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Association between vitamin D and diabetic neuropathy in a nationally representative sample: results from 2001–2004 NHANES

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Abstract

Aims—To evaluate the association between vitamin D insufficiency and peripheral neuropathy in a nationally representative sample of adults with diagnosed diabetes.

Methods—Vitamin D concentrations, medical examination variables and questionnaire results from the 2001–2004 National Health and Nutrition Examination Survey were analysed for adults ≥ 40 years old with diagnosed diabetes (unweighted $n = 591$, weighted $n = 8.82$ million). Neuropathy was defined as self report of peripheral neuropathy symptoms of painful sensation, tingling, numbness or loss of feeling in hands or feet. Additionally, Semmes–Weinstein monofilament test results were used as an indicator of neuropathy. Insufficient vitamin D was characterized as < 30 ng/ml.

Results—In the weighted population, 81% of adults with diabetes had vitamin D insufficiency. Vitamin D insufficiency was more common among Hispanics (92%) and non-Hispanic black people (98%) than among non-Hispanic white people (76%). Within the 3 months preceding the questionnaire, 50% reported experiencing pain or numbness (paresthesia) in their hands or feet; 37% reported pain or tingling in hands or feet; and 38% reported numbness or loss of feeling in hands or feet. Eight per cent had 4–6 insensate areas on their feet as determined by the Semmes–Weinstein monofilament test. Logistic regressions demonstrate vitamin D insufficiency is associated with the adjusted composite paresthesia measure (odds ratio 2.12; 95% CI 1.17–3.85) and the adjusted numbness measure (odds ratio 2.04; 95% CI 1.18–3.52).

Conclusions—Vitamin D insufficiency is associated with self-reported peripheral neuropathy symptoms even after adjusting for demographic factors, obesity, co-morbidities, use of medications for neuropathy and diabetes duration and control.

Keywords

diabetes mellitus; peripheral neuropathy; vitamin D

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Introduction

Vitamin D provides health benefits for diseases including cancer and heart disease [1], osteoporosis [2] and diabetes. Vitamin D insufficiency is common among those diagnosed with diabetes [3,4]. Several studies have suggested that adequate intake of vitamin D may prevent or delay the onset of diabetes, as well as reduce complications for those who have already been diagnosed [3,5–7].

Diabetes is associated with complications such as cardiovascular disease, renal impairment and neuropathy. Specifically, approximately 60–70% of people with diabetes have some type of neuropathy[8], with up to 50% of neuropathic patients experiencing some degree of painful symptoms [9]. Evidence exists that quality of life is significantly more impaired among patients with diabetic peripheral neuropathic pain than among diabetic patients without neuropathy [9].

Vitamin D has been experimentally linked to the regulation of neurotrophin levels and neuronal Ca^{2+} homeostasis, both of which may provide a neuroprotective effect [10]. The influence of vitamin D on nerve function is supported in an animal model of diabetic rats with deficiencies in nerve growth factor synthesis; treatment of these rats with vitamin D increased nerve growth factor production and prevented neurotrophic deficit [11]. The data in humans regarding vitamin D insufficiency and diabetic neuropathy are limited. A recently reported prospective study of 51 patients with Type 2 diabetes and associated chronic, painful neuropathy found that conservative vitamin D supplementation for 3 months resulted in a nearly 50% decrease in pain scores [12]. Lee and Chen's study was the first to investigate this relationship and was carried out in a small racially homogenous sample in Australia. This study will evaluate the association between vitamin D insufficiency and peripheral neuropathy and neuropathic pain in a nationally representative sample of people with diabetes.

Methods

Data source

We analysed data contained in the publicly available National Health and Nutrition Examination Survey (NHANES), 2001–2004, which was implemented by the US National Center for Health Statistics and includes a household interview, physician examination and laboratory and diagnostic testing. The NHANES 2001–2004 is a nationally representative de-identified sample of the non-institutionalized US population. The design includes an over-sampling of minorities and an ability to make estimates for the US population. More information on the methodology of the NHANES 2001–2004 can be found at http://www.cdc.gov/nchs/nhanes.htm.

Our sample consists of adults (ages 40 years and older) diagnosed with diabetes who had data on vitamin D, the Semmes–Weinstein monofilament test and self-reported peripheral neuropathy symptoms. We identified people as having diabetes if they answered 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?'. Individuals who answered no or 'borderline' were excluded from our sample. We limited our population to people 40 years and older because the NHANES only asked peripheral neuropathy questions and performed Semmes–Weinstein monofilament testing for people in this age range. Stroke can cause neuropathy, so we excluded all participants who reported a history of stroke. Because foot ulcers could lead to a reduction in exposure to sunlight and thereby a reduction in vitamin D levels, we excluded participants who had one or more foot lesions upon examination. We

also excluded pregnant women, because of possible temporary changes in blood chemistry, circulation and pain sensitivity.

Serum vitamin D

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 primarily from bone metabolism studies suggest that levels ≥ 30 ng/ml can be considered an indication of sufficient vitamin D [2]. Thus, individuals with 25-OH-D levels < 30 ng/ml were characterized as having vitamin D insufficiency. We also categorized serum vitamin D as < 20 ng/ml, as < 10 ng/ml and as quartiles.

Vitamin D supplements

NHANES participants were asked if they were taking any dietary supplements. If they responded yes, they were asked to provide supplement containers or a list of the supplements they were taking. The NHANES supplement ingredient database was used to determine whether vitamin D was an ingredient in any of the supplements taken by the participants in our sample. Unfortunately, the data set did not allow us to distinguish between the ergocalciferol and colecalciferol forms of vitamin D.

Self report of peripheral neuropathy symptoms

NHANES participants aged 40 years and older were asked the following questions: (1) ‘During the past 3 months, have you had a painful sensation or tingling in your hands or feet? Do not include normal foot aches from standing or walking for long periods.’ and (2) ‘During the past 3 months, have you had numbness or loss of feeling in your hands or feet, other than from your hands or feet falling asleep?’ Participants who answered yes to question 1 were included in the pain group, participants who answered yes to question 2 were included in the numbness group, and participants who answered yes to questions 1 or 2 were included in the composite paresthesia group.

Number of insensate areas on feet; 5.07 Semmes–Weinstein monofilament testing

Loss of protective sensation was ascertained by a standard monofilament test. Slight pressure with a 5.07 Semmes–Weinstein monofilament was applied up to three times to each of three areas on each foot (hallux and first and fifth metatarsal heads). The testing used a two-alternative forced-choice algorithm. Further details of the NHANES testing procedure are available at http://www.cdc.gov/nchs/nhanes.htm. Detection of one or more insensate areas on the feet via 5.07 Semmes–Weinstein monofilament testing in persons with diabetes has been shown to be predictive of future diabetic foot ulceration [13] and it has been used previously to estimate the prevalence of peripheral neuropathy in populations [14]. For the purpose of determining whether vitamin D level is associated with insensate areas on the feet, we compared individuals with 0 insensate areas to individuals with 4–6 insensate areas.

Potential confounders

We investigated demographic characteristics including age, sex and race/ethnicity. Participants self-identified as non-Hispanic white, non-Hispanic black or Hispanic. Because of the small size and heterogeneity of the ‘other’ racial category, this group was not analysed. People were placed in the ‘no health insurance’ group if they answered no to the question ‘Are you covered by health insurance or some other kind of healthcare plan? (Include health insurance obtained through employment or purchased directly, as well as government programs like Medicare and Medicaid that provide medical care or help pay

medical bills.)' We included this variable to control for possible group differences in healthcare access levels.

High body mass index and hypertension are established risk factors for diabetic neuropathy [15]. Participants were classified as having hypertension if they answered yes to the NHANES survey question 'Have you ever been told by a doctor or other health professional that you had hypertension, also called high blood pressure?' or if they had an averaged systolic blood pressure ≥ 140 mmHg or an averaged diastolic blood pressure ≥ 90 mmHg. Body mass index (kg/m^2) was measured in the NHANES 2001–2004 through a physical examination. Smoking has also been demonstrated to be a risk factor for diabetic neuropathy [15,16]. Smoking status was assessed using two questions to characterize individuals as current, former or never smokers. Current cigarette smoking was defined as answering yes to the question 'Have you smoked at least 100 cigarettes in your entire life?' and answering 'every day' or 'some days' to the question 'Do you now smoke cigarettes?' Individuals who answered yes to the first question and answered 'not at all' to the second question were defined as being a former smoker. Those answering no to both questions were defined as never smoking.

We investigated glycaemic control via HbA_{1c} levels. The American Diabetes Association recommends that adults with diabetes should maintain HbA_{1c} levels below 53 mmol/mol (7.0%) in order to reduce the incidence of neuropathic complications [17]. Neuropathic symptoms increase with duration of disease [18]. There is evidence that people who have had diabetes for 25 years or more have the highest rates of neuropathy [8]. Therefore, we grouped people based on years since diagnosis with diabetes. We also examined the medication lists of the NHANES participants to determine whether they were taking neuropathic pain medications, specifically tricyclic antidepressants, paroxetine, duloxetine, venlafaxine, trazodone, carbamazepine, lamotrigine, gabapentin, pregabalin, tramadol or mexiletine [19].

Analysis

We used SUDAAN (Research Triangle Institute, Research Triangle, NC, USA), a specialized statistical program that accounts for the complex survey design of the NHANES sample. As recommended for NHANES analysis, we combined sample weights for the 2001–2002 and 2003–2004 data releases. Using SUDAAN allowed us to correct for unequal probabilities of selection and different response rates, ensuring that the results could be generalized to the non-institutionalized civilian population of the USA. Thus, the percentages and odds ratios in the study represent weighted values. SUDAAN also adjusts standard errors to account for the weighting, stratification and clustering of the complex sampling design to ensure that expressed P is valid.

The prevalence of demographic and disease characteristics were assessed for people with diabetes who reported that they had experienced numbness, loss of feeling, pain or tingling in their hands or feet within the last 3 months (the composite paresthesia group) and for people with diabetes who reported not experiencing these symptoms; these two groups were compared using χ^2 tests.

Logistic regressions were used to determine the independent relationship between vitamin D status and each of the four different measures of diabetic peripheral neuropathy. An unadjusted regression was computed initially. Regressions adjusting for age, sex, race/ethnicity, possession of health insurance, obesity, hypertension, smoking status, HbA_{1c}, time since diabetes diagnosis and use of neuropathic pain medications were also computed. $P < 0.05$ was determined to be significant.

Results

The inclusion criteria for this study provided an unweighted sample size of 591, which may be used to provide population estimates for 8.82 million adults with diabetes (age 40 years and older) in the USA. Overall, 81% of the weighted population had vitamin D insufficiency (< 30 ng/mL). Vitamin D insufficiency was more common among Hispanics (92%) and non-Hispanic black people (98%) than among non-Hispanic white people (76%; $P < 0.01$). The mean vitamin D concentration in the weighted population was 22.2 ng/ml (95% CI, 20.8–23.6).

In terms of peripheral neuropathy measures in the weighted population, 50% reported experiencing paresthesia in their hands or feet within the last 3 months; 37% reported pain or tingling in hands or feet; 38% reported numbness or loss of feeling in hands or feet; and 8% had 4–6 insensate areas on their feet as determined by the Semmes–Weinstein monofilament test.

Demographic and disease characteristics for adults with diabetes are presented in Table 1. As seen in Table 1, significantly higher proportions of individuals with insufficient vitamin D, a history of smoking, 11 or more years since diabetes diagnosis and one or more insensate areas on their feet were observed in the paresthesia group in comparison with the no-paresthesia group. Supplements containing vitamin D were taken by 15.7% of the paresthesia group and 13.0% of the no-paresthesia group ($P = 0.51$). The mean vitamin D supplement content was 305 IU (95% CI 244–366 IU) in the paresthesia group and 302 IU (95% CI 232–371 IU) in the no-paresthesia group.

Table 2 presents results from logistic regressions predicting the presence of self-reported peripheral neuropathy outcomes based on insufficient vitamin D (< 30 ng/ml). A significant association with insufficient vitamin D was found with the composite paresthesia measure and the adjusted numbness measure. No significant association was yielded between insufficient vitamin D and self-reported neuropathic pain.

We also examined the relationship using a vitamin D cut-off of 20 ng/ml (odds ratio 0.76, 95% CI 0.43–1.35) and a vitamin D cut-off of 10 ng/ml (odds ratio 0.57, 95% CI 0.23–1.39), as well as by categorizing serum vitamin D levels into quartiles. With a reference category of > 27.61 ng/ml, the odds ratio for the second quartile of 21.42–27.61 ng/ml was 1.17 (95% CI 0.57–2.42), the odds ratio for the third quartile of 15.36–21.41 ng/ml was 1.01 (95% CI 0.50– 2.05) and the odds ratio for the fourth quartile of < 15.36 ng/ml was 0.83 (95% CI 0.40–1.74). Although the number of insensate areas on the feet as determined by the Semmes– Weinstein test is associated with self-reported paresthesia (Table 1), no significant relationship was yielded between vitamin D levels and 0 vs. 4–6 insensate areas in an adjusted logistic regression (2.11, 95% CI 0.77–5.80).

To evaluate the relationship between vitamin D level and peripheral neuropathy symptoms by race, we ran fully adjusted logistic regressions using insufficient vitamin D to predict self-reported paresthesia for non-Hispanic white people only (odds ratio 2.26, 95% CI 1.23–4.15) and for non-Hispanic black people and Hispanics together (odds ratio 1.67, 95% CI 0.30–9.29). Because of the small proportion of non-Hispanic black and Hispanic participants with sufficient vitamin D in our sample (16/317), we did not have enough power to reliably assess an association between insufficient vitamin D and paresthesia in these race/ethnicity groups.

Discussion

Findings from this study show an association between vitamin D insufficiency (< 30 ng/ml) and self-reported peripheral neuropathy symptoms—numbness, loss of feeling, pain and tingling in hands or feet—in a representative population of US adults with diabetes. This association remains after adjusting for demographic factors, obesity, co-morbidities, use of medications for neuropathy and diabetes duration and control, demonstrating a robust relationship. The mechanism behind this finding is currently unclear. Vitamin D may be acting solely as a marker of good health and may not be directly involved in nerve function. Conversely, vitamin D is known to impact diabetes control [6], so it could be expected that some of the beneficial effects may be attributable to improved disease control. However, as the association remains after controlling for HbA_{1c}, a more direct effect on diabetic neuropathy may be present. Animal studies [10,11] and studies linking vitamin D and cognition [20,21] suggest a direct impact on nerve function may be involved, but further studies are needed to evaluate this and other possible mechanisms.

We found an association between insufficient vitamin D and self-reported peripheral neuropathy using a cut-off of 30 ng/ml, but not when using cut-offs of 20 ng/ml, 10 ng/ml or quartiles. These findings suggest a threshold effect that is near or above 30 ng/ml. The majority of the participants in our sample had insufficient vitamin D, which suggests that many patients with diabetic neuropathy may benefit from treatment to increase serum vitamin D to a sufficient level.

There are limitations to this study that should be considered. The cross-sectional nature of the data limited inferences that could be made and only allowed for the identification of associations. Our methods may underestimate the incidence of peripheral neuropathy in our sample; unfortunately, more sensitive assessments of nerve fibre damage such as quantitative sensory testing were not available. Conversely, while numbness, loss of feeling, pain and tingling are all symptoms of diabetic neuropathy, we cannot conclude that those who reported these symptoms have diagnosable peripheral neuropathy. However, 17.8% of those who reported paresthesia within the past 3 months were taking medication for neuropathy compared to 8.0% of those who did not report paresthesia. We did not find a significant association between insufficient vitamin D and neuropathic pain. Participants in our sample had a minimum age of 40 years, limiting the transferability of our results to younger people with diabetic neuropathy. Also, the NHANES 2001–2004 did not specify whether participants had Type 1 or Type 2 diabetes. Although we do not hypothesize differences in the relationship between vitamin D and neuropathy between these patient groups, there may be some differences which affect the relationship. Finally, because of the small proportion of non-Hispanic black and Hispanic participants in our sample who had sufficient vitamin D, we did not have adequate power to reliably test for an association between insufficient vitamin D and peripheral neuropathy symptoms in that subpopulation; instead, we provide results for the nationally representative sample as a whole.

From this study it is unclear whether supplementation with vitamin D could help decrease the severity of symptoms caused by diabetic neuropathy or whether a low level of vitamin D is a marker for other factors that could increase the severity of symptoms. This suggests that studies to further understand the role of vitamin D in diabetic neuropathy are needed to evaluate the impact of maintaining an adequate level of vitamin D on symptom control. Because non-Hispanic black and Hispanic participants with diabetes have such high rates of vitamin D insufficiency, making it difficult to evaluate whether there is an association between insufficient vitamin D and peripheral neuropathy symptoms in those sub-populations, it would be especially informative to include non-Hispanic black people and Hispanics in a trial of vitamin D supplementation and peripheral neuropathy symptoms in

people with diabetes. Because of the impact of diabetic neuropathy on quality of life, novel interventions that are safe, low in cost and effective are needed. Further studies are needed to evaluate the value of vitamin D supplementation as a novel intervention.

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Table 1

Demographics and disease characteristics of adults (≥ 40 years old) with diagnosed diabetes by self-reported peripheral neuropathy status

	Total sample	Paresthesia symptoms in hands or feet	No paresthesia symptoms in hands or feet	*P*
Unweighted sample size, *n*	591	287	304	
Weighted population size, *n*	8.82million	4.37 million	4.45 million	
Vitamin D, %				0.04
< 30 ng/ml	81.2	85.5	77.0	
≥ 30 ng/ml	18.8	14.5	23.0	
Age, years, %				0.68
40–64	60.7	59.6	61.7	
≥65	39.3	40.4	38.3	
Sex, male, %	51.6	50.5	52.7	0.71
Race/ethnicity, %				0.11
Non-Hispanic white	72.7	73.3	72.2	
Non-Hispanic black	13.8	15.7	11.9	
Hispanic	13.5	11.0	15.9	
No health insurance, %	9.5	12.0	7.1	0.18
Obese (BMI ≥ 30 kg/m^2), %	54.1	55.7	52.6	0.64
Hypertension, %	70.6	74.6	66.6	0.11
Smoking status, %				0.01
Never	44.2	36.4	51.9	
Former	37.3	39.9	34.7	
Current	18.5	23.7	13.4	
HbA_{1c} ≥ 53 mmol/mol (≥ 7.0%), %	46.3	49.7	42.9	0.14
Time since diabetes diagnosis, %				0.04
0–10 years	65.1	57.6	72.4	
11–24 years	21.0	22.9	19.2	
≥ 25 years	13.9	19.5	8.4	
Taking neuropathy meds, %	12.8	17.8	8.0	0.08
Semmes–Weinstein test, %				< 0.01
0 insensate areas	73.0	65.6	80.3	
1–3 insensate areas	18.7	21.4	16.2	
4–6 insensate areas	8.2	13.0	3.5	

Table 2

Logistic regressions predicting self-reported peripheral neuropathy outcomes based on insufficient vitamin D (< 30 ng/ml) among adults ≥ 40 years old with diabetes

	Odds ratio (95% CI)	Odds ratio* (95% CI)
Numbness/pain in hands/feet	1.76 (0.95–3.24)	2.12 (1.17–3.85)
Numbness in hands/feet	1.77 (0.85–3.65)	2.04 (1.18–3.52)
Pain in hands/feet	1.35 (0.73–2.49)	1.49 (0.78–2.84)

*Controlling for age, gender, race/ethnicity, health insurance, obesity, hypertension, smoking status, HbA_{1C}, time since diagnosis and neuropathic pain medication.