Original Article

Association of vitamin D deficiency with diabetic peripheral neuropathy and diabetic nephropathy in Tianjin, China

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Background and Objectives: To evaluate the association of vitamin D deficiency with type 2 diabetic peripheral neuropathy (DPN) and diabetic nephropathy (DN). **Methods and Study Design:** A total of 287 type 2 diabetic patients were categorized in two ways, and each divided into two groups: DPN (n=164) and non-DPN (NDPN) groups (n=123); and DN (n=148) and non-DN (NDN) groups (n=139). Enzyme-linked immunosorbent assay was used to measure the 25-hydroxy vitamin D [25(OH)D_3] level. Correlation analysis between 25(OH)D_3 and other indicators was performed. **Results:** 25(OH)D_3 levels were lower in the DPN and DN groups than in the NDPN and NDN groups, and the difference was statistically significant (t =−6.23, −4.38, p<0.0001). Moreover, a higher proportion of patients in the DPN and DN groups exhibited vitamin D deficiency than those in the NDPN and NDN groups (χ^2=22.231, 15.973, respectively, p<0.0001). Vitamin D was highly correlated with DPN, DN, diabetes duration, age, sex, fasting plasma glucose, blood urea nitrogen, total cholesterol, low density lipoprotein cholesterol, 24-h urinary microalbumin, and beta-2 microglobulin (r=−0.34 ~ –0.133, p<0.05). Binary logistic regression analysis revealed that vitamin D deficiency is an independent risk factor for DPN and DN (OR=3.53, 95% confidence interval [CI]: 2.06–6.03; OR=2.93, 95% CI: 1.71–5.03; respectively, p<0.0001). **Conclusions:** Vitamin D deficiency is closely correlated with DPN and DN and can be considered as an independent risk factor for DPN and DN.

Key Words: type 2 diabetes mellitus, vitamin D, peripheral neuropathy, diabetic nephropathy, diabetes duration

INTRODUCTION

In the human body, vitamin D is mainly converted from 7-dehydrogenation cholesterol in the skin by UV radiation. First, inactive vitamin D is changed to 25-hydroxy vitamin D [25(OH)D] under the catalytic action of 25-hydroxylase in the liver and then to 1, 25-dihydroxy vitamin D_3 [1,25$(OH)_2D_3$] under the catalytic action of 1-alpha-hydroxylase expressed in the renal proximal tubule in the kidney. Serum 1, 25$(OH)_2D_3$ is the active form of vitamin D, and blood typically contains high 25(OH)D_3 levels, which has a long half-life. 25(OH)D_3 can reflect the reserve status of vitamin D and is the main transportation form of vitamin D in the body. Currently, the vitamin D level in the human body is mainly evaluated through 25(OH)D_3 measurement.[1-3] To date, the normal level of serum 25(OH)D_3 is recommended to be 30–60 μg/L (75–150 nmol/L). Vitamin D deficiency is defined as a 25(OH)D_3 level less than 20 μg/L (50 nmol/L), and relative vitamin D insufficiency is diagnosed if the 25(OH)D_3 level ranges from 20 to 30 μg/L (50–75 nmol/L). In addition to bone metabolism-related diseases, vitamin D deficiency is associated with many pathologies such as tumors, infectious diseases, multiple sclerosis, hypertension, and diabetes.[4-7]

382 million people were affected by diabetes in 2013. This number is predicted to increase to 592 million by 2035.[8] Diabetic peripheral neuropathy (DPN), which is one of the major chronic complications of diabetes, may not only seriously reduce the quality of life of diabetic patients, but is also a major cause of disability and death. The prevalence of DPN in type 2 diabetes mellitus (T2DM) patients is more than 50%.[9] Diabetic nephropathy (DN) is the main cause of late-stage renal disease, and the proportion of hemodialysis patients with DN is increasing annually,[10] increasing the risk of CVD mortality.[11]

Vitamin D deficiency is prevalent in T2DM patients.[7,12] Recent studies have shown that vitamin D deficiency is closely related to DPN and DN.[13-15] However, this relationship remains inconclusive and requires further study. Therefore, this study investigated the relationship of vitamin D deficiency with DPN and DN to provide new insights and methods for the prevention and treatment of DPN and DN.

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METHODS

Participants

This prospective observational clinical study included 287 T2DM patients (157 men and 130 women) who were recruited random from the Department of Endocrinology, Tianjin Union Medical Center, from June 2015 to May 2016. The average age was 59.7±10.3years, and the average diabetes duration was 8.49±6.55 years. All the 287 T2DM patients were categorized in two ways, and each divided into two groups: DPN (n=164) and non-DPN (NDPN) groups (n=123); and DN (n=148) and non-DN (NDN) groups (n=139).

Inclusion and exclusion criteria

T2DM was identified by the diabetes diagnostic criteria proposed by the World Health Organization in 1999. These T2DM patients presented with clinical symptoms (e.g., ache, anesthesia, and sense abnormality) and signs related to DPN during and after the diabetes diagnosis. Patients with the clinical symptoms who had abnormal results in any one of five examinations, namely, ankle reflex, acupuncture pain, vibration sense testing using a 128-Hz tuning fork, pressure sensation testing using 10-g monofilament, and temperature sensation, were diagnosed with DPN. Moreover, patients without the clinical symptoms who had abnormal results in any two of the five examinations were diagnosed with DPN. From the second day after admission, in the early morning, 24-h urine samples were collected for assessing 24-h urinary microalbumin (UMA) levels. Normoalbuminuria was defined as 24-h UMA <30 mg/24 h, microalbuminuria as 24-h UMA=30-299 mg/24 h, and macroalbuminuria as 24-h UMA ≥300 mg/24 h. T2DM patients with microalbuminuria or macroalbuminuria were diagnosed as having DN. The estimated glomerular filtration rate (eGFR) was calculated using the simplified Modification of Diet in Renal Disease equation.[16] Patients receiving oral vitamin D supplement within 2 months and those with any one of the following diseases were excluded from this study: type 1 diabetes mellitus or specific types of diabetes mellitus, acute complications of diabetes, inflammatory or autoimmune disease, osteoporosis, thyroid disease, parathyroid disease, malignancies, severe liver or kidney disease, cervical and lumbar vertebra disease, severe arterial and venous vascular disease, and severe cerebral infarction. All participants provided informed consent. This study was approved by the Human Research and Ethics Committee of Tianjin Union Medical Center (2015-06).

Anthropometric and biochemical measurements

Data on gender, age, diabetes duration, smoking and drinking history, coronary artery disease, and cerebral apoplexy were obtained using a questionnaire. The same neurologist performed physical and neurological examinations (ankle reflex, acupuncture pain, vibration sense testing using a 128-Hz tuning fork, pressure sensation testing using 10-g monofilament, and temperature sensation). Weight and height were measured using a stadiometer. BMI was calculated as weight (kg) divided by the square of height (m^2).

For biochemical measurements, morning fasting blood samples were collected from the antecubital veins of all T2DM patients. All tests were conducted in the central laboratory of Tianjin Union Medical Center. Glycosylated hemoglobin (HbA1c) was measured using high-pressure liquid chromatography on an ADAMS HA-8180 automatic glycosylated hemoglobin analyzer (Arkray, Kyoto, JPN). Fasting plasma glucose (FPG; glucose oxidase method), total cholesterol (TC; enzyme colorimetric method), triglyceride (TG; oxidase method), low density lipoprotein cholesterol (LDL-C), alanine aminotransferase (ALT) and aspartate aminotransferase (AST; rate method), blood urea nitrogen (BUN; enzyme coupling rate method), blood uric acid (UA; UA enzyme colorimetric method), serum creatinine (SCr; enzymatic method), and beta-2 microspheres protein (β2MG; latex enhanced immune turbid metric method) were measured on an ARCHITECT c16000 automatic biochemical analyzer (Abbott Diagnostics, Chicago, IL, USA). From the second morning after admission, 24-h urine samples were collected to test urinary albuminuria (immune transmission turbidity method).

25(OH)D_3 assessment

Morning fasting blood samples (5 mL) from the antecubital vein were collected into tubes containing the anticoagulant ethylenediaminetetraacetic acid. Within 4 h, these samples were centrifuged for 8 min at 3000 rpm (radius of the centrifuge head=13 cm) to separate the serum from the plasma and were then stored in a refrigerator at −80 °C for vitamin D determination. 25(OH)D_3 was measured using enzyme-linked immunosorbent assay (Tecan Sunrise enzyme standard instrument, Austria). The biological reference interval of all 25(OH)D_3 kits was 47.7–1.44 nmol/L (19.08−57.60 μg/L; product standard number: YZB/UK 4271-2011, IDS, UK).

Statistical analyses

All statistical analyses were performed using SPSS 17.0 (SPSS Inc, Chicago, IL, USA). Variables with normal distribution were expressed as mean ± standard deviation, and the t test was used to compare the two groups. Variables with non-normal distribution were expressed as median (interquartile), and the Kruskal–Wallis test was used to compare the two groups. Categorical variables were expressed as frequency and percentage, and the difference in the Categorical variables was determined using the test. The relationship of vitamin D with DPN, DN, and other indicators was analyzed using Pearson or Spearman correlation analysis. Binary logistic regression analysis was performed to evaluate the risk factors for DPN and DN. Three-tailed p values of <0.05 were considered statistically significant.

RESULTS

Patient clinical characteristics

The diabetes duration, age, systolic blood pressure, BUN, SCr, UA, 24-h UMA, and β_2MG were higher in the DPN group than in the non-DPN group (NDPN) group (p<0.05). However, sex, BMI, FPG, HbA1c, TC, TG, and LDL-C were not statistically significant (p>0.05). The 25(OH)D_3 level was markedly lower in the DPN group than in the NDPN group (t=−6.23, p<0.0001; Table 1, Figure 1). β_2MG, SCr, and eGFR were higher in the DN

group than in the non-DN (NDN) group (p<0.01). The 25(OH)D_3 level was markedly low in the DN group (t=−4.38, p<0.0001; Table 2, Figure 1).

A markedly higher proportion of patients had vitamin D deficiency in the DPN and DN groups than those in the NDPN and NDN groups (χ^2=22.231, 15.973, respectively, p=0.0001; Table 3, Figures 2 and 3).

Correlation analysis between vitamin D and various indices

Pearson or Spearman correlation analysis results revealed that 25(OH)D_3 was significantly related to DPN, DN, diabetes duration, age, sex, FPG, BUN, SCr, TC, LDL-C, 24-h UMA, and β_2MG (p<0.05), whereas no significant relationship was observed between 25(OH)D_3 and BMI, UA, ALT, AST, and TG (p>0.05; Table 4).

Relationship of vitamin D with DPN and DN

Binary logistic regression analysis results revealed that vitamin D deficiency, diabetes duration, age, 24-h UMA, β_2MG, and other factors were risk factors for DPN. Moreover, the results showed that the occurrence of DN was closely related to vitamin D deficiency, diabetes duration, and β_2MG. Thus, vitamin D deficiency is an independent risk factor for DPN and DN. Moreover, BMI, FPG, HbA1c, TC, and LDL-C showed no significant linear relationship with DPN and DN (Tables 5 and 6).

DISCUSSION

The results of this study revealed that compared with the NDPN and NDN groups, the vitamin D level was markedly lower in the DPN and DN groups, and a higher proportion of patients in the DPN and DN groups had vitamin D deficiency. Moreover, the 25(OH)D_3 level was found to be significantly correlated with DPN and DN; thus, it can be considered an independent risk factor for DPN and DN.

Hermann et al indicated that the incidence of macrovascular and microvascular complications was higher in T2DM patients with vitamin D deficiency than in those with normal or insufficient vitamin D levels.[17] Ahmadieh et al also showed that the averaged 25(OH)D_3 level was lower in T2DM patients in the DPN group than in those in the NDPN group, and the DPN incidence rate of the group with 25(OH)D_3 <20 μg/L was significantly higher than that of the group with 25(OH)D_3 ≥20 μg/L; consequently, 25(OH)D_3, which was significantly correlated with DPN, can predict DPN occurance.[18] QR-333 is a combination of quercetin, ascorbic acid, and vitamin D,. Previous studies have shown that compared with placebo, QR-333 can significantly reduce limb numbness and pain symptoms in DPN patients and can improve quality of life.[19,20] Lee et al showed that in 51 T2DM patients with DPN and vitamin D deficiency, pain symptoms in the extremities were considerably decreased after treatment with vitamin D_3 orally for 3 months.[21] A previous study also demonstrated that vitamin D can promote cell differentiation or proliferation and wound healing in patients with diabetic foot ulcers.[22]

Vitamin D can inhibit macrophages and dendritic cells for inducing IL-12 production, resulting in the reduced expression of interferon-γ and tumor necrosis factor (TNF)-α, the increased expression of inflammatory cells and islet beta cell NO, and the apoptosis of islet beta cells.[23] Active vitamin D can improve the insulin response to glucose transport by promoting the expression of the insulin receptor gene and can increase insulin sensitivity.[24] Decreased vitamin D levels can lead to insulin resistance and hyperlipidemia.[1] Vitamin D can inhibit the inflammatory response by regulating B lymphocyte and T lymphocyte functions, reducing the inflammatory factor C-reactive protein and TNF-α, and upregulating suppressed inflammatory cytokines such as IL-10 and IL-4; thus, vitamin D can prevent and treat diabetic complications.[25] Vitamin D deficiency or insufficiency can reduce the anti-inflammatory effect.[26] Vitamin D combined with its receptor can inhibit the proliferation of vascular smooth muscle cells and angiogenesis, thus reducing the occurrence of arteriosteogenesis and atherosclerosis.[27,28]

A previous study showed that the reduction of nerve nutrition factors, particularly nerve growth factor (NGF) and calcium ions, could accelerate the development of neuropathy under the stimulation of high blood sugar and other toxins.[29] A diabetes animal model experiment found that vitamin D deficiency could reduce NGF production, and that vitamin D analogues could stimulate NGF formation and prevent NGF deficiency. Riaz et al discovered that streptozotocin-induced diabetic mice lack NGF because of muscle and skin damage, and that treatment with vitamin D derivatives (CB1093) could stimulate NGF expression in the skin and muscle of the diabetes and the control groups.[30,31] Another animal experiment showed that vitamin D_3 supplementation increased the pain threshold in diabetic rats, but the effect of exercise training was not substantial.[32] Research has indicated that 1,25$(OH)_2D_3$ affects TH1 cell activation mainly through the inhibition of IL-12, reducing the production of cerebrospinal inflammatory cytokines and preventing the cerebrospinal multiple demyelinating disease—multiple sclerosis. 1,25$(OH)_2D_3$ supplementation can regulate the inflammatory response of the central nervous system, regulate the dynamic balance between inflammatory and anti-inflammatory cytokines, and protect the brain tissue.[33]

Vitamin D deficiency is a prominent feature in chronic kidney disease patients.[34] Previous studies have indicated that the incidence of vitamin D deficiency and insufficiency was significantly higher in DN patients than in NDN patients, and that vitamin D deficiency and insufficiency are related to the occurrence of DN.[15] Vitamin D can inhibit the activation of the renin angiotensin aldosterone system and reduce the formation of renin and angiotensin II through the activation of the vitamin D receptor-mediated nuclear factor-κB pathway.[35] In DN mice, calcitriol could significantly inhibit the transformation growth factor-β and monocyte chemoattractant protein-1 expression in the renal tissue, increase podocyte marker gene expression (NePhrin, NePhl, and a-actinin-4) in the glomerular fissure hole diaphragm, improve podocyte morphology, reduce the thickness of the glomerular basement membrane, reduce urine albumin, inhibit the deposition of extracellular matrix, and improve glomerular sclerosis.[36] Wang et al found that the vitamin D analogue paricalcitol could upregulate podocin protein ex-

Table 1. Comparison of clinical data between DPN group and NDPN group

Group	Num.	Duration (Y)	Sex (M/F)	Age (Y)	BMI (kg/m^2)	SBP (mmHg)	DBP (mmHg)
NDPN group	123	4.67±2.63	68/55	56.5±9.18	26.2±3.61	135±15.1	81.9±8.72
DPN group	164	10.4±7.99**	89/75	62.1±10.4**	26.0±3.74	140±18.9*	81.0±9.30
t/Z value	-	8.12	0.171	4.71	−0.489	2.23	−0.852
p value	-	<0.0001	0.865	<0.0001	0.625	0.026	0.395
Goup	FPG (mmol/L)	HbA1c (%)	BUN (mmol/L)	SCr (umol/L)	UA (umol/L)	ALT (U/L)	AST (U/L)
NDPN group	7.77±2.41	8.92±2.23	4.91±1.35	57.6±12.9	274±79.3	21.0 (14.0, 31.0)	17.0 (14.0, 22.0)
DPN group	8.16±2.97	8.73±2.05	6.63±6.88**	66.3±16.9**	303±107*	19.0 (13.0, 30.0)	16.0 (13.0, 21.8)
t/Z value	1.19	-0.767	2.71	4.78	2.54	−1.05	−0.964
p value	0.234	0.444	0.007	<0.0001	0.012	0.294	0.335
Group	25(OH)D_3 (nmol/L)	TC (mmol/L)	TG (mmol/L)	LDL-C (mmol/L)	24h UMA (mg/24 h)	β_2MG (mg/L)	
NDPN group	48.1±12.7	5.05±1.06	1.46 (1.09, 2.06)	3.04±0.69	22.6 (12.8, 29.6)	2.37±0.72	
DPN group	39.5±10.6**	5.07±1.39	1.54 (1.08, 2.44)	3.04±0.88	89.1 (29.1, 402)**	3.19±1.79**	
t/Z value	−6.23	0.136	−0.813	0.041	−8.88	4.78	
p value	<0.0001	0.892	0.416	0.967	<0.0001	<0.0001	

NDPN group: nondiabetic peripheral neuropathy group of type 2 diabetic patients; DPN group: diabetic peripheral neuropathy group of type 2 diabetic patients; SBP: systolic blood pressure; DBP: diastolic blood pressure; FPG: fasting blood glucose; HbA1c: glycosylated hemoglobin; BUN: blood urea nitrogen; SCr: serum creatinine; UA: uric acid; ALT: alanine aminotransferase; AST: aspartate aminotransferase; TC: total cholesterol; TG: triglyceride; 24-h UMA: 24-h urine microalbumin; β_2MG: β_2-microglobulin.
Compared with the NDPN group, $^{*}p<0.05$; compared with the NDPN group, $^{**}p<0.01$.

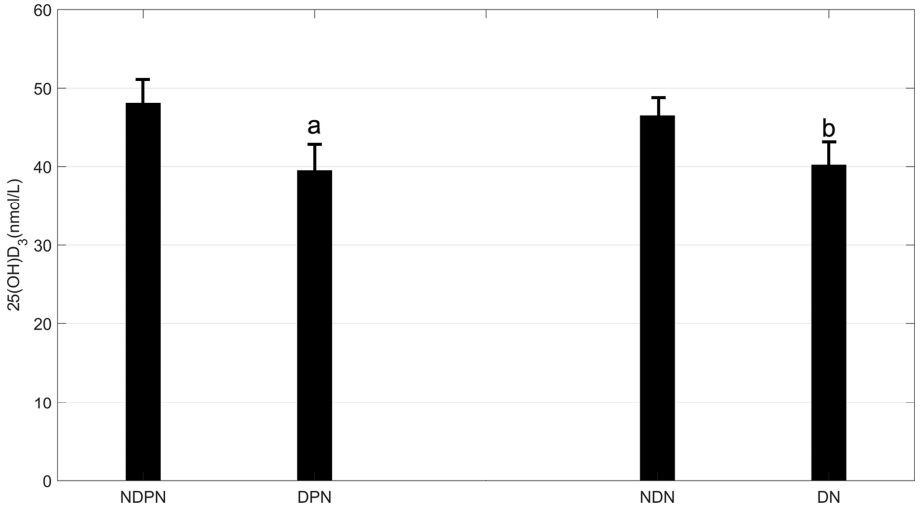

Figure 1. Comparison of 25(OH)D_3 levels between DPN and NDPN groups and between DN and NDN groups. NDPN: nondiabetic peripheral neuropathy of type 2 diabetic patients; DPN: diabetic peripheral neuropathy of type 2 diabetic patients; NDN: nondiabetic neuropathy of type 2 diabetic patients; DN: diabetic neuropathy of type 2 diabetic patients; compared with the NDPN group, $^{a}p<0.01$; compared with the NDN group, $^{b}p<0.01$.

Table 2. Comparison of biochemical index between DN group and NDN group

Variable	Num.	25(OH)D_3 (nmol/L)	β_2MG (mg/L)	eGFR [mL/min ^{per} 1.73m^2]	SCr (umol/L)
NDN group	139	46.4±13.1	2.43±0.87	55.4±29.7	58.4±13.0
DN group	148	40.2±10.8 **	3.23±1.81 **	79.3±99.1**	66.5±17.3**
t value	-	−4.38	4.72	2.74	4.44
p value	-	<0.0001	<0.0001	0.007	<0.0001

NDN group: nondiabetic neuropathy group of type 2 diabetic patients; DN group: diabetic neuropathy group of type 2 diabetic patients; β_2MG: β_2-microglobulin; eGFR: estimated glomerular filtration rate; SCr: serum creatinine.
Compared with the NDN group, $^{*}p<0.05$; compared with the NDN group, $^{**}p<0.01$.

Table 3. Proportion of patients with vitamin D deficiency in DPN and DN groups [n (%)]

Variables	Num.	Vitamin D deficiency (+)	Vitamin D deficiency (−)	χ^2	*p*
NDPN group	123	70(56.9)	53 (43.1)	22.231	<0.0001
DPN group	164	135 (82.3)	29 (17.7)		
NDN group	139	84 (60.4)	55 (39.6)	15.973	<0.0001
DN group	148	121 (81.8)	27 (18.2)		

NDPN group: nondiabetic peripheral neuropathy group of type 2 diabetic patients; DPN group: diabetic peripheral neuropathy group of type 2 diabetic patients; NDN group: nondiabetic neuropathy group of type 2 diabetic patients; DN group: diabetic neuropathy group of type 2 diabetic patients

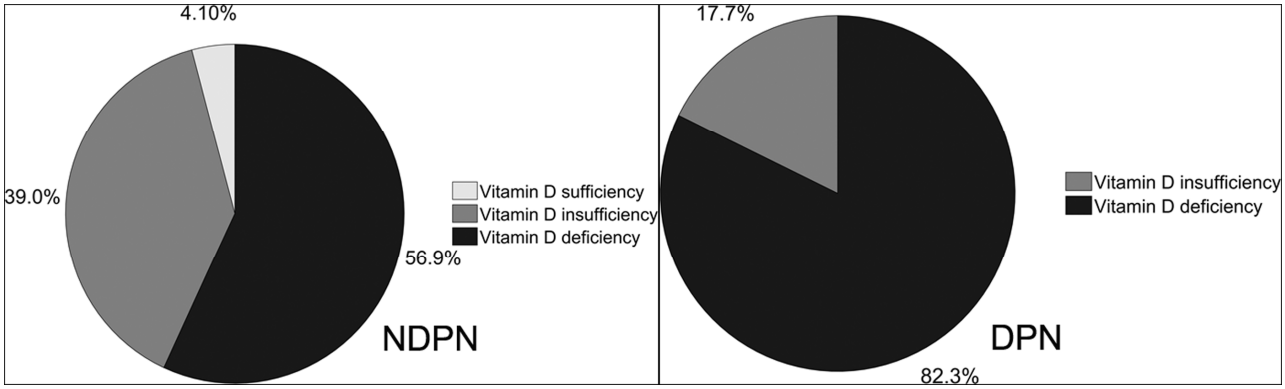

Figure 2. Proportions of patients with vitamin D deficiency in NDPN and DPN groups. NDPN: nondiabetic peripheral neuropathy of type 2 diabetic patients; DPN: diabetic peripheral neuropathy of type 2 diabetic patients.

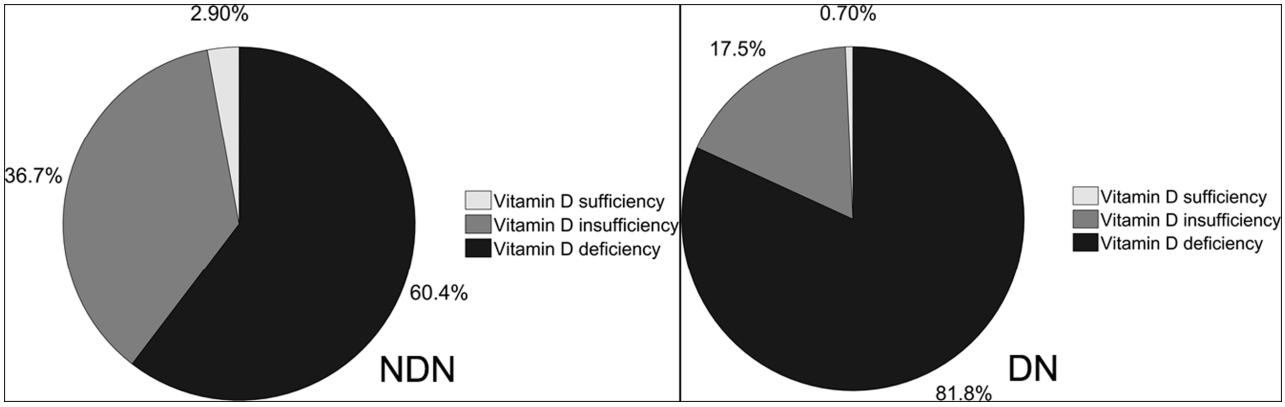

Figure 3. Proportions of patients with vitamin D deficiency in NDN and DN groups. NDN: nondiabetic neuropathy of type 2 diabetic patients; DN: diabetic neuropathy of type 2 diabetic patients.

pression in podocytes and reduce albuminuria in rats with early-stage DN.[37]

Limitation

This was a cross-sectional study, and a cause–effect conclusions should be drawn from the study findings cautiously. Follow-up studies are needed to determine whether vitamin D deficiency is a risk factor for T2DM patients with DPN and DN. The sample size in this study was relatively small. Therefore, the results may not represent all patients with T2DM. Vitamin D levels are affected by many factors, such as daylight hours, race, age, sex, work style, dress code, eating habits, and cultural practices.

Table 4. Correlation analysis between vitamin D and various indices

Variables	*r*	*p*
DPN	−0.346‡	<0.0001
DN	−0.298‡	<0.0001
Duration	−0.239‡	<0.0001
Age	−0.224‡	<0.0001
Sex	−0.139†	0.019
BMI	−0.101	0.087
FPG	−0.187‡	0.002
HbA1c	−0.083	0.158
BUN	−0.165‡	0.005
SCr	−0.188‡	0.001
UA	0.038	0.521
ALT§	−0.005	0.936
AST§	−0.003	0.956
TC	−0.155‡	0.009
TG§	−0.079	0.182
LDL-C	−0.140†	0.018
24hUMA§	−0.255‡	<0.0001
β_2MG	−0.133†	0.025
eGFR	−0.028	0.631
SBP	−0.080	0.175
DBP	0.025	0.676

DPN: diabetic peripheral neuropathy of type 2 diabetic patients; DN: diabetic neuropathy of type 2 diabetic patients; FPG: fasting blood glucose; HbA1c: glycosylated hemoglobin; BUN: blood urea nitrogen; SCr: serum creatinine; UA: uric acid; ALT: alanine aminotransferase; AST: aspartate aminotransferase; TC: total cholesterol; TG: triglyceride; 24-h UMA: 24-h urine microalbumin; β_2MG: β_2-microglobulin; eGFR: estimated glomerular filtration rate; SBP: systolic blood pressure; DBP: diastolic blood pressure.
†Represents that 25(OH)D3 is significantly associated with the comparative factor at the 0.05 level (bilateral).
‡Indicates that 25(OH)D_3 is significantly associated with the comparative factor at the 0.01 level (bilateral).
§Represents that Spearman correlation analysis was conducted between 25(OH)D_3 and the comparative factor. Pearson correlation analysis was conducted between the remaining comparative factors and 25(OH)D_3.

Table 5. Risk factors for DPN analyzed through binary logistic regression analysis

Variables	B	S.E	Wals	OR	95% CI	*p*
25(OH)D_3 (<50nmol/L)	1.26	0.274	21.1	3.53	2.06-6.03	<0.0001
Duration (>10 years)	2.47	0.353	48.9	11.8	5.91-23.5	<0.0001
Age (>50 years)	0.839	0.390	4.63	2.31	1.077-4.971	0.031
BMI (kg/m^2)	0.016	0.032	0.238	1.02	0.953-1.08	0.625
FPG (mmol/L)	−0.053	0.044	1.42	0.234	0.869-1.04	0.948
HbA1c (%)	0.044	0.056	0.604	0.957	0.858-1.07	0.437
TC (mmol/L)	−0.032	0.095	0.116	0.968	0.804-1.17	0.733
LDL-C (mmol/L)	−0.006	0.149	0.002	0.994	0.742-1.33	0.967
24 hUMA (≥30mg/24h)	2.15	0.275	60.9	8.57	5.00-14.7	<0.0001
β_2MG (mg/L)	−0.670	0.142	22.2	0.512	0.387-0.676	<0.0001

DPN: diabetic peripheral neuropathy of type 2 diabetic patients; FPG: fasting blood glucose; HbA1c: glycosylated hemoglobin; TC: total cholesterol; 24-h UMA: 24-h urine microalbumin; β_2MG: β_2-microglobulin.

Table 6. Risk factors for DN analyzed through binary logistic regression analysis

Variables	B	S.E	Wals	OR	95% CI	*p*
25(OH)D_3(<50nmol/L)	1.08	0.275	15.4	2.93	1.71~5.03	<0.0001
Age (>50 years)	0.435	0.385	1.28	1.55	0.727~3.29	0.259
Duration (>10 years)	1.02	0.261	15.3	2.77	1.66~4.61	<0.0001
β_2MG(mg/L)	−0.601	0.133	20.5	0.548	0.423~0.711	<0.0001
BMI(kg/m^2)	−0.018	0.032	0.319	0.982	0.922~1.05	0.572
FPG(mmol/L)	−0.082	0.044	3.44	0.921	0.844~1.01	0.064
HbA1c (%)	0.006	0.056	0.011	1.01	0.902~1.12	0.916
TC(mmol/L)	−0.113	0.094	1.44	0.893	0.742~1.07	0.230
LDL-C(mmol/L)	−0.188	0.150	1.58	0.828	0.618~1.11	0.208

DN: diabetic neuropathy of type 2 diabetic patients; β_2MG: β_2-microglobulin; FPG: fasting blood glucose; HbA1c: glycosylated hemoglobin; TC: total cholesterol

Conclusion

Vitamin D deficiency is a common feature in DPN and DN. Vitamin D deficiency is significantly associated with DPN and DN and can be considered an independent risk factor for DPN and DN. This conclusion requires further confirmation in large-scale clinical trials.

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AUTHOR DISCLOSURES

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