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Comparison of Vitamin D Levels among Patients with Diabetes With or Without Polyneuropathy

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Introduction

Vitamin D deficiency is a globally endemic issue and high prevalance of hypovitaminosis has been observed in different studies [1,2]. It has been reported that vitamin D plays an important role not only in calcium and bone metabolism also in Diabetes Mellitus (DM), hypertension and cardiovascular diseases [3-6]. Few trials showed that insufficiency of vitamin D could be a risk factor for insulin secretion impairment and increase of insulin resistance in diabetic subjects [7,8].

Diabetic Neuropathy (DN) is the most common complication of diabetes and cause of morbidity and disability [9]. It has been estimated that more than half of the diabetic patients suffer from polyneuropathy [10]. Vitamin D deficiency has been also reported to be associated with diabetic peripheral neuropathy and neuropathic pain [11,12]. Some studies mentioned that this may be a result of both lowered pain treshold and a pathologial process of the nerves caused by vitamin D deficiency [13]. Vitamin D deficiency was reported to be associated with neuronal calcium homeostasis, neurotrophin levels and also with neuronal differentiation [14]. Also nociceptor function seemed to be modulated by vitamin D [14]. Morover some previous studies mentioned that treatment of deficiency may also reduce neuropathic pain [15].

In this study we aimed to compare vitamin D levels among two groups of patients with diabetes, one with polyneuropathy and the other one without polyneuropathy. The main point of this study was that both groups had similar disease modifying factors in order to demonstrate the association between the presence of polyneuropathy and vitamin D levels.

Keywords: Vitamin D; Diabetes Mellitus; Polyneuropathy

Materials and Methods

106 patients who were diagnosed as type 2 diabetes mellitus in Pamukkale University Department of Endocrinology between years 2013 and 2015 were included to the study. Diagnosis of DM was based on the criteria laid by the American Diabetes Association [16]. All subjects underwent Electroneurograph (ENG) study by the same neurologist in ENG laboratory (Premiere Plus ENMG Device. Medelec/Vickers Medical, Manor Way, Old Woking, Surrey, United Kingdom) and was approved by the Local Ethical Committee (Clinical Researches Committee, Denizli Province, Ministry of Health, Republic of Turkey). All the patients gave informed consent. The patients were included after undergoing a routine electrophysiological protocol to determine Polyneuropathy (PNP) and DN4 pain scale was used to diagnose neuropathic pain which was performed by the same clinician. Proximal and distal latencies, amplitudes and conduction velocities of both motor and sensory nerves were evaluated. Motor waves were studied for median, ulnar, peroneal and tibial nerves and sensory waves were calculated for median, ulnar and sural nerves.

All patients were using insulin therapy for diabetes. Oral hypoglisemic agents were considered as an exclusion criteria. 49 patients with and 57 patients without polyneuropathy were included to the study. The patients picked up according to ENG findings and clinical scale. Both groups were chosen to have similar demographic features and nerve conduction parameters. Also possible disease modifying factors like duration of diabetes, serum glucose levels, HbA1c, serum cholesterol levels and body mass indexes were similar within groups.

Patients with metabolic disorders like hypothyroidism and uremia; infectious neuropathies; nutritional neuropathies like alcoholism, vitamin B and tiamin deficiency; and toxic neuropathies and malignancies were excluded. Independent sample T test was used for statistical analyses.

Results

Both groups had similar demographic features (Table 1). Duration of diabetes, body mass index, Calcium (Ca) levels, Low Density Lipoprotein (LDL), High Density Lipoprotein (HDL), total cholesterol and triglyserid levels were similar within groups (Table 1). Serum glycosylated hemoglobin (HbA1c) levels were lower in subjects without neuropathy compared with those with neuropathy (p=0,115). Also there were no significant difference between the PTH levels of the groups (p=0,068).

Table 1 : Variables of the Groups

Groups	DM with PNP	DM without PNP	P value
Age (years)	60.82 ± 10.55	58.62 ± 8.94	0.200
BMI (kg/m2)	28.62 ± 4.62	26.90 ± 4.37	0.356
Duration of diabetes (years)	9,70 ± 4,57	8,98 ± 4,00	0,343
HbA1c (mmol (mean ± SD))	74 ± 2 (9.53 ± 4.36)	63±9 (8.47 ± 2.82)	0.115
Glucose (mmol/l)	10,6 ± 4,7	9,91 ± 3,80	0.452
Total cholesterol (mmol/l)	4,65 ± 1,55	4,91 ± 1,16	0.256
Triglyceride (mmol/l)	1,98 ± 1,06	2,08 ± 1,02	0.512
HDL (mmol/l)	1,18 ± 0,4	1,21 ± 0,33	0.512
LDL (mmol/l)	2,68 ± 1,16	2,71 ± 1,03	0.856
Calcium (mmol/l)	2,20 ± 0,02	2,25 ± 0,16	0.824
Phospore (mmol/l)	1,26 ± 0,37	1,23 ± 0,25	0.912
PTH (pg/mL)	72,76 ± 34,58	58,38 ± 23,21	0,068
Vitamin D (ng/ml)	19,78 ± 9,04	26,02 ± 9,62	0.018

HDL: High-density lipoprotein LDL: Low-density lipoprotein
PTH: Parathyroid hormone

The mean 25(OH) vitamin D levels were 19,78 ± 9,04 ng/ml in the group DM with PNP and 26,02 ± 9,62 ng/ml in the group DM without PNP (Table 1). The difference was statistically significant (p=0,018).

Discussion

In this study, serum vitamin D levels of patients with diabetic polyneuropathy were significantly lower than the patients without polyneuropathy. There are some studies comparing vitamin D levels among DN patients with diabetic controls without DN [12,14,15]. However patients with neuropathy included to these studies usually had longer diabetes durations and higher serum glucose levels. So it is still a question whether vitamin D levels would be different if groups with similar features were compared. According to findings in this study, lower serum 25(OH)-D concentration may be an independent contributor involved in the presence and severity of peripheral DN. The mechanism behind this finding is currently unclear. Vitamin D deficiency seems to play an important role in many chronic pathological processes and also in diabetic polyneuropathy [17,18,3,4]. Many of these studies demonstrated that patients with diabetes who had diabetic polyneuropathy had lower vitamin D levels than the patients without polyneuropathy. The patients with polyneuropathy included to these studies were also found to be older and overweighed than the ones without polyneuropathy [19].

DN has been declared as the most common cause of morbidity and also the greatest source of disability and cost in DM [20]. It has been estimated that about 50 % of diabetic patients suffer from polyneuropathy [10]. Alemdari et al. [21] investigated the association between DN severity and serum vitamin D levels. As shown in this study, severity of nerve conduction velocity abnormality had a slightly stronger association with serum 25(OH)-D concentration, which amplifies the link between vitamin D and DN. In humans in the National Health and Nutrition Examination Survey, vitamin D deficiency was associated with the symptoms of diabetic neuropathy like numbness, pain, loss of feeling and tingling after statistical correction for the HbA1c level [19]. In another study vitamin D levels were not only inversely proportional to a neuropathy symptoms score but also showed a statistically significant association with slower nerve conduction velocities after correction for duration of diabetes and levels of HbA1c, LDL and urinary albumin [12]. Prospectively, a nonrandomized study of 51 type 1 diabetic subjects with painful diabetic neuropathy showed a 50% decrease in pain scores with vitamin D repletion [22].

Skalli et al. [11] found an inverse correlation between 25(OH)-D level and the incidence of neuropathy in diabetic subjects using vibration perception and Semmes-Weinstein monofilament tests. In a study of 210 DM individuals, neuropathy symptom score, neuropathy disability score and nerve conduction study score were employed [12] and hypovitaminosis D was declared as a risk factor for DN. Vitamin D is known to impact diabetes control [23].

Animal studies suggested a direct impact on nerve function. Moreover some recent studies reported that oral vitamin D supplements should have beneficial effects on neuropathic process [24,25]. Also the existence of neuropathy, obesity and uncontrolled diabetes may cause depression and immobilization leading lower exposure to sunshine which should modify vitamin D intake and metabolism [26]. Bajaj et al. [27] in their recent case-control study of type 2 diabetic and healthy subjects, reported lower circulating concentration of vitamin D in diabetic patients, a significant reverse relation between serum vitamin D levels and diabetic neuropathy. Also, decreasing levels of vitamin D was associated with existence of multiple microvascular complications of DM.

There were five studies comparing the serum 25(OH) vitamin D levels in DN patients with diabetic controls without DN [11,12,28-30]. A recent meta-analysis [31] showed that vitamin D deficiency was significantly associated with increased risk of diabetic polyneuropathy in patients with type 2 diabetes. There was no obvious change in the pooled estimates and after excluding low quality studies, there were obvious decreased serum 25(OH) D levels in diabetic patients with DN compared with those without DN. Moreover this study also revealed that vitamin D levels were also insufficient in patients with diabetes who did not have polyneuropathy. This should suggest that vitamin D insufficiency might play a role in both diabetic and neuropathic process. Limited studies have linked serum vitamin D to the presence and progression of DN. Our study suggested that low vitamin D levels seems to be associated with both uncontrolled diabetes and diabetic neuropathy. Monitoring serum 25(OH)-D concentration in DM patients suffering from neuropathy would be beneficial as well as vitamin D supplementation especially in deficient patients.

In our study, serum HbA1c levels were lower in subjects without neuropathy compared with those with neuropathy. HbA1c is the gold standard measurement for the assessment of glycemic control, and worldwide large scale clinical studies of diabetes complications have greatly valued HbA1c as an indicator of glycemic control. Many studies have shown that HbA1c is an index of average glucose over the preceding weeks-to-months [32-34]. Erythrocyte life-span averages about 120 days. The level of HbA1c at any point in time is contributed to by all circulating erythrocytes, from the oldest (120 days old) to the youngest. However, HbA1c is a "weighted" average of blood glucose levels during the preceding 120 days, meaning that glucose levels in the preceding 30 days contribute substantially more to the level of HbA1c than do glucose levels 90-120 days earlier. This explains why the level of HbA1c can increase or decrease relatively quickly with large changes in glucose; it does not take 120 days to detect a clinically meaningful change in HbA1c following a clinically significant change in average glucose. Large, randomized, interventional trials have provided conclusive evidence that achieving and sustaining tight glycemic control significantly reduces the risk of developing diabetes-related microvascular and macrovascular complications [33,35,36]

Any reduction in high HbA1c levels was associated with a decrease in the risk of microvascular complications of diabetes and glycemic control is a major factor preventing diabetic neuropathy. On the other hand, the study has some limitations. Our sample size may be one of the limitations. Seperating study groups precisely by performing nerve conduction studies has also some potential limitations. Routine nerve conduction studies represent the involvement of large nerve fibers. Nerve conduction studies of patients in diabetes without neuropathy group were within normal limits. But there is a possibility that these patients might have symptoms or findings which also should indicate a small fiber neuropathy. In this case, future studies can be designed which were evaluating the effect of vitamin D on neuropathic pain by doing large pain scales in addition to routine nerve conduction studies.

Conclusion

Our results suggested that low vitamin D levels seems to be associated with both uncontrolled diabetes and diabetic neuropathy. It would be beneficial that monitoring serum 25(OH)-D concentration in DM patients suffering from neuropathy, as well as vitamin D supplementation especially in deficient patients. Further prospective, randomized, controlled trials are needed to confirm the efficacy and clinical benefits of vitamin D in DN.

Conflict of Interest Disclosures

All co-authors have made a significant contribution to the manuscript. The study complies with ethical standards. The authors declare that they have no financial interests. None of the authors have any conflict of interest.

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