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Research Article

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Does Vitamin- D Have A Relation to Diabetic Peripheral Neuropathy in Egyptian Type 2 Diabetes Mellitus Patients?

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Abstract

Objectives

is to detect relation between vitamin D deficiency and increased risk of peripheral neuropathy in type 2 diabetes (DM).

Methods

The study included total number of 90 subjects; 60 cases with type 2 DM and was divided into two groups; one with peripheral neuropathy, the other group without peripheral neuropathy and 30 healthy subjects as control.

All the included cases were subjected to full history taking, clinical examination (general and neurological), ocular fundus examination and laboratory investigations including Glomerular filtration rate (GFR), glycosylated hemoglobin (HbA1c), assessment of serum level of vitamin D was conducted to all cases. All the included subjects were examined to assess the degree of presence or absence of retinopathy.

Results

We found that HbA1c and hsCRP (high sensitivity C-reactive protein) level was statistically significantly higher in the T2DM with peripheral neuropathy group as compared with T2DM without peripheral neuropathy and control groups.

The serum level of vitamin D was statistically significantly lower in those with peripheral neuropathy group in comparison to those without neuropathy and control groups.

By multivariate regression analysis, DM duration, high values of HbA1c, urinary albumin/creatinine ratio (ACR), hs-CRP, systolic blood pressure (SBP) and decreased serum vitamin D levels were shown to be independent predictors for diabetic peripheral neuropathy.

Conclusion

Serum level of vitamin D was low in Egyptians Type 2 diabetes mellitus patients with neuropathy in comparison to those without.

Keywords: Vitamin D, Diabetes mellitus, Neuropathy, Egypt.

Introduction and Aim of The Work

Diabetic neuropathy is a common complication in patients with diabetes, and it affects up to 50 % of patients with diabetes [1].

Vitamin D deficiency, a common symptom in diabetic patients who have distal symmetrical polyneuropathy, has been associated with type 1 or 2 diabetes and its microvascular and macrovascular complications [2].

The aim of the present study was to detect the relation between vitamin D deficiency and increase risk of peripheral neuropathy in type 2 diabetes.

Patients and Methods

This is a cross sectional descriptive study, was conducted in the Specialized Medical Hospital; Mansoura University, Mansoura, Egypt, for duration of 6 months from January 2021 to June 2021. This study included total number of 90 subjects with age 18-65 years; and were classified into 3 groups (each of 30 subjects) as follows:

First Group

included 30 cases with type 2 diabetes without peripheral neuropathy (19 males and 11 females) with mean age 47.93 years.

Second Group: included 30 patients with type 2 diabetes and peripheral neuropathy (20 males and 10 females) with mean age 49.93 years.

Third Group

included 30 normal subjects as a control group (16 males and 14 females) with mean age 47.17 years. There was no significant difference between different groups regarding age and sex distribution.

Diabetes was diagnosed based on the World Health Organization consulting criteria (i.e., fasting plasma glucose [FPG] ≥7.0mmol/L [126mg/dL] and/or a 2-h postglucose value ≥11.1 mmol/L [200 mg/dL]) [3].

Diabetic peripheral neuropathy was defined as the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes (Combinations of more than 1 following test have>87% sensitivity in detecting DPN: pinprick, temperature, and vibration perception (using a 128-Hz tuning fork), 10-g monofilament pressure sensation at the distal halluces, and ankle reflexes) [4].

Exclusion Criteria

Patients with age >65 years, liver cell failure, heart failure, renal failure, thyroid disease, patients with peripheral neuropathy caused by other factor such as accident, tumors, inflammation, autoimmune disease, patients treated with vitamin D, patients with history of metabolic bone disease, patients suspected of hypovitaminosis such as pregnancy, lactation and postmenopausal, patients with diabetic foot were excluded.

A written informed consent was obtained from all participants.

•The whole study design was approved by the Institutional review board (IRB), Faculty of Medicine, Mansoura University.

All participants were subjected to the following: full history taking and clinical examination, body weight, height, body mass index (BMI=weight (Kg)/height (m2) and neurological *examination including examination of motor and sensory systems in lower limbs.*

o Assessment for loss of protective sensation (LOPS) in lower limbs using the following techniques:
- Pressure perception (Superficial sensation): using Semmes-Weinstein 10-gram monofilament [5].
- Vibration perception (Deep sensation): using 128 Hz tuning fork [6].

Nerve Conduction Velocity (NCV) Assessment

The nerve conduction velocity was assessed in all the cases included in the study. The NCV was considered to be decreased when it was below the normal value (Normal NCV 50-60m/s) [7].

The following laboratory investigations were done for all participants in our study: fasting and two hours postprandial blood glucose, glycosylated hemoglobin (HbA1c), complete blood count (CBC), lipid profile, Urinary albumin/creatinine ratio, urea, creatinine and calculate estimated GFR by using the Modification of Diet in Renal Disease (MDRD) formula ; eGFR (mL/min/1.73 m2) =186× (Scr)-1.154× (Age)-0.203× (0.742 if female) × (1.120 if African-American), hsCRP, liver enzymes, TSH, Serum level of 25 hydroxy vitamin D was measured using a chemiluminescent immunoassay (25-OH-Vitamin D ELISA - IBL international, Kit N: RE53041, Hamburg, Germany) [8].

Results

Table 1: Comparison between T2DM without peripheral neuropathy, T2DM with peripheral neuropathy and control groups regarding clinical and biochemical parameters

Parameters	T2DM without peripheral neuropathy (n=30)	T2DM with peripheral neuropathy (n=30)	Control (n=30)	Significance test	Multiple comparisons
FBG (mg/dL)				P-value **<0.001** HS	**P_1<0.001** HS **P_2<0.001** HS **P_3=0.004** HS
Median (IQR)	122 (26.25)	157.50 (87.75)	94 (10.50)		
Range (Min-Max)	80 - 199	100.00 - 299.00	82 - 110		
2Hr PPBG (mg/dL)				**<0.001** HS	**P_1<0.001** HS **P_2<0.001** HS **P_3=0.022** S
Median (IQR)	181.50 (44)	224.50 (110.50)	107 (51.25)		
Range (Min-Max)	120 - 288	143 - 440	75 - 167		
HbA1c (%)				**<0.001** HS	**P_1<0.001** HS **P_2<0.001** HS **P_3=0.005** HS
Median (IQR)	7 (0.90)	8 (1.80)	5.40 (0.52)		
Range (Min-Max)	5.50 - 9.80	6.90 - 11.90	5 - 6.10		
Total Cholesterol (mg/dL)				=0.415 NS	**NS**
Median (IQR)	202 (79.50)	186.50 (64.75)	182.50 (21.75)		
Range (Min-Max)	115 - 360	112 - 305	137 - 245		
Triglycerides (mg/dL)				**<0.001** HS	**P_1=0.003** HS **P_2<0.001** HS P_3=1.000 NS
Median (IQR)	147.50 (104.25)	163 (74.25)	103 (44.25)		
Range (Min-Max)	56 - 291	60 - 274	62 - 212		
HDL (mg/dL)				**=0.004** HS	**P_1=0.017** S **P_2<0.007** HS P_3=1.000 NS
Median (IQR)	44 (13)	41 (16.73)	51.50 (10.50)		
Range (Min-Max)	25 - 70	16.90 - 139	36 - 68		
LDL (mg/dL)				=0.223 NS	**NS**
Median (IQR)	117 (68.75)	120 (53.25)	104.50 (28.50)		
Range (Min-Max)	15.70 - 293	15.70 - 250	63 - 176		
ALT (U/L)					
Mean ± SD	35.27 ± 6.03	34.57 ± 6.64	20.27 ± 7.92	**<0.001** HS	**P_1<0.001** HS **P_2<0.001** HS P_3=0.919 NS
Range (Min-Max)	26 - 48	22 - 48	9 - 40		
AST (U/L)				***<0.001*** HS	***P_1=0.230*** NS ***P_2=0.001*** HS *P_3=0.245* NS
Median (IQR)	37 (14)	34.50 (13)	19.50 (5.25)		
Range (Min-Max)	22 - 48	22 - 48	11 - 40		
Urea (mg/dL)				**=0.002** HS	P_1=0.230 NS **P_2=0.001** HS P_3=0.245 NS
Median (IQR)	30 (13.75)	35 (13.75)	28 (9.06)		
Range (Min-Max)	21 - 55	21 - 92	17 - 45		
Creatinine (mg/dL)					

Median (IQR)	0.90 (0.50)	0.94 (0.22)	0.77 (0.16)	**=0.004 HS**	**P_1=0.036 S** **P_2<0.005 HS** P_3=1.000 NS
Range (Min-Max)	0.56 - 1.30	0.60 - 1.40	0.60 - 1.05		
Albumin Creatinine Ratio(ACR (mg/gm))				**<0.001 HS**	**P_1=1.000 NS** **P_2<0.001 HS** P_3<0.001 HS
Median (IQR)	19 (8.41)	140 (253.80)	19 (12.25)		
Range (Min-Max)	9-31	30.90-927	10-27		
TSH (µIU/mL)				=0.699 NS	**NS**
Median (IQR)	1.23 (2.02)	1.23 (1.12)	1.70 (1.33)		
Range (Min-Max)	0.55 - 5.04	0.50 - 4.30	0.50 - 4		
HS-CRP (mg/dL)				**<0.001 HS**	**P_1<0.001 HS** **P_2<0.001 HS** P_3=1.000 NS
Median (IQR)	16.97 (12.43)	16.86 (17.83)	3.70 (1.67)		
Range (Min-Max)	2.06 - 56.80	3.40 - 68	1.30 - 6.57		
eGFR (mL/min)				0.014 S	P_1=0.061 NS **P_2=0.017 S** P_3=0.869 NS
Mean ± SD	83.40 ± 21.12	81 ± 19.42	94.33 ± 13.82		
Range (Min-Max)	43.07 - 121.36	53.28 - 119.10	70.96 - 120.55		
BMI (kg/m^3)				0.394 NS	**NS**
Mean ± SD	26.24 ± 2.67	26.94 ± 3.35	27.42 ± 3.87		
Range (Min-Max)	22 - 32	21 - 33	19.40 - 36.90		
SBP (mmHg)				**<0.001 HS**	**P_1<0.001 HS** **P_2<0.001 HS** P_3=0.998 NS
Mean ± SD	132.17 ± 13.04	132.33 ± 11.94	118.33 ± 11.40		
Range (Min-Max)	100 - 160	110 - 160	90 - 140		
DBP (mmHg)				=0.068 NS	**NS**
Median (IQR)	80 (25)	80 (16.25)	80 (10)		
Range (Min-Max)	60 - 100	70 - 100	60 - 90		
serum level of 25(OH) vitamin D (ng/ml)				**<0.001 HS**	**P_1=0.001 HS** **P_2<0.001 HS** **P_3=0.001 HS**
Mean (SD)	27.52±6.68	19.24 ± 5.17	36.84 ± 7.91		

- P1: P-value for the difference between T2DM without peripheral neuropathy group and control group.
- P2: P-value for the difference between T2DM with peripheral neuropathy group and control group.
- P3: P-value for the difference between T2DM without peripheral neuropathy group and T2DM with Peripheral neuropathy group

Table 2: Correlation between serum level of 25 (OH) and various parameters in groups of T2DM without peripheral neuropathy and T2DM with peripheral neuropathy

Parameters correlated	Serum level of 25 (OH) vitamin D (ng/ml)			
	T2DM without peripheral neuropathy group (n = 30)		T2DM with peripheral neuropathy group (n = 30)	
	r_s	P-value	r_s	P-value
Age (years)	0.11	0.560 NS	-0.17	0.358 NS
FBG (mg/dL)	**0.47**	**0.009 HS**	**0.45**	**0.013 S**
2Hr PPBG (mg/dL)	**0.46**	**0.011 S**	**0.41**	**0.024 S**
HbA1c (%)	**0.45**	**0.010 HS**	**0.46**	**0.011 HS**
Total cholesterol (mg/dL)	0.04	0.833 NS	0.06	0.755 NS
Triglycerides (mg/dL)	0.00	0.985 NS	0.21	0.262 NS
HDL-c (mg/dL)	0.07	0.701 NS	0.12	0.525 NS
LDL-c (mg/dL)	0.28	0.135 NS	-0.09	0.654 NS
ALT (U/L)	-0.11	0.558 NS	-0.13	0.482 NS
AST (U/L)	0.02	0.903 NS	-0.18	0.339 NS
Urea (mg/dL)	-0.07	0.711 NS	-0.06	0.762 NS
Creatinine (mg/dL)	0.12	0.535 NS	0.26	0.160 NS
Uric acid (mg/dL)	0.04	0.834 NS	0.08	0.679 NS
TSH (□IU/mL)	0.03	0.861 NS	0.02	0.913 NS
HS-CRP (mg/dL)	0.11	0.567 NS	**0.49**	**0.006 HS**
eGFR (mL/min)	-0.21	0.275 NS	-0.20	0.301 NS
BMI (kg/m3)	-0.12	0.530 NS	0.34	0.063 NS
SBP (mmHg)	0.11	0.550 NS	0.21	0.269 NS
DBP (mmHg)	0.01	0.969 NS	0.20	0.282 NS
Hb (g/dL)	-0.06	0.748 NS	-0.16	0.403 NS
Platelets (103/□□L)	0.19	0.321 NS	-0.07	0.726 NS
WBCs (103/□L)	-0.34	0.066 NS	-0.01	0.966 NS

Hb: hemoglobin, WBC: white blood cells, TSH: thytrophic stimulation hormone, ALT: alanine aminotransferase, AST: aspartate aminotransferase, DBP: diastolic blood pressure, SBP: systolic blood pressure, LDL-c: low density lipoprotein cholesterol, HDL-c: high density lipoprotein cholesterol, , hsCRP: high sensitive C-reactive protein, FBG: fasting blood glucose

Table 3: Univariate and multivariate analysis of predictors of diabetic peripheral neuropathy

Variables	Univariate analysis	Multivariate analysis		
		B	95% CI	P value
Age	0.395			
Male sex	0.123			
Disease duration	0.001*	3.016	2.140- 3.847	0.001*
FBG	0.038*	1.456	1.162-2.546	0.076
2 Hours post prandial	0.011*	0.736	0.427- 1.326	0.338
HBAIC	0.001*	2.112	1.746– 2.837	0.001*
Cholesterol	0.385			
TGs	0.639			
HDL	9.971			
ALT	0.229			
Urea	0.01*	0.645	0.308-1.31	0.126
Creatinine	0.032*	0.363	0.108- 0.958	0.437

ACR	0.001*	2.116	1.857- 2.784	0.005*
TSH	0.246			
hsCRP	0.01*	1.775	1.426- 2.665	0.035*
BMI	0.118			
e-GFR	0.012*	0.735	0.236-1.08	0.436
SBP	0.004*	1.365	1.045– 2.125	0.045*
DBP	0.131			
vitamin D levels	0.001*	0.412	0.232- 0.842	0.003*

ACR: albumin/creatinine ratio, hsCRP: high sensitive C-reactive protein, DBP: diastolic blood pressure, e-GFR: estimated glomerular filtration rate, FBG: fasting blood glucose, HbA1c: glycosylated hemoglobin, SBP: systolic blood pressure, TG: triglycerides

Discussion

Diabetic peripheral neuropathy (DPN) is one of the most common chronic complications of diabetes mellitus (DM). Studies of American Diabetes Association (ADA) showed that 26.4% of the Type 2 Diabetes Mellitus (T2DM) patients are complicated by painful DPN, while up to 50% of the DPN patients may be asymptomatic [9]. Vitamin D deficiency is a common public health problem all over the world [10]. Vitamin D deficiency contributes significantly to the pathogenesis of the two types of diabetes by impairing insulin secretion from pancreatic beta-cells and increasing insulin resistance [11]. Clinical studies reported that vitamin D deficiency is more common in patients with diabetes and plays an important role in pathogenesis of diabetic neuropathies [2, 12].

In the current study, there were 7 cases (23.3%) with retinopathy in the T2DM without peripheral neuropathy and there were 18 cases (60%) in the T2DM with peripheral neuropathy group, with high statistically significant difference between the three groups.

This came in accordance with Khawaja et al. (2018) who revealed that the likelihood of DPN was higher among patients with diabetic retinopathy. Previous studies clearly demonstrated that diabetic patients having other microvascular and macrovascular complications were more likely to have DPN [13]. This finding can be attributed to common pathogenic mechanisms as the toxic effect of hyperglycemia in the form of increasing thickness of endo-neural micro-vessels, accumulation of advanced glycation end products (AGEs), activation of the polyol pathway and oxidative stress [12].

In the current study, serum 25 hydroxy vitamin D level was significantly lower in the group of diabetic patients with neuropathy than in those without. The level was statistically significantly lower in the T2DM without peripheral neuropathy as compared with the control group (table 1).

Moreover, serum level of vitamin D in our study was correlated with FBG, PPBG, HbA1c and hsCRP in the neuropathy group (table 2).

Our results came in accordance with Abdelsadek et al. (2018) who reported that the mean serum level of 25(OH) vitamin D in patients with DPN (group I) (21.09 ± 8.38) was highly statistically significant lower than patients without DPN (group II) (31.12 ± 14.85) with p value = 0.001 [14]. Consistent with the present research, the FIELD study has shown that vitamin D deficiency was present in 50% of 9795 patients with type 2 diabetes, and it predicted microvascular complications [15].

Some animal studies demonstrated the associations between vitamin D deficiency and low levels of nerve growth factors (neurotrophins) which are required for the development and survival of both sympathetic and sensory neurons, and cause defective neuronal calcium homeostasis [16]. Decrease in neurotrophins and defective calcium homeostasis increase nerve damage by toxins including hyperglycemia, also vitamin D receptor modulates neuronal cells differentiation and function. So, vitamin D deficiency impairs nociceptor function, worsens nerve damage, and lowers the pain threshold [17].

In the current study, the best cutoff point of serum level of 25 hydroxy vitamin D to differentiate between the T2DM with peripheral neuropathy group and T2DM without peripheral neuropathy group was 20.17 ng/ml with 95.5% sensitivity, 98 specificity, and 97.6 % accuracy.

He and his colleagues showed by receiver operating characteristic analysis was performed to reveal the optimal cutoff point of 25 hydroxy vitamin D for predicting signs of DPN the cutoff point was17.22 ng/mL [18]. Different cutoff points could be attributed to different kits used for assessment of vitamin D levels.

In the current study, with multivariate regression analysis, increased disease duration, HbAIC, ACR, hsCRP, SBP and decreased vitamin D were shown to be independent risk predictors for diabetic peripheral neuropathy (table 3). This agreed with Abdelsadek et al. (2018) who showed that long duration of DM, presence of hypertension, high HbA1c, and old age were independent predictors of microvascular complications including DPN among T2DM. Besides these strong and well-known risk factors, vitamin D levels revealed a significant and independent association with DPN. In the logistical regression model, Vitamin D deficiency was associated with increased risk of diabetic neuropathy, after adjustment of age, gender, duration of diabetes, smoking, body mass index, systolic blood pressure, fasting glucose, HbA1c, fasting C-peptide, total cholesterol, and microalbuminuria. Our results

also agreed with Tesfaye et al. who reported that systolic hypertension was an independent predictor for diabetic sensory neuropathy after adjustment for age, duration of diabetes, and metabolic control [19]. Also, in agreement with our study, Jhoun et al 2009 concluded that Peripheral diabetic neuropathy is associated with increased biochemical markers of inflammation and endothelial dysfunction [20]. Painful neuropathy is associated with further increase in inflammation and markers of endothelial dysfunction and preservation of the nerve axon reflex. This rising a question that whether inflammation has a relation to low serum level of vitamin D in those patients?

In our study; the values of FBG, PPBG, HbA1c, urine albumin/creatinine ratio (ACR) were higher in patients with diabetic neuropathy than in those without. On the other hand, serum 25- hydroxyl vitamin D level was significantly lower in diabetic neuropathy group in comparison to those without it (table 1). This might be because of the exposure to high blood glucose level increases the risk of developing macro vascular and micro vascular complications. Especially, a good glycemic control for the first year of diagnosis highly reduces the risk of complications [21]. Patients with dyslipidemia appeared to be more vulnerable to develop DPN. The possible explanation of nerve damage in such cases might be attributed to fat deposition, oxidative stress, activation of counter regulatory signaling pathways, and mitochondrial dysfunction, which ultimately lead to progressive inflammation and damage of the peripheral nerves [22].

The affection of renal functions in our study as indicated by low e-GFR, and increased serum creatinine and urine ACR in patients with diabetic neuropathy was supported by previous studies like Parkash et al 2019 who stated that reduction in eGFR is significantly associated with microvascular complications, such as diabetic neuropathy [23].

Summary and Conclusion

Serum level of vitamin D was low in Egyptians Type 2 diabetes mellitus patients with neuropathy. Whether it is mere association or it is a cause effect? This needs further large randomized controlled trials of use of vitamin D in treatment of diabetic neuropathy.

The authors declared that there is no conflict of interest.

References

1. Callaghan, B. C., Cheng, H. T., Stables, C. L., Smith, A. L., & Feldman, E. L. (2012). Diabetic neuropathy: clinical manifestations and current treatments. The lancet NEUROLOGY, 11(6), 521-534.
2. Bell, D. S. (2012). Reversal of the symptoms of diabetic neuropathy through correction of vitamin D deficiency in a type 1 diabetic patient. Case Reports in endocrinology, 2012.
3. American Diabetes Association. (2021) Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2021. Diabetes Care.
4. Boulton, A. J., Vinik, A. I., Arezzo, J. C., Bril, V., Feldman, E. L., Freeman, R., ... & Ziegler, D. (2005). Diabetic neuropathies: a statement by the American Diabetes Association. Diabetes care, 28(4), 956-962.
5. Bakker, K., Apelqvist, J., Schaper, N. C., & International Working Group on the Diabetic Foot Editorial Board. (2012). Practical guidelines on the management and prevention of the diabetic foot 2011. Diabetes/metabolism research and reviews, 28, 225-231.
6. Lai, S., Ahmed, U., Bollineni, A., Lewis, R., & Ramchandren, S. (2014). Diagnostic accuracy of qualitative vs. quantitative tuning forks: outcome measure for neuropathy. Journal of clinical neuromuscular disease, 15(3), 96.
7. Misra, U. K., & Kalita, J. (2006). Clinical application of EMG and nerve conduction. Clinical neurophysiology, 2, 80-4.
8. Levey, A. S., Coresh, J., Greene, T., Stevens, L. A., Zhang, Y., Hendriksen, S., ... & Chronic Kidney Disease Epidemiology Collaboration*. (2006). Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Annals of internal medicine, 145(4), 247-254.
9. Xu, T., Weng, Z., Pei, C., Yu, S., Chen, Y., Guo, W., ... & Sun, J. (2017). The relationship between neutrophil-to-lymphocyte ratio and diabetic peripheral neuropathy in Type 2 diabetes mellitus. Medicine, 96(45).
10. Hilger, J., Friedel, A., Herr, R., Rausch, T., Roos, F., Wahl, D. A., ... & Hoffmann, K. (2014). A systematic review of vitamin D status in populations worldwide. British journal of nutrition, 111(1), 23-45.
11. 11-Berridge, M. J. (2017). Vitamin D deficiency and diabetes. Biochemical Journal 2017, 474(8), 1321-1332.
12. Tesfaye, S., & Selvarajah, D. (2012). Advances in the epidemiology, pathogenesis and management of diabetic peripheral neuropathy. Diabetes/metabolism research and reviews, 28, 8-14.
13. Bansal, D., Gudala, K., Muthyala, H., Esam, H. P., Nayakallu, R., & Bhansali, A. (2014). Prevalence and risk factors of development of peripheral diabetic neuropathy in type 2 diabetes mellitus in a tertiary care setting. Journal of diabetes investigation, 5(6), 714-721.
14. Abdelsadek, S. E., El Saghier, E. O., & Abdel Raheem, S. I. (2018). Serum 25 (OH) vitamin D level and its relation to diabetic peripheral neuropathy in Egyptian patients with type 2 diabetes mellitus. The Egyptian journal of neurology, psychiatry and neurosurgery, 54(1), 1-8.
15. 15- Herrmann M., Sullivan D. R., Veillard A.S., et al : Serum 25-hydroxyvitamin D: a predictor of macrovascular and microvascular complications in patients with type 2 diabetes. Diabetes care 2015, 38(3), 521-528.
16. Hamidi, O., Hashemvarzi, S. A., & Porghasem, M. (2019). The effect of 6 weeks progressive aerobic training with consumption of vitamin D3 on nerve growth factor levels in streptozotocin-Induced diabetic rat's hippocampus. Journal of Applied Exercise Physiology, 14(28), 191-200.
17. Chen, J. Y., Lin, Y. T., Wang, L. K., Hung, K. C., Lan, K. M.,

Ho, C. H., & Chang, C. Y. (2019). Hypovitaminosis D in postherpetic neuralgia—High prevalence and inverse association with pain: A retrospective study. Nutrients, 11(11), 2787.
18. Vitamin D. (2017). deficiency increases the risk of peripheral neuropathy in Chinese patients with type 2 diabetes. Diabetes/Metabolism Research and Reviews, 33(2), e2820.
19. Tesfaye, S., Chaturvedi, N., Eaton, S. E., Ward, J. D., Manes, C., Ionescu-Tirgoviste, C., ... & Fuller, J. H. (2005). Vascular risk factors and diabetic neuropathy. New England Journal of Medicine, 352(4), 341-350.
20. Doupis, J., Lyons, T. E., Wu, S., Gnardellis, C., Dinh, T., & Veves, A. (2009). Microvascular reactivity and inflammatory cytokines in painful and painless peripheral diabetic neuropathy. The Journal of Clinical Endocrinology & Metabolism, 94(6), 2157-2163.
21. Laiteerapong, N., Ham, S. A., Gao, Y., Moffet, H. H., Liu, J. Y., Huang, E. S., & Karter, A. J. (2019). The legacy effect in type 2 diabetes: impact of early glycemic control on future complications (the Diabetes & Aging Study). Diabetes care, 42(3), 416-426.
22. Aguiar, P. M., Coletta, M., & de Souza, J. S. (2016). The association of dyslipidemia and peripheral diabetic neuropathy: The influence of urea. Diabetes Case Rep, 1(109), 1-3.
23. Babaliche, P., Nadpara, R. A., & Maldar, A. (2019). Association between estimated glomerular filtration rate and microvascular complications in type II diabetes mellitus patients: a 1-year cross-sectional study. Journal of the National Medical Association, 111(1), 83-87.