Research article

Correlation of peripheral neuropathy with serum vitamin D levels and HbA_1C variations in type 2 diabetes mellitus patients

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ABSTRACT

Introduction and Aim: The burden of diagnosed and undiagnosed diabetes will increase in the coming decade. Vitamin D deficiency and HbA1C variability are risk factors for diabetic neuropathy, and the association was studied in the present study.

Materials and Methods: Data from 346 Type II diabetes patients reporting in a tertiary care Hospital in North India after approval of the ethics committee was analyzed. Michigan Neuropathy Screening Instrument (MNSI) was used to screen the patients for neuropathy. Vitamin D levels were measured. Four HbA1C levels (once every three months) done at least one-year preceding enrolment in the study were analyzed. A nerve conduction study was performed in the Neurophysiology lab. Data were analyzed using SPSS 21.0.

Results: Diabetic peripheral neuropathy (DPN) was present in 54.91% of patients. They had a higher BMI, HbA1C %, fasting blood glucose, and low Vitamin D levels. Nerve conduction studies showed more pronounced changes in patients with severe DPN grades. Variability of HbA1C% correlated positively with the duration of diabetes and BMI, and the relation was negative with vitamin D levels. Vitamin D correlated negatively with duration, Hb A1C variability, and BMI. The correlation of HbA1C variability with motor and sensory conduction velocity and amplitude was negative, and with latency, it was positive. Vitamin D correlated positively with amplitude and conduction velocity and negatively with latency.

Conclusion: Nerve conduction study, variability in HBA1C, and Vitamin D levels can act as tools to detect DPN. Vitamin D is a modifiable risk factor that needs monitoring in people with diabetes.

Keywords: Nerve conduction; peripheral neuropathy; vitamin D deficiency; correlation; glycated hemoglobin; body mass index.

INTRODUCTION

Six hundred forty-two million adults are expected to be diabetic worldwide by 2040; by then, India is expected to be home to 123.5 million diabetics. 95% of people with diabetes have Type 2 diabetes (1). Research is suggestive that there is a tendency for early-onset type 2 diabetes in India, which is the risk for macro and microvascular complications (2). Diabetic peripheral neuropathy (DPN), the presence of symptoms or signs after excluding other causes, is a complication mainly attributed to inflammation and hyperglycemia (3-5). Vitamin D deficiency impairs the pancreas's beta cell functions, increases insulin resistance, and is an independent risk factor for neuropathy (6). The possible connection between hyperglycemia, Vitamin D deficiency, and complications in diabetes is shown in Fig. 1.

HbA_1C variability (better index of insulin resistance and inflammatory responses) is independently associated with diabetic neuropathy by mechanisms attributed to oxidative stress, inflammation, increase in advanced glycation end products, increased expression of p53, and markers of DNA damage. Higher variability is associated with an increased risk of micro and macrovascular complications.

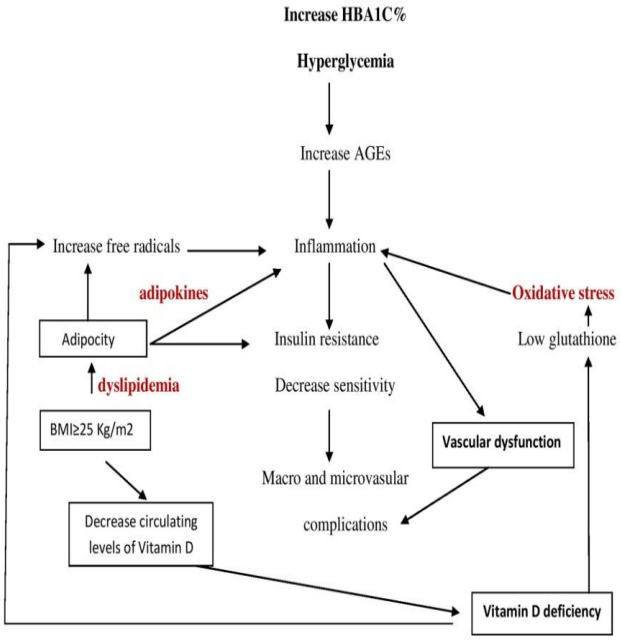

Fig. 1: Possible connection between hyperglycemia and vitamin D deficiency with macro and micro vascular complication in diabetes

Long-term hyperglycemia and glycemic variability indicated by M-HbA_1C and CV-HbA_1C are associated with diabetic peripheral neuropathy (7). Very few studies are available to associate the HbA_1C variability with the severity of neuropathy in type 2 diabetics. Contrasting results are available concerning the association of neuropathy with Vitamin D and HbA_1C in diabetics (8). Thus, the present study was designed to find the association of peripheral neuropathy with serum Vitamin D levels and HbA_1C variations in type 2 diabetes mellitus patients. The aim of this study was to correlate peripheral neuropathy with serum Vitamin D levels and HbA_1C variations in type 2 diabetes mellitus patients.

MATERIALS AND METHODS

The present study was a cross-sectional study conducted in a tertiary care Hospital in North India. The study duration was three months (August to October 2022). The Institutional Ethics Committee approved the study (Ref. No. IEC/JNMC/662 dated 04/06/2022). The project was granted, and the report was approved by the Indian Council of Medical Research (ICMR).

Study population

Diagnosed patients of type 2 diabetes mellitus (revised American Diabetes Association Classification) were selected from the centre of diabetes and endocrinology after fulfilling the inclusion and exclusion criteria.

Inclusion criteria

Type II diabetics, both males and females between 30-60 years of age, willing to participate in the study and giving consent, were included.
Cases: Patients with diabetic neuropathy were further divided into three groups based on the severity of the neuropathy (mild, moderate, and severe).
Controls: Patients without diabetic neuropathy.

Exclusion criteria

Patients with type 1 diabetes; females with gestational diabetes; patients with Vitamin B12 and folate deficiency; patients with a history of stroke, CVA; those with hyper/hypothyroidism and with parathyroid disease; alcoholics, smokers, severely anemic; CKD and chronic liver disease patients; patients taking vitamin D supplements and on medications known to affect Vitamin D metabolism, like steroids, were excluded from the study.

Sample size calculation

With the prevalence of peripheral neuropathy in type 2 diabetics at 40% (9) relative precision as 60, and degree of freedom as 0.05, the sample size was 384. Data from 346 patients was analyzed on account of patients not reporting for investigations.

Data collection

A pre-designed proforma was used to obtain the general information of the patient, including age, gender, BMI, duration of diabetes, history of any other chronic/ debilitating disease, and drug usage. Recent investigations of the patients were used to record the fasting plasma glucose, 2-hour plasma glucose, and HbA_1C %. Michigan Neuropathy Screening Instrument (MNSI) was used to screen the patients for neuropathy (1).

The bilateral examination was carried out

(a) Foot inspection for deformity, dry skin, nail, or hair abnormalities, callous or infection; (b) Vibration sensation at the dorsum/apex of great toe using 128 Hz tuning fork; (c) Ankle reflex grading; (d) Temperature sensation (dorsum of foot); (e) Pinprick sensation (proximal to the big toenail. Patients scoring more than two on a maximum 10-point scale were considered neuropathic (8). Vitamin D levels were measured using the Access 25(OH) Vitamin D total assay kit and Beckman Coulter Access 2 machine. The levels were graded as mild to severe (10). HBA1C levels (once every three months) done at least one-year preceding enrolment in the study were analyzed for HBA1C variability (7). NCS was performed in the Neurophysiology Lab of the Department (Physiology and Medicine) using the Medicaid System's EMG/NCV equipment with Neuroperfect software.

Statistical analysis

Patients were divided into two subgroups, i.e., with and without DPN. The data (variables) were coded and entered in the Statistical Package for Social Sciences 24.0 IBM (SPSS 24.0) and Microsoft Excel. Quantitative data were expressed as mean ± SD, and qualitative variables were expressed as numbers and percentages. An unpaired student t-test was used to find the differences in study variables between DPN and non-DPN groups. ANOVA and Nonparametric chi-square (for categorical variables) tests were also used. The correlation of HbA_1C variability and vitamin D with study variables was assessed using Pearson's correlation test. Binary logistic regression was used to find the interactions. DPN was coded as (0=no, 1=yes), duration of diabetes (0<10 years, 1>10 years), vitamin D (0>20 ng/ml, 1<20 ng/ml) and obesity (0<25 Kg/m2, 1>25 Kg/m2). The odds ratio and confidence interval of 95% were evaluated. A p-value of < 0.05 was taken as significant.

RESULTS

The results show that 190 (54.91%) had DPN (mean duration of diabetes 9.13 ±4.48 years), and 156 (45.09%) were without DPN (mean duration 5.25 ±2.27years).

Table 1: Differences in study variables between type 2 diabetics with and without DPN

Variable		Type 2 DM Patients		
		with DPN (n=190)	without DPN (n=156)	p value
Age (years)		42.29±9.58	39.24±9.69	0.004*
Gender	Male	130 (68.42 %)	101(64.74 %)	0.472
	Female	60(31.58 %)	55(35.26 %)	
BMI(Kg/m^2)		24.76±1.79	23.64±1.60	<0.001*
Duration of diabetes (years)		9.13±4.48	5.25±2.27	<0.001*
Fasting plasma glucose(mg/dl)		179.56± 47.89	154.67±31.64	0.001*
HbA_1C %		6.93±0.69	6.56±0.51	<0.001*
Vitamin D (ng/ml)		25.67±6.34	29.89±6.82	<0.001*
m- HbA_1C %		6.96±0.67	6.50±0.89	<0.001*
HbA_1C -CV %		9.13±0.08	9.07±0.06	<0.001*

Difference is significant p<0.05*

BMI, fasting blood glucose, and HBA1C% levels were significantly higher (p<0.001) in the DPN group than in the non-DPN group. Vitamin D levels were significantly reduced in the DPN group (p<0.001) (Table 1).

Within the neuropathy groups (mild, moderate, and severe) significant reductions in velocity and amplitude and significant increase in latencies of motor median, ulnar and common peroneal nerves was found. Results of the sensory nerve conduction studies indicated significant differences within the DPN groups classified based on severity. Motor ulnar and common peroneal nerve conduction velocities and amplitude were reduced, and latencies were significantly higher in patients with DPN than those without DPN. The motor median nerve conduction velocity and latency were decreased significantly and higher in patients with DPN, respectively. The reduction in CV and amplitude and increase in latencies were more in patients with severe DPN grades than those with moderate and mild grades of DPN. Sensory median, ulnar, and sural nerve conduction velocity and amplitude were significantly reduced in the DPN group, and the latencies were higher in the DPN group than in patients without DPN. The values were deranged more in patients with severe grades of DPN (Tables 2, 3, 5 and 6). Chi square test results showed significant difference between the Vitamin D levels and HbA1C% between DPN and non-DPN groups (p<0.001).

Out of the 26 patients with severe neuropathy, 61.50 % had severe deficiency of vitamin D (<20 ng/ml) whereas 10.20% of 156 diabetics without neuropathy had severe deficiency of Vitamin D. Poor glycemic control was found in 53.80% i.e., 14/26 patients with severe DPN (Table 4). In Type 2 diabetics with DPN a significant negative correlation of vitamin D was observed with HbA_1C%, m-HbA_1C%, BMI and duration of diabetes whereas the correlation was found to be positive with CV-HbA_1C%. The correlation between motor and sensory nerve conduction velocity and amplitude with CV-HbA_1C% and vitamin D were found to be negative and positive respectively whereas the correlations with motor and sensory nerve latency were found to be positive and negative respectively (Table 7). In logistic regression, duration of diabetes (OR 3.69, 95% CI 2.328-5.848, P<0.001), vitamin D deficiency (or 2.136, 95% CI 1.041-4.381, P=0.03), obesity, i.e., BMI>25 Kg/m2 (OR 3.357, 95% CI 1.905-5.918, P<0.001) and higher HBA_1C % (OR 4.125, 95% CI 2.442-6.966, P<0.001) were found to be risk factors for DPN in type 2 diabetic patients (Table 8).

Table 2: Differences in motor nerve conduction study in diabetics with and without neuropathy

Nerve conduction study	With DPN	Without DPN	p value
Median Nerve			
Conduction velocity(m/sec)	54.32±1.90	55.70±2.37	<0.001*
Amplitude	5.16±1.09	5.37±1.34	0.106
Latency	4.04±0.92	3.25±1.17	<0.001*
Ulnar nerve			
Conduction velocity(m/sec)	55.01±1.88	56.51±2.25	<0.001*
Amplitude	5.07±1.08	5.39±1.16	0.008*
Latency	3.19±0.29	2.78±0.41	<0.001*
Com**mon Peroneal Nerve**			
Conduction velocity(m/sec)	45.73±1.10	48.53±2.30	<0.001*
Amplitude	4.77±1.26	5.16±1.34	0.006*
Latency	3.99±0.57	3.79±0.59	0.001*

Difference is significant with p<0.05*

Table 3: Differences in sensory nerve conduction study in diabetics with and without neuropathy

Nerve conduction study	With DPN	Without DPN	p value
Median Nerve			
Conduction velocity (m/sec)	52.27±2.42	55.32±3.55	<0.001*
Amplitude	34.10±5.79	35.30±6.53	0.01*
Latency	2.67±0.43	2.40±0.19	<0.001*
Sural nerve			
Conduction velocity (m/sec)	53.24±2.42	55.06±1.88	<0.001*
Amplitude	20.88±4.33	23.58±3.64	0.06*
Latency	2.64±0.37	2.53±0.25	0.07*
Ulnar Nerve			
Conduction velocity(m/sec)	53.17±2.43	54.78±2.68	<0.001*
Amplitude	20.88±4.33	23.58±3.64	<0.001*
Latency	2.64±0.37	2.53±0.25	0.001*

Difference is significant with p<0.05*

Table 4: Differences on basis of vitamin D and HbA_1C % control in type 2 diabetics with different grades of severity and without DPN

Variable	Type 2 DM patients with and without peripheral neuropathy								
	mild (n=113)		Moderate (n=51)		Severe (n=26)		No DPN (n=156)		p value
	n	%	n	%	n	%	n	%	
Vitamin D (ngm/ml)									
>30	38	32.60	12	23.50	00	00	72	46.20	df=6
20-30	56	49.60	23	45.10	10	38.50	68	43.60	p<0.001
<20	19	16.80	16	31.40	16	61.50	16	10.20	
HbA_1C %									
Fair	60	53.10	14	27.50	00	00	121	77.60	df=6
good	50	44.20	25	49.0	12	46.20	35	22.40	p<0.001
poor	03	2.70	12	23.50	14	53.80	00	00	

Table 5: Motor nerve conduction studies in different grades of severity of DPN in type 2 diabetic patients

Variable	DPN in Type 2 DM patients			
	Mild	Moderate	Severe	p value
Median nerve				
Velocity(M/Sec)	54.94±2.01	53.55±1.06	53.17±1.69	<0.001*
Amplitude (Mv)	5.35±1.24	5.02±0.74	4.56±0.63	0.006*
Latency	3.32±0.18	4.86±0.30	5.57±0.29	0.001*
Ulnar nerve				
Conduction velocity	55.58±1.80	54.48±1.74	53.64±1.44	<0.001*
Amplitude	5.28±1.11	4.99±0.98	4.30±0.69	<0.001*
Latency	3.06±0.27	3.32±0.18	3.51±0.20	<0.001*
Common peroneal				
Conduction velocity	46.09±0.73	45.49±0.72	44.66±1.96	<0.001*
Amplitude	5.14±1.32	4.11±0.51	4.01±0.56	<0.001*
Latency	3.82±0.56	4.11±0.51	4.48±0.29	<0.001*

Difference is significant with p<0.05*

Table 6: Sensory nerve conduction studies in different grades of severity of DPN in type 2 diabetic patients

Variable	DPN in Type 2 DM patients			
	Mild	Moderate	Severe	p value
Median nerve				
velocity(m/sec)	53.18±1.93	51.76±1.05	49.33±3.52	<0.001*
amplitude(mV)	36.35±10.24	33.21±7.04	31.96±1.37	0.004*
Latency	3.07±0.30	3.29±0.52	3.71±0.44	<0.001*
Ulnar nerve				
conduction velocity	53.75±2.21	52.91±2.33	51.19±2.49	<0.001*
Amplitude	34.91±6.03	33.36±5.05	32.01±5.51	0.029*
Latency	2.55±0.30	2.75±0.57	3.05±0.37	<0.001*
Sural nerve				
Conduction velocity	53.82±2.18	52.71±2.67	51.80±2.15	<0.001*
Amplitude	21.56±4.54	19.92±4.24	19.77±2.74	<0.001*
Latency	2.57±0.25	2.64±0.40	2.94±0.58	<0.001*

Difference is significant with p<0.05*

Table 7: Association of vitamin D and HbA_1C % variations with DPN in type 2 DM patients

Study variables	CV- HbA_1C %		Vitamin D	
	r	p	r	p
HbA_1C %	0.953	<0.001*	-0.214	<0.001*
m- HbA_1C %	0.993	<0.001*	-0.278	<0.001*
BMI	0.212	<0.001*	-0.204	<0.001*
Duration of diabetes	0.234	<0.001*	-0.181	0.001*
Vitamin D	-0.255	<0.001*	1	
CV- HbA_1C %	1		-0.255	<0.001*
Motor median nerve				
Conduction velocity	-0.284	<0.001*	0.130	0.016*
Amplitude	-0.088	0.104	0.120	0.026*
Latency	0.508	<0.001*	-0.382	<0.001*
Motor ulnar nerve				
Conduction velocity	-0.252	<0.001*	0.206	<0.001*
Amplitude	-0.183	<0.001*	0.115	<0.001*
Latency	0.292	<0.001*	-0.170	0.002*
Motor common peroneal nerve				
Conduction velocity	-0.324	<0.001*	0.203	<0.001*
Amplitude	-0.154	<0.001*	0.103	0.055
Latency	0.137	<0.001*	-0.155	0.004*
Sensory median nerve				
Conduction velocity	-0.368	<0.001*	0.068	0.204
Amplitude	-0.150	<0.001*	0.057	0.290
Latency	0.190	<0.001*	-0.319	<0.001*
Sensory ulnar nerve				
Conduction velocity	-0.168	0.002*	0.185	0.001*
Amplitude	-0.044	0.41	0.032	0.548
Latency	0.342	<0.001*	-0.253	<0.001*
Sensory sural nerve				
Conduction velocity	-0.239	<0.001*	0.248	<0.001*
Amplitude	-0.197	<0.001*	0.167	0.002*
Latency	0.146	<0.001*	-0.138	0.01*
DPN	0.306	0.001*	-0.339	0.02*

Table 8: With DPN as dependant variable analysis using logistic regression

Variable	B	Exp (B)	95% C.I. for Exp(B)	P value
Duration of Diabetes (> ten years)	1.306	3.690	2.328-5.848	<0.001*
Vitamin D deficiency (<20 ngm/ml)	0.759	2.136	1.041-4.381	0.03*
Obesity (BMI>25 Kg/m2)	1.211	3.357	1.905-5.918	<0.001*
Glycemia control (HBA1C%>6.8)	1.417	4.125	2.442-6.966	<0.001*

ANOVA (results not shown) showed a non-significant decrease in median nerve amplitude in severe and mild grade DPN compared to moderate and no DPN, respectively (p=0.577 and 0.346). The ulnar nerve amplitude was also non-significantly higher in the mild group compared to no DPN (P=0.601). The amplitude of the ulnar nerve in severe DPN was non-significantly reduced compared to moderate DPN (P=0.360). Also, ulnar nerve amplitude was non-significantly reduced in moderate DPN compared to mild DPN (p=0.133). Sural nerve amplitude in severe DPN was non-significantly reduced compared to moderate DPN (P=0.874) and was reduced non-significantly in moderate DPN compared to mild DPN (p=0.209). The latency of the sural nerve was non-significantly higher in mild compared to patients without DPN (p=0.248).

DISCUSSION

The results are in line with earlier studies. The risk of DPN correlates with the duration of diabetes. An increased BMI is associated with insulin resistance, resulting in neuropathy due to endothelial dysfunction (11,12).

The present study showed significantly higher mean–HbA1C % and CV- HbA1C % in DPN patients compared to those without DPN (p<0.001). Mean HbA1C (M- HbA1C) and coefficient of variance of HbA1C (CV- HbA1C) were reportedly higher in diabetes patients with neuropathy. M- HbA1C and CV- HbA1C are indicators of long-term hyperglycemia and its variability, respectively, which results in enhanced markers of DNA cellular damage and expression of p53, thereby resulting in "memory,"

which is implicated in metabolic consequences leading to neuronal damage (7).

In the present study, 16/26, i.e., 61.50 % of patients with severe DPN, had Vitamin D deficiency, i.e., levels < 20 ng/ml. Also, 14/26, i.e., 53.80 % of severe DPN patients had poor glycemic control (HbA1C % >7.6). Qu *et al.,* showed that vitamin D deficiency is associated with diabetic neuropathy. A decrease in the level of nerve growth factor and defective calcium homeostasis in the nerve is implicated in vitamin D deficiency-associated neuropathy. The vitamin D receptor is up regulated, correlating with DPN severity (13,14). A significant negative correlation was found in our study between vitamin D and glycated hemoglobin, which is in line with the result reported earlier (15). In our study, vitamin D levels in DPN patients were 25.67±6.34 ng/ml, and the correlation with DPN was significant (r=-0.339, p=0.02). Vitamin D levels of 21.2±11.5 ng/ml were found by Anodiyil *et al.,* in diabetes patients with neuropathy. An inverse correlation of vitamin D deficiency with diabetic neuropathy and its severity is reported (14). In the DPN group, mild, moderate, and severe DPN grades were present in 59.48%, 26.84%, and 13.68 %, respectively, and the association of vitamin D with DPN was negative. Similar results were obtained by Pinzon *et al.,* (16). A previous study has shown that 45% of people with diabetes had vitamin D deficiency, and 87.6% of patients with vitamin deficiency had neuropathy. Results also showed a negative correlation of vitamin D with DPN severity and sensory (sural) conduction velocities and amplitude (peroneal motor, median sensory, and sural sensory) (14). A reduction in vitamin D levels was reported by Dalia *et al.,* in patients with neuropathy, wherein the vitamin D levels correlated negatively with the severity of neuropathy (18).

The results of the nerve conduction study in our study are in line with earlier studies, and as per literature, the common peroneal nerve is affected most (19, 20). In our study, sensory sural nerve amplitude, conduction velocity, and motor and median and peroneal conduction velocities showed a significant positive correlation with vitamin D, aligning with earlier reports (21). Motor and sensory nerves showed a negative correlation of conduction velocities and amplitude with HBA1C variability, whereas a positive correlation was observed with latency.

Increased motor and sensory latency and decreased amplitude and conduction velocities were detected by Mankar *et al.,* in diabetic patients. In general, there is a correlation between HbA1C levels and conduction velocity. An improvement in conduction velocity by 1.3 m/second for every 1 % decrement in the HbA1C level is reported (20). A significant (P<0.05) negative correlation of HbA1C levels with conduction velocity (r=0.4 was reported in the previous study. Hypoxia and ischemia-induced nerve damage secondary to decreased nitric oxide-induced vasoconstriction, neurotoxicity due to sorbitol accumulation, and inflammation are implicated in diabetic neuropathy. A decrease in amplitude signifies axonal damage. Duration and severity of hyperglycemia are a risk for neuropathy in diabetes (23). Results of a previous study show that variability in HBA1C is associated with the severity of the neuropathy and low amplitude and reduction in conduction velocity of motor and sensory nerves (24). In our study, the nerve conduction tests were more deranged in patients with severe DPN grades, per those reported earlier (25). As discussed previously, the results may be attributed to hypoxia-induced diminished blood flow, derangement of the electrogenic pump, capillary dysfunction, and diminished axonal transport.

The results of the logistic regression in our study are per those obtained in earlier studies, our results showed a significant association of vitamin D deficiency with DPN (odds ratio = 3.47; 95% CI = 1.04-11.56, P = 0.043) (10). The earlier study also found a similar association (11, 26). Less than 20 ng/mL vitamin D level had a greater risk for symptomatic DPN (odds ratio [OR] = 2.04; 95% CI, 0.99–4.02; *P* = 0.054). Body mass index, diabetes duration, and 25(OH) D levels are significant predictors of DPN (27).

CONCLUSION

Poor glycemic control, vitamin D levels, higher BMI, and duration of diabetes are significant risks for developing DPN in type 2 diabetics. There is an alteration in the motor and sensory nerve conduction velocity and amplitude and latency, which correlates with HbA1C variability and Vitamin D. Nerve conduction study, variability in HbA1C and vitamin D levels can act as tools to detect DPN, an essential complication in diabetics. If controlled and monitored, BMI, blood glucose, and vitamin D have preventive and therapeutic potential in controlling the progression and management of DPN in type 2 diabetics. Vitamin D is a modifiable risk factor that needs monitoring in people with diabetes.

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CONFLICT OF INTEREST

None declared.

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