ORIGINAL ARTICLE

Oman Medical Journal [2020], Vol. 35, No. 5: e168

Modulation of Interleukin-8 Production by Vitamin D Supplementation in Indonesian Patients with Diabetic Polyneuropathy: A Randomized Clinical Trial

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ARTICLE INFO

Article history:
Received: 21 August 2019
Accepted: 6 April 2020

Online:
DOI 10.5001/omj.2020.110

Keywords:
Diabetic Neuropathies; Interleukin-8; Calcifediol; Indonesia.

ABSTRACT

Objectives: We sought to assess the modulation of interleukin-8 (IL-8) production by vitamin D supplementation in Indonesian patients with diabetic polyneuropathy (DPN). ***Methods***: We conducted a cohort prospective, randomized, placebo-controlled, double-blind trial. This study was approved by the Local Ethical Committee and conducted from July 2018 to February 2019. We recruited 50 subjects with type 2 diabetes mellitus attending Haji Adam Malik General Hospital Medan, and divided them into two groups. The groups were treated for 10 weeks, either with placebo or vitamin D (D_3) supplementation of 50 000 IU/week. They were evaluated by routine nerve conduction study (NCS) in the upper and lower limbs, and their serum vitamin 25-hydroxyvitamin D (25(OH)D) and IL-8 levels before and 10 weeks after placebo or vitamin D supplementation were measured. The role of IL-8 and vitamin D supplementation on the NCS was analyzed using linear regression. ***Results:*** There was a significant difference between the mean vitamin 25(OH) D (p = 0.001) and IL-8 levels (p = 0.002) before and after vitamin D supplementation. There was no significant correlation between changes in vitamin 25(OH)D and IL-8 levels (p = 0.743). There was significant role of IL-8 on amplitude of the sensory sural nerve (p = 0.047; B = -0.009) and the nerve conduction velocity (NCV) of the motor tibial nerve (p = 0.007; B = -0.027). There was a significant role of vitamin D supplementation on NCSs. ***Conclusions:*** Higher IL-8 levels were correlated with poorer amplitude of the sensory sural nerve and the NCV of motor tibial nerves. Lower vitamin 25(OH)D levels were correlated with poorer distal latencies, amplitudes, and NCVs. There was no significant correlation between vitamin 25(OH)D and IL-8 levels. Thus, no sufficient evidence that vitamin D supplementation modulates IL–8 in Indonesian patients with DPN. Vitamin D_3 improved NCSs in diabetic patients.

Type 2 diabetes mellitus (T2DM) is associated with systemic inflammation that results in insulin resistance.[1] Increased oxidative stress and several other pathways cause inflammation, which is responsible for most of the complications of diabetes.[2] Characteristics of systemic inflammation are increased levels of inflammatory biomarkers in the bloodstream, such as tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-2, IL-6, IL-8, and IL-12.[3] T2DM patients with diabetic polyneuropathy (DPN) have increased serum levels of inflammatory cytokines.[4,5]

Inflammatory cytokines directly induce insulin resistance by interrupting insulin signal transduction.[6,7] A review by Wilson and Wright stated several studies on the role of inflammatory mediators in diabetic neuropathy (DN), including TNF-α and IL-6 in animal models induced by streptozotocin and T2DM patients with or without DN. They also explained the role of IL-8 in T2DM patients compared with controls.[8]

Treatment of aggressive hyperglycemia is not effective in T2DM. The treatment of DN should be developed outside of the treatment of hyperglycemia and, if possible, begin early in the course of the disease.[9] Inhibition of the inflammatory response is effective in preventing DN.[10] Human studies examining the effects of vitamin D supplementation on inflammatory biomarkers in subjects with or at

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high risk of developing T2DM are scarce and produce conflicting results. Vitamin D supplementation or bioactive form 1,25(OH)2D improves insulin sensitivity by preventing the synthesis of excessive inflammatory cytokines.[11]

We sought to assess the modulation of IL-8 production by vitamin D supplementation in Indonesian patients with DPN.

METHODS

This study was a cohort prospective, randomized, placebo-controlled, double-blind trial. The study was approved by the Faculty of Medicine Universitas Sumatera Utara/Haji Adam Malik General Hospital Ethical Committee. All subjects signed informed consent before examination. Fifty subjects with T2DM in Haji Adam Malik General Hospital Medan were enrolled in this study from July 2018 to February 2019. They were divided into two groups, which were treated for 10 weeks with either placebo or vitamin D (D_3) supplementation (Natrol® 10 000 IU) of 50 000 IU/week. The placebo contained saccharum lactis with the same weight as vitamin D supplementation. They were evaluated by routine nerve conduction study (NCS) in the upper and lower limbs, and their serum vitamin 25-hydroxyvitamin D (25(OH)D) and IL-8 levels before and 10 weeks after placebo or vitamin D supplementation were measured.

Before the blood test, the patient was asked to fast for about eight hours. The subjects were randomized in a double-blind fashion; 25 subjects had placebo and 25 had vitamin D supplementation. The placebo or vitamin D supplementation was taken as three capsules a day, once a week, for 10 weeks. The selection of treatment group was done randomly using a random table. Patients and researcher did not know the patient got a placebo or vitamin D supplementation.

T2DM patients with mild to moderate DPN were included in the study. Patients who took vitamin D in the last three months, were taking anti-tuberculous drugs or chemotherapy, with renal, hepatic, gastrointestinal, stroke, malignancy or infection problems, pregnant, breastfeeding, or using oral contraceptives were excluded from the study. Patients allergic to vitamin D and did not regularly take medication were also excluded. NCS examination was performed by the same neurologist using Cadwell electroneuromyography machine. NCS consisted of distal latencies (DL), amplication, and nerve conduction velocity (NCV). Serum vitamin 25(OH)D status was evaluated using the chemiluminescent immunoassay method by DiaSorin Liaison, and IL-8 was evaluated using enzyme-linked immunoassay method by Quantikine® HS ELISA.

Changes in the vitamin D and IL-8 levels were considered independent variables and NCS changes as a dependent variable. The mean difference was analyzed using T dependent test and correlation was analyzed using Pearson's correlation. The role of IL-8 and vitamin D supplementation on NCSs was analyzed using linear regression. The results were considered significant at $p < 0.050$. The correlation coefficient (R) measures strength and direction. If R is negative, the direction is negative relationship. If r is positive, the direction is positive relationship. R value of 0.300 indicates weak strength, 0.500 is moderate strength, and 0.700 means strong strength. The statistical calculations were done using a computerized program.

RESULTS

All randomized subjects (n = 50) completed this study. Their characteristics data were similar in both groups at baseline ($p > 0.050$) as shown in Table 1.

There were significant differences between the mean vitamin 25(OH)D and IL-8 levels before and after receiving vitamin D supplementation [Table 2].

We found no significant correlation between vitamin 25(OH)D and IL-8 levels [Table 3]. There were significant correlations with negative direction and weak strength between IL-8 level with DL of sensory ulnar, amplitude of sensory sural, and NCV of motor tibial nerves. On the other hand, we observed a positive direction and weak strength with NCV of the motor median nerve. There were significant correlations between changes in vitamin 25(OH)D levels with DLs, amplitudes, and NCVs of the nerves examined, where strength was moderate and negative direction with DLs, while positive direction with amplitudes and NCVs.

The role of IL-8 on NCSs among subjects who received placebo or vitamin D supplementation was not significant. The role of IL-8 on amplitudes of sensory sural nerve and NCV of motor tibial nerve were significant with regression coefficient values of

Table 1: Characteristics data of the subjects.

Characteristics	Placebo group	Vitamin D group	*p*-value
Gender			
Male, n (%)	9 (36.0)	4 (16.0)	0.111
Female, n (%)	16 (64.0)	21 (84.0)	
Age, years, mean ± SD	58.2 ± 9.4	54.5 ± 7.1	0.232
Duration of DM, years, mean (min–max)	5.0 (0.5–20.0)	4.0 (0.5–28.0)	0.539
HbA_{1c}, %, mean ± SD	8.3 ± 1.5	9.2 ± 2.7	0.130
25(OH)D level at baseline, ng/mL, mean ± SD	18.5 ± 5.1	16.0 ± 5.0	0.091
IL-8 level at baseline, pg/mL, mean ± SD	54.3 ± 54.8	52.1 ± 31.4	0.866

SD: standard deviation; DM: diabetes mellitus; HbA_{1c}: hemoglobin A_{1c}; IL: interleukin.

Table 2: The differences between mean vitamin 25(OH)D and interleukin-8 (IL-8) levels before and after vitamin D supplementation.

Levels	Vitamin D supplementation		
	Before	After	*p*-level
25(OH)D, ng/mL	16.0 ± 5.0	36.0 ± 12.3	0.001*
IL-8, pg/mL	52.1 ± 31.4	29.7 ± 23.1	0.002*

*T dependent test. *p < 0.050.*

Table 3: The correlation between changes in vitamin 25(OH)D, interleukin-8 (IL-8) levels, and NCS.

Variables	IL-8		25(OH)D	
	R	*p*-value	R	*p*-value
25(OH)D level, ng/mL	0.048	0.743		
Distal latency, ms				
Motor median nerve	-0.026	0.856	-0.362	0.010*
Motor ulnar nerve	0.058	0.691	-0.514	< 0.001**
Sensory median nerve	-0.028	0.849	-0.056	0.698
Sensory ulnar nerve	-0.340	0.016*	-0.513	< 0.001**
Motor peroneal nerve	0.066	0.649	-0.469	0.001*
Motor tibial nerve	-0.071	0.623	-0.537	< 0.001**
Sensory sural nerve	0.000	0.999	-0.132	0.361
Amplitude, mV				
Motor median nerve	-0.126	0.383	0.625	< 0.001**
Motor ulnar nerve	-0.050	0.728	0.551	< 0.001**
Sensory median nerve	-0.184	0.202	0.493	< 0.001**
Sensory ulnar nerve	-0.092	0.527	0.494	< 0.001**
Motor peroneal nerve	-0.131	0.364	0.564	< 0.001**
Motor tibial nerve	-0.037	0.801	0.520	< 0.001**
Sensory sural nerve	-0.282	0.047*	0.461	0.001*
Nerve conduction velocity, m/s				
Motor median nerve	0.289	0.042*	0.525	< 0.001**
Motor ulnar nerve	0.059	0.686	0.438	0.001*
Sensory edian nerve	-0.246	0.086	0.257	0.072
Sensory ulnar nerve	-0.008	0.958	0.527	< 0.001**
Motor peroneal nerve	0.073	0.377	0.494	< 0.001**
Motor tibial nerve	-0.378	0.007*	0.235	0.101
Sensory sural nerve	-0.074	0.611	0.231	0.106

NCS: nerve conduction study ; R: correlation coefficient; Pearson's correlation test.
**p < 0.050; **p < 0.001.*

Table 4: The role of interleukin-8 (IL-8) on nerve conduction studies (NCSs).

NCS	IL–8		
	C	B	*p*-value
Distal latency, ms			
Motor median nerve	-0.275	0.000	0.856
Motor ulnar nerve	0.025	0.000	0.691
Sensory median nerve	0.003	0.000	0.849
Sensory ulnar nerve	0.116	-0.003	0.016*
Motor peroneal nerve	-0.085	0.001	0.649
Motor tibial nerve	-0.149	-0.001	0.623
Sensory sural nerve	-0.172	-1.661	0.999
Amplitude, mV			
Motor median nerve	-0.271	-0.003	0.383
Motor ulnar nerve	0.006	-0.001	0.728
Sensory median nerve	-0.934	-0.020	0.202
Sensory ulnar nerve	1.115	-0.012	0.527
Motor peroneal nerve	0.006	-0.002	0.364
Motor tibial nerve	0.346	-0.002	0.801
Sensory sural nerve	-0.077	-0.009	0.047*
Nerve conduction velocity, m/s			
Motor median nerve	0.162	0.024	0.042*
Motor ulnar nerve	0.503	0.003	0.686
Sensory median nerve	-0.007	-0.024	0.086
Sensory ulnar nerve	-0.425	-0.001	0.958
Motor peroneal nerve	0.053	0.011	0.377
Motor tibial nerve	-0.427	-0.027	0.007*
Sensory sural nerve	0.032	-0.010	0.611

Linear regression.
**p <0.050; C = constanta; B = regression coefficient.*

Table 5: The role of vitamin D supplementation on nerve conduction studies (NCSs).

NCS	Vitamin D supplementation		
	C	B	*p*-value
Distal latency, ms			
Motor median nerve	0.104	-0.035	0.010*
Motor ulnar nerve	0.242	-0.020	< 0.001**
Sensory median nerve	0.060	-0.005	0.698
Sensory ulnar nerve	0.450	-0.028	< 0.001**
Motor peroneal nerve	0.314	-0.037	0.001*
Motor tibial nerve	0.197	-0.031	< 0.001**
Sensory sural nerve	-0.071	-0.009	0.361
Amplitude, mV			
Motor median nerve	-1.220	0.089	< 0.001**
Motor ulnar nerve	-0.760	0.071	< 0.001**
Sensory median nerve	-3.912	0.286	< 0.001**
Sensory ulnar nerve	-2.572	0.346	< 0.001**
Motor peroneal nerve	-0.489	0.047	< 0.001**
Motor tibial nerve	-1.087	0.133	< 0.001**
Sensory sural nerve	-0.853	0.077	0.001*
Nerve conduction velocity, m/s			
Motor median nerve	-2.536	0.233	< 0.001**
Motor ulnar nerve	-0.979	0.134	0.001*
Sensory median nerve	-1.349	0.139	0.072
Sensory ulnar nerve	-3.491	0.282	< 0.001**
Motor peroneal nerve	-2.452	0.223	< 0.001**
Motor tibial nerve	-1.243	0.092	0.101
Sensory sural nerve	-1.729	0.168	0.106

Linear regression.
**p < 0.050; **p < 0.001; C = constanta; B = regression coefficient.*

-0.009 and -0.027. This means an increase in IL-8 resulted in a decrease on amplitudes of sensory sural nerve and NCV of motor tibial nerve by 0.009 and 0.027 [Table 4].

The role of vitamin D supplementation on NCSs was significant, except for DLs and NCVs of sensory median and sural nerves, and NCV of motor tibial nerve [Table 5].

DISCUSSION

Interleukins, such as IL-8, play an important role in inflammation because they mediate inflammatory cells in the acute and chronic inflammatory processes.[12] Early inflammatory stimulus leads to the release of IL-8.[13,14]

In this study, there were significant differences between mean vitamin D25 (OH) and IL-8 levels before and after receiving vitamin D supplementation (p = 0.001 and p = 0.002). The Endocrine Society Clinical Practice Guidelines recommends that adults with vitamin D deficiency are given vitamin D_2 or D_3 50 000 IU/week for eight weeks to reach vitamin 25(OH)D level > 30 ng/mL, followed by a maintenance dose of 1500–2000 IU/day.[15] Supplementation of vitamin D at a dose of 30 000 IU/week increased vitamin 25(OH)D level by 2.26–2.92 ng/week for the first eight weeks and followed by a slight increase of 1.64–1.73 ng/week over 12 weeks.[16]

Vitamin D metabolites and their analogs could reduce IL-8 as hyperinflammatory macrophages.[17] Glucose regulates IL-8 production at the transcription level.[13,14] Vitamin D deactivates NF-kB, which regulates transcription of pro-inflammatory cytokine encoding genes.[11,18]

In cell culture experiments, there was a decrease in IL-8 by vitamin D metabolites and its analogs

only if high vitamin D concentrations were achieved.[17] Normal vitamin D levels for a tropical country were 54–90 ng/mL.[19] In our study, the mean vitamin 25(OH)D level after receiving vitamin D supplementation was 36.0±12.3 ng/mL. So, vitamin 25(OH)D level still has not reached normal or adequate levels. Therefore, this study found no significant correlation between vitamin 25(OH)D and IL-8 levels.

Inflammatory mechanisms have an important role in neuropathy.[20] Pro-inflammatory cytokines affect glia cells and neurons involved in the pathological process of DN. Pro-inflammatory cytokines, such as TNF-α, IL-1, IL-6, IL-8, monocyte chemoattractant protein 1, and C-reactive protein.[10] Our study found that significant correlations with negative direction and weak strength between IL-8 levels with DL of sensory ulnar, amplitudes of sensory sural, and NCV of motor tibial nerves. On the other hand, we found a positive direction and weak strength with NCV of motor median nerve. The increase in IL-8 levels resulted in the decrease in DL of sensory ulnar, amplitude of sensory sural, and NCV of motor tibial nerves, but an increase in NCV of motor median. Tumor necrosis factor induces IL-6 and IL-8 production by schwann cells.[21] Myelin damage affects nerve conduction, resulting in prolonged DL and slowing NCV.[22] The most common compression neuropathies in DM patients are carpal tunnel syndrome (30%) and ulnar neuropathy (2.1%).[23,24]

We found significant correlations between changes in vitamin 25(OH)D levels with DLs, amplitudes, and NCVs of the nerves examined, where strength was moderate and negative direction with DLs, while positive direction with amplitude and NCVs. A decrease in vitamin 25(OH)D levels resulted in the increase in DLs, whereas amplitude and NCVs decreased.

Abdelsadek et al,[25] also found significant correlations between vitamin 25(OH)D level and amplitudes of motor peroneal, sensory median, and sensory sural nerves and the NCV of the sensory sural nerves ($p < 0.001$). Lower levels of vitamin 25(OH)D were associated with a decrease in NCV of peroneal and sural nerves.[26] The severity of NCV abnormality was closely associated with serum 25(OH)D concentrations.[27]

Our study found no significant correlations between changes in vitamin 25(OH)D levels with DL and NCV of sensory median, NCV of motor tibial, and the NCV of sensory sural nerves. DPN patients show varying degrees of nerve regeneration and degeneration. Axonal regeneration is the body's natural response to compensate for damage caused by DM, but only partial regeneration is an important component of DN development. Regeneration of nerve fibers is delayed in the tibial (motor) and sural (sensory) nerves.[28]

The role of IL-8 on NCSs among patients who received placebo or vitamin D supplementation was not significant. The role of IL-8 on the amplitude of the sensory sural nerve and NCV of motor tibial nerve were significant with regression coefficient values of -0.009 and -0.027.

Immunohistochemical detection of IL-8 was used as a diagnostic marker of traumatic axonal lesions.[29] Axonal degeneration results in a decrease in sensory and motor amplitude. There is a linear relationship between the number of missing axons and sensory amplitude. Motor amplitude is less sensitive at the onset of axonal lesions.[22] DPN first affects the longest axon in the extremities and progresses to the proximal.[28] Abnormal NCV was most often affecting the tibial and sural nerves (86% and 82%, respectively).[30] The sural nerve is one of the nerves most commonly involved in DN.[28]

Animal studies have indicated that vitamin D is efficient in protecting neurons and reducing neuronal toxicity and damage. Another study also found modification of the expression of several genes involved in axonogenesis and myelination, after 24 hours of vitamin D supplementation.[31] The role of vitamin D supplementation on NCSs was significant. That means vitamin D supplementation resulted in decreased DLs, increased amplitudes and NCVs (except for DLs and NCVs of sensory median and sural nerves, and NCV of the motor tibial nerve). These could be related to the pathophysiology underlying DPN, where the duration of DM was prolonged and the pathophysiology was mainly axonal, and in which case would take more than eight weeks for nerves to regenerate or correct the effects of vitamin D deficiency.[32] In this study, vitamin D supplementation was for 10 weeks, so some nerves did not experience significant improvement.

We did not document the patients' diets and their duration of sun exposure, which contributes as a limitation of this study. Further studies should be conducted on a large number of patients

before coming to definitive conclusions, especially modulation of IL-8 by vitamin D supplementation.

CONCLUSION

Higher IL-8 levels were correlated with poorer amplitudes of sensory sural nerves and NCV of motor tibial nerves. Lower vitamin 25(OH)D levels were correlated with poorer DLs, amplitudes, and NCVs. There was no significant correlation between vitamin 25(OH)D and IL-8 levels. Thus, no sufficient evidence that vitamin D supplementation modulates IL–8 in Indonesian patients with DPN. Our results show that a weekly dose of 50 000 IU of vitamin D_3 for 10 weeks was effective at improving the manifestation of polyneuropathy (NCSs) in diabetic patients.

Disclosure

The authors declared no conflicts of interest. No funding was received for this study.

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