The relationship between serum vitamin D and vitamin B12 levels and diabetic peripheral neuropathy

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Abstract

Objective: Diabetic peripheral neuropathy (DPN) is one of the most common complications of diabetes. Beside the known factors such as hyperglycemia in the pathogenesis of this complication, other etiologies may play role in the pathogenesis of this complication. The aim of this study was the evaluation of the role of serum vitamin D and vitamin B12 levels in this process.

Material and Methods: We enrolled 76 diabetic patients (38 patients with DPN and 38 patients without DPN) who were matched in the terms of age, gender, BMI and duration of diabetes. Diagnosis of DPN was based on nerve conduction studies on sural, peroneal and tibial nerves. Serum vitamin D and vitamin B12 levels were measured in these two groups.

Result: Case and control groups had not significant differences in demographic characteristics. Serum vitamin D level was slightly lower in case group (24.1 ± 19.3 ng/ml vs. 24.9 ± 22.3 ng/ml), but the difference was not significant (P=0.857). Serum vitamin B12 level was higher in patients with DPN without significant difference in the two groups (444.2 ± 273.5 pg/ml vs. 390.4 ± 213.9 pg/ml) (P=0.343).

Conclusion: The results of this study showed that serum vitamin D and vitamin B12 levels had not significant difference in patients with and without DPN. Further studies are required to better evaluate the role of these factors in development and progression of DPN.

Keywords: Diabetes Mellitus, Diabetic Peripheral Neuropathy, Vitamin D, Vitamin B12

Introduction

Peripheral neuropathy is one of the most common complications of diabetes (1). The factors contributing in the pathogenesis of this complication are not understood completely, and multiple theories have been proposed but it is commonly accepted to be a multifactorial process (2). Various factors, such as duration of hyperglycemia and other risk factors such as dyslipidemia, hypertension, smoking, increased height, and exposure to other neurotoxic agents such as ethanol are involved in this process. Polyol pathway, non-enzymatic glycation, free radical and oxidative

stress are the probable etiologic factors (3). In addition to these factors, it seems that some other etiologies influence the pattern and presentation of clinical diabetic neuropathy. In this field, the role of the factors such as vitamin D or vitamin B12 deficiency is doubtful. Some studies suggested the relationship between low vitamin D and neuropathy or other neurodegenerative disorders (4-6). On the other hand, the association between vitamin D and diabetic neuropathy is revealed in some cross sectional studies (7,8). Vitamin B12 contributes to the fatty acids metabolism and the maintenance of nerve myelin. Long-term B12 deficiency can lead to nerve degeneration and irreversible neurological damage (9). The role of the vitamin B12 in diabetic neuropathy is originated from the response of neuropathic symptoms to treatment with vitamin B12 in a few clinical trials (10,11). The aim of this study was to compare the serum vitamin D and vitamin B12 levels in the diabetic patients with and without peripheral neuropathy.

Material and Methods

This was a case-control study and we recruited 76 patients with type 2 diabetes with and without peripheral diabetic neuropathy. Thirty eight type 2 diabetic patients with diabetic peripheral neuropathy and 38 patients without neuropathy matched for age, gender, duration of diabetes and body mass index (BMI) were selected. Patients were recruited from the data of a basic evaluation of the prevalence of peripheral neuropathy in 600 type 1 and 2 diabetic patients in Hamedan Diabetes Center, Hamedan University of Medical Sciences, Iran (12). Excluding criteria were: Age less than 30 and more than 70 years, other causes of neuropathy, use of vitamin B12 or vitamin D supplements in the last three months, history of hepatic or renal dysfunction (Cr>1.5), malabsorption or malnutrition and alcohol abuse. After signing an informed consent for each patient, a questionnaire including data on general information, smoking status, duration of diabetes, type of medication and history of foot ulcer was completed. Then, height, weight and blood pressure were recorded. We used standard NSS (Neuropathy Symptom Score) and NDS (Neuropathy Disability Score) criteria (12-13) for the initial screening of diabetic neuropathy in this population. Then, we performed a nerve conduction study to diagnose peripheral diabetic neuropathy. Nerve conduction studies were performed on sural, peroneal and tibial nerves in lower limbs and amplitude, nerve conduction velocity and latency were measured. The obtained values were compared with normal values listed in the resources to be normal or abnormal (14). Diagnosis of DPN was based on the recommended protocol. The case definition criterion for confirmation of DPN was an abnormality ($\geq$99th or $\leq$1st percentile) of any attribute of nerve conduction in two separate nerves, one of which must be the sural nerve (15). Biochemical parameters including serum creatinine, HbA1c, 25(OH) vitamin D and vitamin B12 were measured in the fasting state. Serum creatinine was measured by enzymatic colorimetry using an autoanalyzer (Selectra-2, Italy) and relevant commercial kits (Pars Azmoon, Tehran, Iran). HbA1c was assessed by colour reflectometer using an analyzer and kit (NycoCard, England). Serum vitamin D was measured by the chemiluminescence method (Liaison, USA and Italy) using the kit from DiaSorin, Italy. Serum vitamin B12 was assessed by electrochemiluminescence method (Elecsys 2010) (Roche and Hitachi, US and Japan) using the kit from Roche, US. In data analysis, we used t-test for comparisons between the two groups. For comparing qualitative variables between two groups Chi-square test was used. SPSS 16 software was used for performing statistical analysis. P values less than 0.05 were considered significant. The study was approved by the research ethics review committee at the Hamedan University of Medical Sciences, Hamedan, Iran.

Results

In the first step, 142 patients were selected to

include in this study. Ninety five patients were invited by telephone to participate after inclusion and exclusion criteria were considered. Finally, 76 patients including 38 patients with DPN and 38 patients without DPN enrolled the study. General characteristics and biochemical parameters of the case and control groups are presented in table 1. The groups had not significant difference in age, BMI, duration of diabetes and glycemic control. Only history of diabetic foot ulcer was higher in patients with DPN (P=0.003). Serum vitamin D was slightly lower in case group (24.1 ± 19.3 ng/ml vs. 24.9 ± 22.3 ng/ml), but the difference was not significant (P=0.857). Serum vitamin B12 level was higher in patients with DPN with no significant difference between the groups (444.2 ± 273.5 pg/ml vs. 390.4 ± 213.9 pg/ml) (P=0.343).

Discussion

The results of this study showed that the serum levels of the 25(OH) vitamin D and vitamin B12 did not differ significantly between diabetic patients with and without peripheral neuropathy. Several studies have separately investigated the role of each of these factors in the diabetic neuropathy. Vitamin D insufficiency is common among patients with diabetes (16-18). The effect of vitamin D in some complications of diabetes has suggested in a few studies (19-21). The role of vitamin D in diabetic neuropathy is investigated in two observational studies. In one study by Soderstrom and colleagues, vitamin D insufficiency was associated with peripheral neuropathy in 591 diabetic patients. Their definition for neuropathy was self-reported symptoms of neuropathy in addition to Semmes Weinstein monofilament test (8). As a strength, our study had case-control design and also we used NSS-NDS criteria and electrodiagnostic tests as the minimal criteria for the diagnosis of DPN (22), but we did not find any association between vitamin D level and diabetic neuropathy. Our study had some limitations such as the season of doing the project or using vitamin D supplements not withstanding to our patients in the past. In the other hand, high prevalence of vitamin D deficiency may be an effective confounder in our population. Shehab and colleagues investigated the association between peripheral neuropathy and vitamin D level in 210 diabetic patients in a cross sectional study and showed the high prevalence of vitamin D deficiency in type 2 diabetic patients with peripheral neuropathy (7). To the best of our knowledge, the association between vitamin B12 and peripheral diabetic neuropathy has not been evaluated. Its role in diabetic neuropathy is originated from clinical trials of

Table 1- General characteristics and biochemical parameters of the case and control groups

Variable	With DPN (n=38)	Without DPN (n=38)	*P* value
Female [n (%)]	24 (63.1)	24 (63.1)	1.000
Age (years)	55.0 ± 6.9	56.5 ± 5.6	0.305
BMI (Kg/m^2)	29.2 ± 4.2	27.3 ± 4.0	0.056
Duration of Diabetes (years)	9.8 ± 4.3	9.2 ± 5.1	0.582
Medication [n (%)]			
Oral agent	12 (31.5)	15 (39.4)	0.237
Insulin	17 (44.7)	10 (26.3)	
Both	9 (23.6)	13 (34.2)	
Smoking [n(%)]	6 (15.7)	2 (5.2)	0.135
History of diabetic foot ulcer [n(%)]	8 (21.0)	0 (0)	0.003
History of hypertension [n(%)]	25 (65.7)	19 (50.0)	0.163
Systolic blood pressure (mm/Hg)	134.3 ± 16.9	131.7 ± 17.7	0.511
Diastolic blood pressure (mm/Hg)	82.6 ± 9.7	81.0 ± 11.5	0.520
Serum creatinine (mg/dl)	1.0 ± 0.1	1.0 ± 0.1	0.517
HbA1c %	8.0 ± 1.3	7.9 ± 1.6	0.680
Vitamin D (ng/ml)	24.1 ± 19.3	24.9 ± 22.3	0.857
Vitamin B12 (pg/ml)	444.2 ± 273.5	390.4 ± 213.9	0.343

The numbers are presented as mean ± SD

vitamin B12 treatment in diabetic neuropathy. A systematic review in this field showed beneficial effects of vitamin B12 treatment in relief of somatic symptoms of diabetic neuropathy (10). From clinical point of view, while hyperglycemia is the main etiologic factor in the pathogenesis of diabetic neuropathy and its consequences, it seems that modification of other factors may decrease residual risk. Vitamin D and vitamin B12 and many unknown factors may play role in this context. The results of our study did not show any significant difference in vitamin D and vitamin B12 levels in diabetic patients with peripheral neuropathy in comparison with diabetic patients without neuropathy; but according to the results of the previous studies, further studies are needed to document or reject the hypothesis of their role in diabetic neuropathy. Also, diabetic patients with peripheral neuropathy who have vitamin D or vitamin B12 deficiency must be evaluated in other clinical trials for the effect of supplemental therapy in treatment of peripheral neuropathy.

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