic intervention for HAND if such an association is found.

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TABLE 1.

Demographic characteristics of participants at baseline and the two-year follow-up visits.

	Baseline (n=399)	Follow-Up (n=312)
Male sex [n (%)]	211 (53%)	158 (51%)
Age (years) [mean (SD)]	35 (8)	37 (8)
Education (years) [mean (SD)]	5 (3)	6 (3)
Body Mass Index [mean (SD)]	21.8 (3.5)	22.8 (3.5)
Underweight [n (%)]	51 (13%)	16 (5%)
Normal [n (%)]	295 (74%)	234 (75%)
Overweight/Obese [n (%)]	53 (13%)	62 (20%)
CD4 count [median (IQR)]	---	394 [278, 530]
CD4 < 200 cells/μL [n (%)]	200 (50%)	---
CD4 350–500 cells/μL [n (%)]	199 (50%)	---
Plasma HIV viral load [median (IQR)]	52510 [9050, 164,064]	0 [0, 0]
HAND Category [n (%)]		
Normal	164 (41%)	150 (48%)
ANI	24 (6%)	42 (13%)
MND	151 (38%)	105 (34%)
HAD	60 (15%)	15 (5%)
25-OH vitamin D (ng/mL) [mean (SD)]	36 (10)	---
Low (≤ 20 ng/mL) [n (%)]	16 (4%)	---
Sufficient (21–40 ng/mL) [n (%)]	251 (63%)	---
Optimal (>40 ng/mL) [n (%)]	132 (33%)	---
Serum VDBP (ng/mL) [mean (SD)]	316 (61)	---
CSF VDBP (ng/mL) [mean (SD)]	238 (33)	---

Abbreviations: 25-OH vitamin D: 25-hydroxyvitamin D; ANI: asymptomatic neurocognitive disorder; CSF: cerebrospinal fluid; HAD: HIV-associated dementia; HAND: HIV-associated neurocognitive disorder; HIV: human immunodeficiency virus; MND: minor neurocognitive disorder; SD: standard deviation; VDBP: vitamin D binding protein

TABLE 2.

Vitamin D status and HIV-associated neurocognitive disorder (HAND) stage at baseline and two-year follow-up.

	25-OH vitamin D [mean (SD)]	p	Vitamin D Deficiency* [n (%)]	p	Optimal Vitamin D+ [n (%)]	p	Serum VDBP [mean (SD)]	p	CSF VDBP [mean (SD)]	p
Baseline HAND Stage										
Normal	36.5 (9.0)	0.77	4 (2%)	0.37	55 (34%)	0.97	310 (5)	0.52	236 (32)	0.54
ANI	34.0 (8.4)		1 (4%)		7 (29%)		321 (49)		216 (49)	
MND	35.6 (9.4)		7 (5%)		49 (32%)		320 (60)		242 (31)	
HAD	37.0 (12.7)		4 (7%)		21 (35%)		321 (87)		243 (33)	
Follow-Up HAND Stage										
Normal	35.2 (9.5)	0.29	5 (3%)	0.7	43 (29%)	0.34	313 (61)	0.22	236 (27)	0.69
ANI	35.7 (8.7)		1 (2%)		12 (28%)		324 (42)		251 (31)	
MND	36.6 (9.7)		5 (5%)		41 (39%)		317 (68)		232 (39)	
HAD	36.5 (12.2)		1 (7%)		5 (33%)		286 (58)		257 (41)	

*Vitamin D deficiency: serum 25-hydroxyvitamin D ≤ 20 ng/mL

+Optimal vitamin D: serum 25-hydroxyvitamin D > 40 ng/mL

Abbreviations: 25-OH vitamin D: 25-hydroxyvitamin D; ANI: asymptomatic neurocognitive impairment; CSF: cerebrospinal fluid; HAD: HIV-associated dementia; HAND: HIV-associated neurocognitive disorder; MND: minor neurocognitive disorder; SD: standard deviation; VDBP: vitamin D binding protein