The Association of Vitamin D Deficiency and Insufficiency with Diabetic Nephropathy: Implications for Health Disparities

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Objective: To evaluate the association between vitamin D deficiency and insufficiency with diabetic nephropathy across racial/ethnic groups.

Methods: Cross-sectional analysis of the 2001 to 2006 National Health and Nutrition Examination Survey. A nationally representative sample of 1216 adults (≥20 years old) with diagnosed diabetes provides population estimates for >12.6 million individuals. Nephropathy was defined as urinary albumin-to-creatinine ratio ≥30 mg/g in a random spot urine sample. Serum 25-hydroxycholecalciferol vitamin D levels were characterized as <20 ng/mL vitamin D deficiency, 20 to 29 ng/mL vitamin D insufficiency, and ≥30 ng/mL normal vitamin D.

Results: Overall, 30.7% of adults with diabetes have nephropathy, 48.9% have vitamin D deficiency and 36.6% have vitamin D insufficiency. Minorities are more likely to have nephropathy (non-Hispanic whites, 27.8%; non-Hispanic blacks, 36.2%; Hispanics 38.5%; P = .02) and vitamin D deficiency (non-Hispanic whites, 39.5%; non-Hispanic blacks, 80.4%; Hispanic, 59.0%; P < .01). Higher proportions of individuals with nephropathy have vitamin D deficiency than individuals without nephropathy (53.2% vs 47.0%; P = .03). Logistic regressions demonstrate vitamin D deficiency and insufficiency are associated with the presence of nephropathy after adjustment for race/ethnicity, age, sex, hypertension, high cholesterol, smoking status, and use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (odds ratio, 1.85; 95% CI, 1.06–3.23 for vitamin D deficiency; and odds ratio, 1.79; 95% CI, 1.12–2.85 for vitamin D insufficiency).

Conclusions: There is a high prevalence of vitamin D deficiency and insufficiency in individuals with diabetes; minorities have the highest prevalences. Thus, evaluating vitamin D levels in people with diabetes may be warranted. There is an independent association between vitamin D deficiency and vitamin D insufficiency with the presence of nephropathy, even after adjustment for race/ethnicity and other variables. Further studies of this relationship may lead to new interventions that decrease health disparities in the progression of diabetic nephropathy. (J Am Board Fam Med 2009;22:521–527.)

Background

Diabetic nephropathy is a risk factor for cardiovascular disease and the leading cause of chronic kidney disease in patients starting renal replacement therapy. Racial and ethnic differences exist in the prevalence of diabetic nephropathy. A study evaluating people with diabetes in the United States shows that non-Hispanic blacks and Hispanics are less likely to have normal renal function than non-Hispanic whites. Similarly, the incidence of reported end-stage renal disease in people with diabetes is more than 4 times as high in African Americans and 4 to 6 times as high in Mexican Americans than in the general population of diabetes patients. These disparities exist despite similar proportions of blacks, whites, and Hispanics meeting recommendations for glycated hemoglobin and blood pressure control and similar proportions with rennin-angiotensin system blockade via use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin II type 1 receptor blockers (ARBs). Thus, reasons for the racial/ethnic disparities seen in diabetic nephropathy are unclear.

A factor that may impact the differential development of diabetic nephropathy is vitamin D. The
role of the kidney in the hydroxylation of the vita-
mim D metabolite 25-hydroxycholecalciferol (25-OH-D)
from the liver to the biologically active form of
1,25(OH)2D3 is well established.4,5 Animal studies
suggest that, in addition to the impact that chronic
renal failure has on increasing the likelihood of
1,25(OH)2D3 deficiency and insufficiency caused
by the kidney’s role in vitamin D metabolism, vi-
tamin D deficiency and insufficiency also have an
active role in the progression of kidney disease.6–9
Inhibition of the renin-angiotensin system by the
vitamin D metabolite has been demonstrated in
vitro; animal studies suggest that receptor-medi-
vated vitamin D actions have a renoprotective role in
diabetic nephropathy.6,7 These findings are sup-
ported by rat studies that show 1,25(OH)2D3 ad-
ministration attenuates the development of glo-
merulosclerosis and the progression of proteinuria
through parathyroid hormone-independent anti-
proliferative actions and decreases in podocyte loss
and podocyte hypertrophy.8,9 These findings may
be especially pertinent in individuals with diabetic
nephropathy because, in addition to the direct im-
 pact on renal function, adequate levels of vitamin D
are also associated with decreased insulin resistance
and reduced blood pressure, the 2 main, potentially
modifiable risk factors for diabetic nephropathy
initiation and progression.1,10 However, little in-
formation is available about the association be-
tween diabetic nephropathy and vitamin D levels in
humans.

It has been estimated that 1 billion people
worldwide have vitamin D deficiency or insuffi-
ciency.10 Minorities are more likely to be deficient
in vitamin D because of low dietary intake as well as
the role of solar ultraviolet B radiation in vitamin D
metabolism, causing the increased pigmentation in
groups with darker skin to reduce vitamin D pro-
duction in the skin.11,12 Thus, the health disparities
currently seen in diabetic nephropathy may be par-
tially explained by differences in vitamin D levels
by race/ethnicity. Therefore, this study will eval-
uate the association between Vitamin D and diabetic
nephropathy in a nationally representative sample
of people with diabetes.

Methods
Survey Description
Data from the 2001 to 2006 National Health and
Nutrition Examination Survey (NHANES) was an-
alyzed. The NHANES is a product of the National
Center for Health Statistics. It is a continuous,
annual survey involving participants from a nation-
ally representative sample of noninstitutional-
ized residents of the United States. Samples are
weighted so they are representative of the US pop-
ulation. Sampling weights are calculated by taking
into account unequal probabilities of selection
caused by sample design, nonresponse and planned
over-sampling of minorities, and then matched to
population control totals known to be representa-
tive of the US population. This allows for the
calculation of population estimates for the United
States.13 The NHANES includes a detailed house-
hold interview and physical examination plus labo-
atory information obtained through mobile exam-
ination centers. Data are collected throughout the
year across designated data collection communities
in the United States. To protect the anonymity of
the respondents, the month of data collection and
the specific community of origin of the respondent
is not released to the public. The reported investiga-
tions have been conducted in accordance with
the principles of the Declaration of Helsinki as
revised in 2000.

Sample
Adults (≥20 years of age) who reported a diagnosis
of diabetes by answering yes to the question,
“Other than during pregnancy, have you ever been
told by a doctor or health professional that you
have diabetes or sugar diabetes?” were included in
this sample. Participants self-identified as non-His-
panic white, non-Hispanic black, or Hispanic. Be-
cause of the small size and heterogeneity of the
“Other” racial category, this group was not ana-
alyzed.

Definition of Diabetic Nephropathy
Consistent with American Diabetes Association
guidelines, albumin and creatinine were measured
in a random spot urine sample.14 These measure-
ments were used to calculate the urinary albumin-
to-creatinine ratio. Values of <30 mg/g were char-
acterized as being normal, whereas values ≥30
mg/g describe either microalbuminuria or mac-
roalbuminuria.14 Thus, in this study, nephropathy
was defined as a urinary albumin-to-creatinine ratio
≥30 mg/g.
**Definition of Vitamin D Deficiency and Vitamin D Insufficiency**

Vitamin D status in the serum is evaluated based on the Diasorin 25-OH-D assay, which measures 25-OH-D. This is the predominant circulating form of vitamin D in the normal population and is the most commonly used to determine vitamin D status. Although there is no consensus on optimal levels of 25-OH-D, data suggests that levels ≥30 ng/mL can be considered an indication of sufficient vitamin D. Thus, individuals with 25-OH-D levels <20 ng/mL and 20 to 29 ng/mL were characterized having vitamin D deficiency and vitamin D insufficiency, respectively. This is consistent with recommendations from the National Kidney Foundation.

**Medication Use**

Participants were asked to present the containers for all the prescription medications taken during the past month and to report any medications taken for which the container was not available. These medications were then matched by trained survey interviewers to an annually updated comprehensive database of all prescription drugs in the US market. Products not matched to the drug database were edited after data collection at the National Center for Health Statistics, where quality control activities resulted in <1% of medications being listed as unknown. All reported medication names were converted to their standard generic ingredient name for data release. These generic names were used to identify medications as ACE inhibitors or ARBs. Use of these medications was included in addition to the diagnosis of hypertension because data suggests that they provide benefits beyond their effect on blood pressure in the prevention and delay of diabetic kidney disease.

**Definitions of Disease**

Hypertension was assessed by self-report. Individuals who reported ever being told they had hypertension or high blood pressure were classified as having hypertension. Having diagnosed high cholesterol were assessed as possible confounding variables because dyslipidemia and hypertension are established risk factors for diabetic nephropathy. Obesity was based on body mass index (BMI), calculated using measured weight and height (kg/m²). BMI categories were consistent with 1998 National Heart, Lung and Blood Institute guidelines, which classify obesity as a BMI of ≥30.0.

**Smoking Status**

Smoking has been demonstrated to be a putative risk factor for diabetic nephropathy. Smoking status was assessed using 2 questions to characterize individuals as never, former, or current smokers.

**Analysis**

Because the NHANES 2001 to 2006 is a complex, stratified cluster sample, standard statistical techniques could not be used. Therefore, we used SUDAAN (Research Triangle Institute, Research Triangle, NC), a specialized statistical program that accounts for the complex weighting of the NHANES sample. Using SUDAAN allowed us to correct for unequal probabilities of selection and different response rates, ensuring that the results could be generalized to the noninstitutionalized civilian population of the United States. Thus the percentages and odds ratios in this study represented weighted values. SUDAAN also adjusts the standard errors to account for the weighting, stratification, and clustering of the complex sampling design to ensure that expressed P is valid. The prevalences of demographic and disease characteristics were assessed within the overall population and also by race/ethnicity, where they were compared using χ² tests. Similarly, the prevalences of these characteristics were also assessed and compared in those with and without nephropathy. Logistic regressions were used to determine the independent relationship between vitamin D status and high cholesterol.
diabetic nephropathy. An unadjusted regression was computed initially. Regressions adjusting for race/ethnicity, age, sex, and for these demographic variables in addition to other predictor variables were also computed. The other predictor variables evaluated were hypertension, high cholesterol, smoking status, obesity, and use of an ACE inhibitor or ARB.

Results

The inclusion criteria for this study provided an unweighted sample size of 1216, which could be used to provide population estimates for more than 12.6 million individuals. Overall, 48.9% of the participants had vitamin D deficiency (<20 ng/mL) and 36.6% of the participants had vitamin D insufficiency. The mean vitamin D concentration in our sample was 20.6 ng/mL (95% CI, 19.6–21.6). Demographic and disease characteristics for adults with diabetes by race/ethnicity are presented in Table 1. Differences in age and sex exist by race/ethnicity, with non-Hispanic whites being older and a higher proportion of non-Hispanic blacks being women. Minorities had a higher proportion of individuals with nephropathy and were more likely to have vitamin D deficiency. In fact, 80% of non-Hispanic blacks and 59% of Hispanics with diabetes exhibited vitamin D deficiency.

As seen in Table 2, higher proportions of individuals with nephropathy had vitamin D deficiency versus individuals without nephropathy. Table 3 presents results from logistic regressions, which demonstrate that this relationship remains even after controlling for demographic variables such as race/ethnicity, age, and sex as well as other variables. The odds ratios for the unadjusted and adjusted relationships remained similar, demonstrating the independent nature of the relationship between low levels of serum vitamin D and the presence of nephropathy. We also tested the relationship between urinary albumin-to-creatinine ratio and vitamin D (both continuous) in linear regressions. The unadjusted β for vitamin D was −9.49 (95% CI, −15.09 to −3.88) and was significant at $P = .01$. Adjusting for demographic vari-

| Table 1. Demographics and Characteristics of Adults (≥20 Years Old) with Diagnosed Diabetes |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                                  | Total           | Non-Hispanic White | Non-Hispanic Black | Hispanic        |     |
| Weighted sample size (n, in millions) | 12.6            | 8.8              | 2.0              | 1.8             |     |
| Age (%)                          |                 |                  |                  |                 |     |
| 20 to 45                         | 18.4            | 15.0             | 23.8             | 28.4            | <.01 |
| >45                              | 81.6            | 85.0             | 76.2             | 71.6            |     |
| Sex (%)                          |                 |                  |                  |                 |     |
| Male                             | 47.9            | 49.0             | 42.6             | 48.4            | .18  |
| Female                           | 52.1            | 51.0             | 57.4             | 51.6            |     |
| Smoking status (%)               |                 |                  |                  |                 |     |
| Never                            | 47.4            | 47.3             | 44.9             | 50.2            | <.01 |
| Former                           | 33.4            | 35.9             | 28.0             | 27.3            |     |
| Current                          | 19.2            | 16.7             | 27.0             | 22.5            |     |
| BMI [kg/m²] (%)                  |                 |                  |                  |                 |     |
| <30                              | 43.3            | 41.6             | 38.3             | 57.0            | .01  |
| ≥30                              | 56.7            | 58.4             | 61.7             | 43.0            |     |
| Nephropathy (%)                  | 30.7            | 27.8             | 36.2             | 38.5            | .02  |
| Diagnosed hypertension (%)       | 64.2            | 65.5             | 74.9             | 46.0            | <.01 |
| Diagnosed high cholesterol (%)   | 57.6            | 60.8             | 50.2             | 50.7            | .02  |
| On ACE inhibitors/ARB (%)        | 11.9            | 12.8             | 11.1             | 8.6             | .37  |
| Vitamin D (%)                    |                 |                  |                  |                 |     |
| <20 ng/mL                        | 48.9            | 39.5             | 80.4             | 59.0            | <.01 |
| 20 to 29 ng/mL                   | 36.6            | 41.2             | 18.1             | 34.8            |     |
| ≥30 ng/mL                        | 14.5            | 19.2             | 1.5              | 6.1             |     |

*P calculated using χ² tests.

BMI, Body Mass Index; ACE, angiotensin-converting enzyme; ARB, angiotensin II type 1 receptor blockers.
ables the β for vitamin D was −8.77 (95% CI, −13.93 to −3.61), which was significant at \( P = .01 \).

In the fully adjusted regression, vitamin D had a β of −8.94 (95% CI, −14.29 to −3.60), significant at \( P = .01 \). In a subanalysis excluding persons with macroalbuminuria, vitamin D <30 ng/mL had an odds ratio of 1.78 (95% CI, 1.02–3.08) for nephropathy when compared with vitamin D >30 ng/mL, indicating that the relationship holds for persons with less significant disease.

**Discussion**

Findings from this study show an association between vitamin D deficiency and vitamin D insufficiency with nephropathy in a sample of US adults with diabetes. Furthermore, this association remains despite adjusting for race/ethnicity, the presence of hypertension, and medication use as well as other factors, demonstrating a robust relationship. This is one of the first studies in humans showing this association. Because of the cross-sectional na-

Table 2. Demographics and Characteristics of Adults (≥20 Years Old) with Diagnosed Diabetes by Nephropathy Status

<table>
<thead>
<tr>
<th></th>
<th>Nephropathy</th>
<th>No Nephropathy</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20 to 45</td>
<td>17.8</td>
<td>18.6</td>
<td>.81</td>
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<tr>
<td>&gt;45</td>
<td>82.2</td>
<td>81.4</td>
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<tr>
<td>Sex (%)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>56.4</td>
<td>44.1</td>
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</tr>
<tr>
<td>Female</td>
<td>43.6</td>
<td>55.9</td>
<td></td>
</tr>
<tr>
<td>Race/Ethnicity (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic white</td>
<td>62.9</td>
<td>72.3</td>
<td>.02</td>
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<tr>
<td>Non-Hispanic black</td>
<td>18.9</td>
<td>14.8</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>18.2</td>
<td>12.9</td>
<td></td>
</tr>
<tr>
<td>BMI [kg/m²] (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30</td>
<td>42.9</td>
<td>43.5</td>
<td>.87</td>
</tr>
<tr>
<td>≥30</td>
<td>57.1</td>
<td>56.5</td>
<td></td>
</tr>
<tr>
<td>Diagnosed hypertension (%)</td>
<td>72.3</td>
<td>60.6</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Diagnosed high cholesterol (%)</td>
<td>52.8</td>
<td>59.8</td>
<td>.08</td>
</tr>
<tr>
<td>Smoking status (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>39.9</td>
<td>50.7</td>
<td>.01</td>
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<tr>
<td>Former</td>
<td>37.4</td>
<td>31.7</td>
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</tr>
<tr>
<td>Current</td>
<td>22.7</td>
<td>17.7</td>
<td></td>
</tr>
<tr>
<td>On ACE inhibitors/ARB (%)</td>
<td>15.3</td>
<td>10.4</td>
<td>.02</td>
</tr>
<tr>
<td>Vitamin D (%)</td>
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<tr>
<td>&lt;20 ng/mL</td>
<td>53.2</td>
<td>47.0</td>
<td>.03</td>
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<tr>
<td>20 to 29 ng/mL</td>
<td>37.2</td>
<td>36.4</td>
<td></td>
</tr>
<tr>
<td>≥30 ng/mL</td>
<td>9.6</td>
<td>16.6</td>
<td></td>
</tr>
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</table>

* \( P \) calculated using \( \chi^2 \) tests.

BMI, Body Mass Index; ACE, angiotensin-converting enzyme; ARB, angiotensin II type 1 receptor blockers.

Table 3. Logistic Regression Predicting Nephropathy Among Adults (≥20 Years Old) With Diabetes

<table>
<thead>
<tr>
<th>Vitamin D (ng/ML)</th>
<th>Odds Ratio (95% CI)</th>
<th>Odds Ratio (95% CI)*</th>
<th>Odds Ratio (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20</td>
<td>1.96 (1.21–3.19)</td>
<td>1.78 (1.04–3.06)</td>
<td>1.85 (1.06–3.23)</td>
</tr>
<tr>
<td>20 to 29</td>
<td>1.77 (1.11–2.81)</td>
<td>1.62 (1.03–2.55)</td>
<td>1.79 (1.12–2.85)</td>
</tr>
<tr>
<td>≥30</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
</tbody>
</table>

*Regression also controls for: age, gender, race/ethnicity.

†Regression also controls for: age, gender, race/ethnicity, hypertension, high cholesterol, smoking status, use of angiotensin-converting enzyme inhibitor or angiotensin II type 1 receptor blockers, obesity.
ture of this study, we were unable to determine whether this association is present because vitamin D deficiency increases the risk of nephropathy or because nephropathy increases the risk of vitamin D deficiency. Previous studies suggest that the relationship between these 2 variables is such that both of these interactions may be occurring simultaneously. This study evaluates 25-OH-D, the circulating metabolite produced in the liver that is later metabolized in the kidneys to 1,25(OH)2D3. Based on this well-established pathway, renal insufficiency could not be the reason for the low levels of 25-OH-D seen in study. This suggests that studies to further describe the role of vitamin D as a possible risk marker or risk factor in diabetic nephropathy are needed to evaluate the impact of maintaining an adequate level of vitamin D on the progression of diabetic nephropathy. Studies demonstrating a benefit to vitamin D supplementation for total mortality suggest that this may be a strategy to consider in future studies. Further studies should also evaluate the value of vitamin D as an independent predictor of the progression of nephropathy as compared with other possible predictors.

This study also described the high prevalence of vitamin D deficiency in patients with diabetes, regardless of their kidney function. This finding highlights the need to improve screening for vitamin D deficiency in patients with diabetes, especially minority populations, because vitamin D is known to have a role in decreasing the risk of many chronic illnesses, including cancer, cardiovascular disease, and infectious diseases. This is especially pertinent for individuals with diabetes, who are at a higher risk of developing these conditions than the general population and thus may receive a greater benefit from having higher vitamin D levels.

There are limitations to this study that should be considered. As previously mentioned, the cross-sectional nature of the data limited inference and only allowed for the identification of associations. We were only able to measure 25-OH-D in this study, which did not allow us to evaluate the role of the kidney in metabolizing this form of vitamin D to the biologically active metabolite 1,25(OH)2D3. This is an accepted approach to the evaluation of vitamin D status because only a small amount of 25-OH-D is metabolized in the kidney. We were unable to identify the month of the year in which respondents participated in the examination because of confidentiality issues in the NHANES. However, NHANES data are collected throughout the year and across the country so we would not expect a bias in racial data collection during specific seasons of the year. Finally, there was no consensus on the level of 25-OH-D that denotes insufficiency. Thus, analyses were also performed evaluating another commonly used threshold (≥32 ng/ml), and these yielded similar results.

**Conclusion**

This study demonstrated an association between vitamin D deficiency and vitamin D insufficiency with nephropathy in individuals with diabetes even after controlling for factors such as race/ethnicity and the presence of hypertension and use of ACE inhibitors or ARBs. The high prevalence of vitamin D deficiency and vitamin D insufficiency in individuals with diabetes, especially in minorities, suggest that further study of this relationship may lead to new interventions to delay the progression of diabetic nephropathy.

**References**


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