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Original Research Paper

Physiology

STUDY OF POTENTIAL ROLE OF VITAMIN-D DEFICIENCY IN DIABETIC PERIPHERAL NEUROPATHY

Dr. Sanjeev Kumar	Associate Professor, Department of Physiology, Madhubani Medical College, Madhubani, Bihar, India.
Dr. Md. Anzarul Hasan*	Assistant Professor, Department of Physiology, Madhubani Medical College, Madhubani, Bihar, India. *Corresponding Author
Dr. Mohammad Zakiuddin	Professor & Head, Department of Physiology Madhubani Medical College, Madhubani, Bihar, India.
Dr. Gauhar Hussain	Professor, Department of Physiology, Madhubani Medical College, Madhubani, Bihar, India.

ABSTRACT

BACKGROUND: Diabetes is a highly prevalent disease. Vitamin D deficiency is prevalent in most parts of the world. Its insufficiency or deficiency is implicated in bone diseases, infectious diseases, heart disease, autoimmune and metabolic diseases including type 2 diabetes mellitus.

AIMS AND OBJECTIVE: To study the possible relation between vitamin D deficiency and diabetic peripheral neuropathy in a sample of patients.

METHODS AND MATERIALS: A case-control study included 30 type 2 diabetic patients with diabetic peripheral neuropathy and 30 healthy controls. The patients included were subjected to clinical evaluation including Michigan Neuropathy Screening Instrument and nerve conduction study. And all patients and control were subjected to assessment of fasting and 2-h post prandial blood sugar, hemoglobin A1C, and serum vitamin D level.

RESULT: Serum vitamin D level was significantly lower in patients compared to control (P value = 0.005). For the patients group, females and patients with Michigan neuropathy screening instrument score more than 4 had statistically significant lower vitamin D level (P value = 0.003 and 0.006, respectively). No statistically significant difference in vitamin D level was found between patients below and above the age of 50 years, duration of diabetes less and more than 6 years, different types of diabetes medications, or patients with fair and poor control (P value = 0.534, 0.600, 0.870 and 0.252, respectively). No significant correlation was found between vitamin D level and the results of nerve conduction study.

CONCLUSION: Vitamin D deficiency was highly prevalent in diabetic peripheral neuropathy patients. Females and patients with severe form of neuropathy are more liable for lower vitamin D levels.

KEYWORDS : Diabetic peripheral neuropathy, Vitamin D

INTRODUCTION:

Diabetes is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. Diabetes can be classified into the following general categories: Type 1 diabetes (due to β-cell destruction, usually leading to absolute insulin deficiency), type 2 diabetes (due to a progressive insulin secretory defect on the background of insulin resistance), gestational diabetes mellitus (GDM) (diabetes diagnosed in the second or third trimester of pregnancy that is not clearly overt diabetes), and specific types of diabetes due to other causes, e.g., monogenic diabetic syndromes (such as neonatal diabetes and maturity-onset diabetes of the young, diseases of the exocrine pancreas (such as cystic fibrosis), drug- or chemical-induced diabetes such as in the treatment of HIV/AIDS or after organ transplantation [1,2]. Vitamin D was originally classified as merely a vitamin but recently is classified as a hormone and involved in a plethora of physiological processes. Its insufficiency or outright deficiency is implicated in not only bone diseases but also numerous serious and often fatal diseases, including many cancers, infectious diseases, heart disease, autoimmune and metabolic diseases including type 2 Diabetes Mellitus (t2DM), vitamin D status has been verified to be inversely associated with future risks of t2DM. [3].

Vitamin D deficiency is prevalent in most parts of the world; generally, humans receive vitamin D by being exposed to the sunlight or dietary intake, such as fish oil and nutritional supplements. There is an association between low vitamin D levels and decreased insulin sensitivity, vitamin D stimulates insulin production, low vitamin D concentrations are associated with a higher likelihood of the occurrence of diabetic complications, such as cardiovascular disease, renal impairment, and peripheral arterial disease [4–6]. A normal level of vitamin D is defined as a 25(OH)D concentration greater than 30ng/mL (75nmol/L), vitamin D insufficiency is defined as a 25(OH)D concentration of 20–30ng/mL (50–75nmol/L), vitamin D deficiency is defined as a 25(OH)D level less than 20ng/mL (50nmol/L) [7]. The prevalence of diabetic peripheral neuropathy in newly diagnosed diabetic patients reaches about 8% and more than 50% in patients with long-standing disease [8]. Furthermore, about 15% of all diabetic patients will develop foot ulcer [9] and greater than 50% of non-traumatic amputation of lower limbs is due to diabetes and its complications [10]. The pathogenesis of diabetic peripheral neuropathy is not understood completely. It is a multifactorial process and multiple hypotheses have been postulated, such as abnormal expression of sodium and calcium channels, metabolic and autoimmune disorders which lead to glial cell activation, blood vessel changes that affect the blood supply to the peripheral nerves and, recently, activation of central pain mechanisms as a result of imbalance between the facilitatory/inhibitory descending pathways [11]. In general, low vitamin D levels are associated with obesity and insulin resistance [12]. There is growing evidence that vitamin D plays an important role in the prevention of islet cell death and may be useful to improve the survival of islet cell grafts [13]. Low 25-hydroxyvitamin D levels have been associated with sensory neuropathy in diabetes and furthermore, vitamin D concentrations might be correlated with the severity of the neuropathy [14].

AIMS AND OBJECTIVE:

To study the possible relation between vitamin D deficiency and diabetic peripheral neuropathy in a sample of patients.

MATERIAL AND METHODS:

This study is a case-control study conducted in the Department

of General Medicine in collaboration with the department of physiology, Madhubani Medical College, Madhubani, Bihar, from March-2019 to November-2019 after obtaining the ethical clearance from the ethical committee of the institute. Sixty subjects were included. 30 type 2 diabetic patients with diabetic peripheral neuropathy (12 males and 18 females) and 30 age- and sex-matched healthy controls (12 males and 18 females).

Study Period:
From March-2019 to November-2019

Exclusion Criteria:
Patients with the following conditions were excluded from this study: history of malignancy or degenerative disease of the nervous system, diabetic macrovascular complications, chronic hepatitis, pregnancy, and history of drug abuse, renal impairment with renal replacement therapy, and subjects on vitamin D supplementation.

Diabetic patients were diagnosed according to the American Diabetic Association criteria 2015 [15], when one of the following criteria is fulfilled: fasting plasma glucose ≥ 126mg/dL (7.0mmol/L), fasting is defined as no caloric intake for ≥ 8 h; 2-h plasma glucose ≥ 200 mg/dL (11.1 mmol/L) during oral glucose tolerance test using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water; hemoglobin A1C ≥ 6.5% (48mmol/l), or random plasma glucose ≥ 200 mg/dL (11.1mmol/L) in individuals with symptoms of hyperglycemia. The presence of diabetic peripheral neuropathy was confirmed by Michigan Neuropathy Screening Instrument (MNSI) physical assessment [16]. All patients included in this study had a score of more than 2. A questionnaire was administered to determine the demographics of the patients like age, sex and residency, diabetes duration, Smoking, body mass index (BMI) and dyslipidemia was examined. Selection of cases and healthy controls was carried out by using a random sampling technique. A written informed consent was obtained from each participant in this study and the study was approved by the ethical committee. BMI was calculated for each subject. None of the females was pregnant. Diabetes mellitus type 2 patients included in the study were on treatment either with diet only or with diet and oral antidiabetic drugs. Initial consultation and examination involved the routine assessment of Serum 25(OH) D and glycemic control (HbA1c) concentration, and also following laboratory parameters were done including (complete blood count, blood sugar, lipid profile, renal function test, liver function test). Serum concentration of 25(OH) D was measured by enzyme linked immunosorbent assay (ELISA) method. HbA1c was measured by spectrophotometer.

Laboratory assessment
Patients and control groups were subjected to the following laboratory investigations: fasting and 2-h post prandial test and hemoglobin A1C test: level of HbA1C was classified into good control: 5.5–6.8%, fair control: 6.8–7.6%, and poor control: > 7.6% [17]. Serum vitamin D level was assessed in patients and control groups using Sat fax 303 plus made in the USA to measure serum 25(OH) level. 25-OH vitamin D is an ELISA-based test system intended for the quantitative measurement of total concentration of 25(OH)-vitamin D in human serum or plasma samples (EDTA plasma, heparin plasma, citrate plasma) measuring 5–120ng/ml. Serum vitamin D level was classified into sufficiency: more than 30ng/ml, insufficiency: between 20 and 30ng/ml, and deficiency: below 20ng/ml [18]. Biochemical blood measurements were determined by a standard laboratory procedure.

Neurophysiological assessment
Nerve conduction study was done for all patients with diabetic peripheral neuropathy using Nihon Kohden Neuropack machine. The test was explained to the patient who was seated on a long comfortable chair before the test proper sterilization of the skin with alcohol was done. The protocol used in this study was median and ulnar nerves (motor and sensory parts) in the upper limbs and peroneal nerve (motor part), tibial nerve (motor), and sural nerve (sensory part) in the lower limbs.

Statistical Analysis:
The Statistical Package for Social Sciences (SPSS version 21) was used for data analysis, and data were presented as mean ± standard deviation. The descriptive statistics of participants were obtained by determining frequency distributions of categorical data and weighted means and standard errors of continuous variables, such as age, gender, BMI, dyslipidemia, DM, smoking and serum vitamin D. Significant differences in categorical and continuous variables between the cases and control groups were analyzed using the chi-squared test. Level of statistical significance was set at < 0.05.

RESULT:
The age of diabetic peripheral neuropathy patients ranged from 30 to 60 years with a mean value of 47.55 ± 10.12 years, while the age of controls ranged from 30 to 60 years with a mean value of 47.55 + 10.12 years. Both of patients and control groups had the same gender distribution shown in **table 1.**

Table 1: Demographic data of diabetic peripheral neuropathy patients and controls

	Patients (n = 30)	Controls (n = 30)
Age (mean ± SD)	47.55 ± 10.12	47.55 ± 10.12
Sex Male (Number, %)	12 (40%)	12 (40%)
Female (Number, %)	18 (60%)	18 (60%)

The clinical characteristics of diabetic peripheral neuropathy patients, duration and types of medical treatment of diabetes mellitus, level of glycosylated hemoglobin, and diabetic neuropathy syndromes (based on clinical examination and neurophysiological studies) were shown in table 2.

Table 2: Clinical characteristics of diabetic peripheral neuropathy patients

Clinical characteristics Patients (%, number)		
Duration of diabetes mellitus	≤ 5 years > 5 years	60% (n= 18) 40% (n= 12)
Treatment of diabetes mellitus	Insulin therapy Oral hypoglycemic drugs Combination of both	46.67% (n= 14) 36.66% (n= 11) 16.67% (n= 5)
Level of glycosylated hemoglobin	Fair control (68-7.6) Poor control (> 7.6)	56.66% (n= 17) 43.34% (n= 13)
Diabetic neuropathy syndromes	Sensory neuropathy Sensorimotor neuropathy Radiculopathy Carpal Tunnel syndrome	46.67% (n= 14) 20% (n= 6) 16.66% (n= 5) 16.67% (n= 5)

All patients with diabetic peripheral neuropathy underwent nerve conduction study including parts of median and ulnar nerves (both sensory and motor), tibial, peroneal and sural nerves. The velocity, amplitude and latency were assessed in such nerves (Table 3).

Table 3: Result of nerve conduction studies

Nerve	Minimum Value	Maximum Value		Mean ± SD
Median (motor)	Velocity	38	70	48.13 ± 8.47
	Amplitude	2.3	13.3	7.12 ± 2.94
	Latency	3.4	8.4	5.16 ± 1.57
Median (sensory)	Velocity	19	59	38.49 ± 8.44
	Amplitude	0.10	37	16.74 ± 10.36
	Latency	2.5	6	4.45 ± 1.53

Ulnar (motor)	Velocity	37	68	52.24 ± 6.27
	Amplitude	3	10.5	6.33 ± 1.84
	Latency	2.4	6.3	4.04 ± 1.42
Ulnar (sensory)	Velocity	31	58.4	47.38 ± 6.62
	Amplitude	0.10	42.5	16 ± 10.41
	Latency	1.7	3.8	2.70 ± 0.55
Peroneal (motor)	Velocity	30	53	41.25 ± 6
	Amplitude	0.2	5	3.06 ± 1.67
	Latency	3.2	13.7	5.63 ± 3.12
Tibial (motor)	Velocity	27	48	37.76 ± 5.37
	Amplitude	1.4	13	5.11 ± 3.40
	Latency	2.5	14	5.81 ± 3.78
Sural (sensory)	Velocity	28	58	38.26 ± 8.10
	Amplitude	0.2	16	5.86 ± 4.75
	Latency	2.2	10	4.77 ± 1.82

The serum vitamin D level was evaluated for both control and diabetic peripheral neuropathy patient groups. The level in the patient group ranged from 11.1 to 39.2 with a mean value 19.216 + 7.59. While the level in the control group ranged from 18.9 to 73.2 with a mean value 34.15 + 13.35. The serum vitamin D level was significantly lower in diabetic peripheral neuropathy patients P value = 0.008 (Table 3). Different vitamin D level categories in diabetic peripheral neuropathy patients and control groups are shown in **Table 4.**

Table 4: Comparison between diabetic peripheral neuropathy patients and healthy controls regarding serum level of vitamin D

Diabetic peripheral neuropathy patients		Control	p Value	
Serum level of vitamin D (Mean ± SD)		18.205 ± 6.55	33.14 ± 12.34	0.007*
Classification of vitamin D level	**Normal** (number, %)	2(6.66%)	13 (43.34%)	<0.001 *
	Insufficiency (number, %)	10(33.34%)	12 (40%)	
	Deficiency (number, %)	18 (60%)	5 (16.66%)	

There was no statistically significant difference in the vitamin D level between patients below and above the age of 50 years, diabetic peripheral neuropathy patients with a duration of diabetes less and more than 5 years, diabetic patients receiving insulin, oral hypoglycemic drugs or combined insulin and oral hypoglycemic medications, and diabetes mellitus patients with fair and poor control (P value = 0.534, 0.600, 0.870 and 0.252, respectively.

DISCUSSION:

The prevalence of diabetic peripheral neuropathy is a function of disease duration; of all patients with diabetes, about 60 to 70% will eventually develop peripheral neuropathy, even though not all will suffer pain [19]. Diabetic peripheral neuropathy is as a major cause for disability due to foot laceration, gait disturbance, fall-related injuries, and even amputation. The aim of this work was to study the possible relation between vitamin D deficiency and diabetic peripheral neuropathy in a sample of patients.

The study was conducted on 25 type 2 diabetic patients with diabetic peripheral neuropathy and 25 healthy controls. Sixty-four percent of the patients were found to have vitamin D deficiency, 28% were found to have vitamin D insufficiency, and only 8% of them were found to have normal serum vitamin D level. Our findings are in accordance to the findings of Bayani and colleagues [20] who found vitamin D deficiency in 64.2% of their patients and vitamin D insufficiency in 25% and just 10.3% had normal vitamin D level.

A higher prevalence was found in a Korean study done by Lee and colleagues [21], 89% of their type 2 diabetic patients suffered vitamin D deficiency and only 9 out of 300 persons (3%) had sufficient vitamin D concentration. They attributed high prevalence of vitamin D deficiency to the little duration of sunshine in Korea. Also, compared to healthy controls from the same geographical area, matched in sex and age, patients with diabetic peripheral neuropathy have significantly lower serum vitamin D level.

Older adults have more liability for vitamin D deficiency as a result of many interacting factors: decreased the number of vitamin D receptor, intestinal resistance to calcium absorption in response to circulating 1, 25(OH) 2D.

CONCLUSION:

Vitamin D deficiency was highly prevalent in diabetic peripheral neuropathy patients compared to controls. Attention should be paid to the link between vitamin D level and diabetic peripheral neuropathy and whether routine testing of serum vitamin D level in all diabetes mellitus patients should be done. Further studies should be conducted on a larger number of patients and for a longer duration to explore whether supplementation with vitamin D could prevent the development or improve the manifestations of peripheral neuropathy in diabetic subjects.

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