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Vitamin D and Insulin Resistance in Non-Diabetic Women's Interagency HIV Study Participants

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Abstract

We explored the relationship between vitamin D levels and insulin resistance (IR) among 1082 nondiabetic (754 HIV-infected) women enrolled in the Women's Interagency HIV study (WIHS), a large and well-established cohort of HIV infected and uninfected women in the US. Vitamin D levels 20–29 ng/mL were considered insufficient and <20 ng/mL deficient. IR was estimated using the homeostasis model assessment (HOMA) and a clinically significant cut-off ≥2.6 was used for HOMA-IR. In the unadjusted analysis, women who were vitamin D insufficient or deficient were 1.62 (95% CI: 1.01–2.61, $p=0.05$) and 1.70 (95% CI: 1.11–2.60, $p=0.02$) times more likely to have HOMA values ≥2.6 compared to women with sufficient vitamin D. The association did not remain significant after adjustment for factors associated with IR. Among the 754 HIV-infected women, current PI use (OR 1.61, 95% CI: 1.13–2.28, $p=0.008$) remained independently associated with HOMA ≥2.6 while vitamin D insufficiency (OR 1.80, 95% CI: 0.99–3.27, $p=0.05$) was marginally associated with HOMA ≥2.6 after adjustment. Ethnicity, body mass index, smoking status, and hepatitis C status were independently associated with insulin resistance in HIV-infected and uninfected women. We found a marginally significant association between vitamin D insufficiency and insulin resistance among nondiabetic HIV-infected WIHS women.

Introduction

Vitamin D deficiency is common in the general population and has been associated with insulin resistance (IR) and diabetes in several recent studies.[1–8] Vitamin D deficiency may influence insulin secretion and sensitivity through its role on insulin target tissues such as the pancreatic β cells, skeletal muscle, and adipose tissue, all of which express vitamin D receptors. Both IR and vitamin D deficiency have been increasingly identified in HIV-infected men and women on antiretroviral therapy.[9–16] The prevalence of vitamin D deficiency in the Women's Interagency HIV study (WIHS) was high at 63%, with HIV-uninfected women having a higher prevalence of vitamin D deficiency compared with HIV-infected women (72% vs. 60%).[15] Similar to men,[11] longer cumulative exposure to nucleoside reverse transcriptase inhibitors has been associated with insulin resistance in HIV-infected women.[9] A recently published study showed an independent association between vitamin D deficiency and type 2 diabetes mellitus (DM) among HIV-infected patients.[17] In a study of HIV-infected men, lower vitamin D was associated with higher serum insulin.[18] In this current study, we examine whether vitamin D levels are associated with insulin resistance estimated using the homeostasis model assessment (HOMA) among nondiabetic women enrolled in the WIHS, an ethnically diverse cohort of HIV-infected and uninfected women. Our analyses consider the entire cohort, as well as the subgroup of HIV-infected women. To our knowledge, this is the largest study to explore the relationship between vitamin D and insulin resistance in nondiabetic HIV-infected adults.

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Methods

Setting and participants

The WIHS is a prospective cohort study of HIV-infected and uninfected at-risk women enrolled during either 1994–1995 or 2000–2001 at six consortia in Chicago, the San Francisco Bay Area, Brooklyn and Bronx/Manhattan, New York City, and the metropolitan areas surrounding Washington, DC, and Los Angeles. Women were seen semiannually for an interview and a physical exam with collection of blood and genital specimens. Informed consent was obtained from all participants in accordance with the US Department of Health and Human Services guidelines and the institutional review boards of participating institutions. The cohort reflects the socio-demographics of women affected by HIV in the United States. Details of cohort recruitment, retention, and demographics have been published elsewhere.[19]

Inclusion and exclusion criteria

We examined the vitamin D levels of WIHS participants who had a study visit between October 2007 and March 2008. Of the 1760 participants whose vitamin D level was available, 1350 also had a HOMA-IR level measured at the same visit. Per study criteria, 240 participants with DM were excluded. Diabetes was defined as having any one of the following: fasting glucose during the study >126 mg/dL that was confirmed, HgbA1c during the study >=6.5% that was confirmed, self-report of diabetes or high blood sugar ever, or self-report of being on a diabetes medication during the study. Participants who reported current pregnancy ($n=19$) or whose current pregnancy information was missing ($n=4$) were excluded. Of the 1087 remaining participants, 5 had extreme values of vitamin D ($n=2$) or HOMA-IR ($n=3$) and were excluded from the analysis. Thus, a total of 1082 participants were included in the analysis.

Assessment of outcomes

Vitamin D. 25-Hydroxyvitamin D [25 (OH) D] testing was performed by Quest Diagnostics on frozen sera stored at −70°C using the liquid chromatography/mass spectroscopy/tandem spectroscopy (LC-MS/TS) method. The LC/MS/TS method is sensitive with the average inter-assay coefficient of variation (CV) % across the analytical range of 7%. Sufficient vitamin D was defined as >30 ng/mL and vitamin D insufficiency as 20–30 ng/mL. Vitamin D deficiency was defined as 25 (OH) D <20 ng/mL, as reported in the literature. Fasting specimens for glucose determination were collected in tubes with glycolytic inhibitors. Fasting serum for insulin determination was obtained at the same time, and all specimens were stored at −70°C until the day of assay. Plasma glucose was measured using the hexokinase method, and insulin was measured using the IMMULITE 2000 assay at a central laboratory.

Insulin resistance. IR was quantified using the HOMA, defined as (insulin × glucose)/405 with insulin measured in μIU/mL and glucose measured in mg/dL.[20]

Statistical analysis

In univariate analysis, characteristics of participants by HIV status were examined using Chi-square and Mantel-Haenszel Chi-square tests for trend, as appropriate, to examine the relationship between HIV status and categorical variables, while the nonparametric Wilcoxon signed rank test was used to examine the relationship between HIV status and continuous variables. We used a logistic regression model to examine the association between HOMA-IR level and exposure variables in unadjusted and adjusted analyses. A clinically meaningful cut-off of ≥2.6 was used for HOMA-IR, the dependent variable, because reliable detection of IR has been documented at this level using the HOMA method.[21] In addition to vitamin D status, other covariates adjusted for in the logistic regression analysis included the following: age, race/ethnicity, current smoking status, BMI, menopause status, hepatitis C (HCV) antibody status, and HIV status, due to existing findings in the literature between these variables and HOMA-IR levels. Covariates, with the exception of baseline race/ethnicity and HCV antibody status, were measured at the same WIHS visit. A p value <0.05 was considered statistically significant.

Results

Characteristics of study participants by HIV serostatus are shown in Table 1. The majority of women in this study were African American (57%). Compared to HIV-uninfected women, HIV-infected women were older (median age 44 vs. 41 years), less likely to smoke (36% vs. 55%), and less vitamin D-deficient [25 (OH) level <20 ng/dl] (60% vs. 74%). HIV-infected women also had a lower body mass index (BMI) (median 27.5 vs. 29.2 kg/m^2). HOMA-IR levels were similar among HIV-infected and HIV-uninfected women (median 1.93 vs. 1.76). Among HIV infected women, 70% were on HAART, and of these 59% were on a protease inhibitor based regimen. The associations between vitamin D status and HOMA-IR ≥2.6, and menopausal status and HOMA-IR ≥2.6 were significant in the unadjusted logistic regression analysis, but did not remain significant in the adjusted analysis (Table 2). In the adjusted analysis, Hispanic women were almost twice as likely to have a HOMA value ≥2.6 compared to African American women (OR 1.77, 95% CI 1.29–2.44, $p=0.0004$). Increased BMI per kg/m^2 (OR 1.12, 95% CI 1.10–1.14, $p<0.0001$), being a current smoker (OR 1.49, 95% CI 1.11–2.02, $p=0.009$), and HCV seropositivity (OR 1.49, 95% CI 1.03–2.17, $p=0.03$) were also positively associated with having a HOMA value ≥2.6 (Table 2).

In the adjusted logistic regression analysis restricted to HIV-infected women, we found an association of current and past 6-month PI use with HOMA-IR ≥2.6 (OR 1.61, 95% CI: 1.13–2.28, $p=0.008$), as well as vitamin D insufficiency with HOMA-IR ≥2.6 (OR 1.80, 95% CI: 0.99–3.27, $p=0.05$). HCV status (OR 1.55, 95% CI 1.00–2.39, $p=0.05$), increased BMI (OR 1.12, 1.09–01.15, $p<0.0001$), being a current smoker (OR 1.48, 95% 1.03–2.13, $p=0.03$), and Hispanic versus African American race/ethnicity (OR 1.53, 95% CI: 1.04–2.25, $p=0.03$) were also associated (Table 3).

Discussion

In this large study of nondiabetic HIV-infected and uninfected women, we found a marginal association of vitamin D status with insulin resistance as measured by HOMA-IR after adjustment for traditional factors associated with IR. Consistent with prior studies, including our own,[9] Hispanic

Table 1. Characteristics of 1082 WIHS Participants by HIV Status

Characteristics	*HIV positive*	*HIV negative*	p *Value*
Total, *n* (%)	754	328	____
Age, years, *n* (%)			
24–39	229 (30)	150 (46)	<0.0001
40–47	264 (35)	91 (28)	
48–73	261 (35)	87 (27)	
Race, *n* (%)			
African American	416 (55)	197 (60)	0.31
Hispanic	239 (32)	95 (29)	
White/other[a]	99 (13)	36 (11)	
Current smoker, *n* (%)[b]	271 (36)	180 (55)	<0.0001
BMI, kg/m^{2*b}	27.5 (23.6–32.3)	29.2 (24.7–35.1)	0.0002
Menopausal, *n* (%)[b]	207 (28)	59 (18)	0.0009
HCV antibody positive, *n* (%)[b]	180 (24)	51 (16)	0.002
Vitamin D status, *n* (%)			
Normal (>30 ng/mL)	110 (15)	26 (8)	<0.0001
Insufficient (20–30 ng/mL)	194 (26)	58 (18)	
Deficient (<4–19 ng/mL)	450 (60)	244 (74)	
HOMA-IR*	1.93 (1.17–3.04)	1.76 (1.03–3.11)	0.15
HOMA-IR ≥2.6, *n* (%)	245 (32)	109 (33)	0.81
Fasting insulin (μIU/mL)*[b]	9 (6–14)	8 (5–13)	0.05
Fasting glucose (mg/dL)*[b]	86 (80–93)	87 (81–94)	0.04
Hypertensive, *n* (%)[b]	221 (30)	91 (29)	0.67
Estimated glomerular filtration rate*	94.9 (77.0–111.9)	94.0 (82.6–108.9)	0.30
HIV-positive only (n=*754)*			
CD4 cell count*[b]	459 (298–649)	–	–
HIV RNA ≤80 cp/mL *n* (%)	427 (57)	–	–
HAART use, *n* (%)	532 (71)	–	–
PI use, *n* (%)	317 (42)	–	–
NNRTI use, *n* (%)	212 (28)	–	–
Efavirenz use, *n* (%)	144 (19)	–	–

*Value is median (interquartile range).
[a]includes *n*=4 Asian/Pacific Islander; *n*=1 Native American/Alaskan; *n*=13 Other among HIV positive participants, and *n*=4 Asian/Pacific Islander; *n*=2 Native American/Alaskan; *n*=4 Other among HIV negative participants.
[b]Not all cells total 1082 due to missing data.

ethnicity, higher BMI, HCV seropositivity, current smoking, and current/recent PI use among HIV infected women were associated with insulin resistance. Among the 754 HIV-infected women, vitamin D insufficiency was independently associated with IR when using the clinically relevant cut-off of HOMA-IR ≥2.6. This association was not seen in the HIV-uninfected women or among HIV-infected women with vitamin D deficiency. We are unable to explain this finding except that the prevalence of high BMI and vitamin D deficiency was significantly higher among HIV uninfected women. Of note, the existing literature on the role of vitamin D in insulin sensitivity is conflicting and primarily includes HIV-uninfected adults. In a study of 126 adults, there was a positive correlation between vitamin D concentration and insulin sensitivity; people with hypovitaminosis D were at a higher risk of insulin resistance and the metabolic syndrome.[1]

In an analysis of men in Finland, there was an 82% reduced risk of type 2 diabetes mellitus in the highest versus the lowest quartile of vitamin D after adjustment for BMI and other factors.[22] These results and others have led to the exploration of the role of vitamin D replacement in improving insulin sensitivity in ongoing clinical trials in HIV-uninfected children and adults. It is important to note that most of the available studies have been conducted in men, the majority non-black, and the impact of co-morbidities, host genetics, and menopausal status on the vitamin D-IR relationship remains poorly defined. However, there are other studies that do not show an independent association between vitamin D and insulin sensitivity. In one study, there was no cause–effect relationship between vitamin D and insulin sensitivity, and the authors found that both low vitamin D levels and insulin resistance were dependent on the increased body mass index.[23] In addition, the NHANES III data did not show a significant relationship between vitamin D and HOMA-IR in African Americans, who are the majority of our study participants, despite significant results in Caucasian and Mexican Americans.[8] The NHANES study and our study both suggest that in African Americans, who have the highest rates of vitamin D deficiency, other host factors are the major drivers of insulin resistance. Similarly, in the setting of HIV infection, other HIV-related factors may be the major drivers of HOMA-IR. For example, we found a positive association between PI use and HOMA-IR in HIV infected women, which is consistent with other studies.[24,-25] In addition, a recent article showed an association of inflammation with incident diabetes mellitus among HIV-infected adults[26] and this area of research is being actively explored in the WIHS. Vitamin D deficiency has also recently been linked to poor clinical outcomes among HIV-infected women in Tanzania,[27] and the issue of vitamin D deficiency in HIV remains an area of active research interest.

Table 2. Factors Associated with Having a HOMA Value ≥2.6 Among 1082 WIHS Participants

	Unadjusted		*Adjusted*[a]	
Characteristics	*Odds ratio*	*Confidence interval*	*Odds ratio*	*Confidence interval*
Age, years				
24–39	1.00 (reference)		1.00 (reference)	
40–47	0.91	0.66–1.24	0.85	0.59–1.21
48–75	1.32	0.97–1.79	1.32	0.85–2.06
Race				
African American	1.00 (reference)		1.00 (reference)	
Hispanic	1.33	1.00–1.75	1.77	1.29–2.44
White	0.70	0.46–1.07	0.95	0.58–1.55
Current smoker				
No	1.00 (reference)		1.00 (reference)	
Yes	1.14	0.88–1.47	1.49	1.11–2.02
BMI, kg/m^2 (per 1 unit)	1.11	1.08–1.13	1.12	1.10–1.14
Menopausal				
No	1.00 (reference)		1.00 (reference)	
Yes	1.46	1.10–1.95	1.43	0.95–2.14
HCV antibody positive				
No	1.00 (reference)		1.00 (reference)	
Yes	1.30	0.96–1.76	1.49	1.03–2.17
HIV status				
Negative	1.00 (reference)		1.00 (reference)	
Positive	0.97	0.73–1.27	1.23	0.89–1.70
Vitamin D status				
Normal (>30 ng/dL)	1.00 (reference)		1.00 (reference)	
Insufficient (20–30 ng/dL)	1.62	1.01–2.61	1.44	0.85–2.45
Deficient (<4–19 ng/dL)	1.70	1.11–2.60	1.33	0.81–2.18

[a]n = 1047 WIHS participants included in the adjusted model, the model is adjusted for all variables presented.

Table 3. Factors Associated with Having a HOMA Value ≥2.6 Among 754 HIV+ WIHS Participants

	Unadjusted		*Adjusted*[a]	
Characteristics	*Odds ratio*	*Confidence interval*	*Odds ratio*	*Confidence interval*
Age, years				
24–39	1.00 (reference)		1.00 (reference)	
40–47	0.77	0.52–1.13	0.73	0.47–1.14
48–75	1.17	0.81–1.70	1.09	0.64–1.86
Race				
African American	1.00 (reference)		1.00 (reference)	
Hispanic	1.19	0.85–1.66	1.53	1.04–2.25
White	0.85	0.52–1.38	1.29	0.74–2.26
Current smoker				
No	1.00 (reference)		1.00 (reference)	
Yes	1.42	0.83–1.57	1.48	1.03–2.13
BMI, kg/m^2 (per 1 unit)	1.10	1.08–1.13	1.12	1.09–1.15
Menopausal				
No	1.00 (reference)		1.00 (reference)	
Yes	1.46	1.05–2.04	1.44	0.90–2.31
HCV antibody positive				
No	1.00 (reference)		1.00 (reference)	
Yes	1.24	0.87–1.76	1.55	1.00–2.39
Current & past 6 month PI use				
No	1.00 (reference)		1.00 (reference)	
Yes	1.31	0.97–1.78	1.61	1.13–2.28
Vitamin D status				
Normal (>30 ng/dl)	1.00 (reference)		1.00 (reference)	
Insufficient (20–30 ng/dl)	1.78	1.05–3.03	1.80	0.99–3.27
Deficient (<4–19 ng/dl)	1.62	1.00–2.61	1.53	0.87–2.68

[a]n = 734 HIV+ WIHS participants included in the adjusted model, the model is adjusted for all variables presented.

Limitations of our study include our use of HOMA-IR as our measure of insulin sensitivity. While this has been used and validated in the literature,[9,28,29] the gold standard remains the euglycemic clamp. However, given the difficulty of using a clamp technique in a large group of patients, we used the HOMA-IR as a reasonable surrogate. Other limitations include not having bone mineral density data on the women at the time of the vitamin D and insulin measurements. We also did not have detailed nutritional information on all the women, which did not allow us to assess for the impact of nutritional status on vitamin D and insulin resistance measurements.

The strengths of our study include the large dataset of HIV-infected and uninfected women, which allowed us to examine the proposed question adequately of whether vitamin D status is independently associated with insulin resistance using a clinically relevant cut-off of HOMA-IR ≥ 2.6. Second, we were able to determine associations by type of HAART regimen being used and confirm an association between PI use and IR. Finally, our findings confirmed the association of traditional risk factors for insulin resistance in this cohort of HIV infected and at risk seronegative women, similar to other published reports.

In summary, traditional risk factors such as Hispanic ethnicity, higher body mass index, HCV seropositivity, and current smoking were associated with HOMA-IR in nondiabetic HIV-infected and uninfected WIHS women. Among HIV-infected women, in addition to these traditional factors, protease inhibitor use was independently associated with having an elevated HOMA-IR of ≥ 2.6, our marker of significant insulin resistance. Vitamin D insufficiency remained only marginally associated with insulin resistance after controlling for other risk factors.

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Author Disclosure Statement

No competing financial interests exist.

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