Is There an Association between Vitamin D Level and Microvascular Complications of Type 2 Diabetes Mellitus?

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ABSTRACT

Objective: *Vitamin D deficiency is associated with impaired glucose tolerance and the development of Type 1 and 2 diabetes mellitus. The aim of this study was to compare the 25-hydroxyvitamin D (25-OH-vitamin D) levels between Type 2 diabetic patients with and without microvascular complications and healthy subjects to identify any possible associations with vitamin D levels and microvascular complications.*

Methods: *One hundred and one patients with microvascular complications (nephropathy, retinopathy or neuropathy), 102 patients without microvascular complications and 81 healthy subjects were compared in terms of serum levels of 25-OH-vitamin-D, calcium, phosphorus, parathyroid hormone (PTH), and glycated haemoglobin (HbA$_{1c}$).*

Results: *No significant differences were found among the three groups with respect to serum calcium, phosphorus and PTH levels, and no correlation was identified between HbA$_{1c}$ and 25-OH-vitamin D levels. The healthy group had higher vitamin D levels than both diabetic groups, while the vitamin D levels were similar in the diabetic groups.*

Conclusion: *Although vitamin D deficiency is more common in patients with Type 2 diabetes mellitus than healthy subjects, no relationship between vitamin D deficiency and microvascular complications of diabetes was found.*

Keywords: Diabetes mellitus, nephropathy, neuropathy, retinopathy, vitamin D

INTRODUCTION

Although vitamin D mainly regulates calcium and phosphate metabolism, its deficiency may also be involved in the aetiopathogenesis of carcinomas, autoimmune diseases, infections, respiratory and cardiac diseases (1–6). In addition, some studies reported an association between vitamin D deficiency and impaired glucose tolerance (7); hypovitaminosis D has also been suggested to contribute to the development of Type 1 and 2 diabetes mellitus (8, 9). Furthermore, vitamin D deficiency seems to have a higher frequency in Type 2 diabetic patients compared to the non-diabetic population (10).

Diabetic retinopathy, neuropathy and nephropathy are the microvascular complications of diabetes which worsen the quality of life in diabetic patients. Previous studies reported conflicting results regarding the association between microvascular complications of diabetes and vitamin D deficiency (11, 12). Therefore, the aim of this study was to compare the vitamin D levels between Type 2 diabetic patients with and without microvascular complications and healthy subjects to identify any possible associations with vitamin D levels and microvascular complications.

SUBJECTS AND METHOD

This cross-sectional, observational study was undertaken in the outpatient clinics of the endocrinology department. The protocol was approved by the local ethics committee and informed consent was obtained from each patient.

A total of 203 patients with Type 2 diabetes mellitus was enrolled in the study, of which 101 had microvascular complications (nephropathy, retinopathy or neuropathy) and 102 did not have any microvascular complications. Eighty-one healthy subjects were also enrolled as a control group. Exclusion criteria were as follows: serum creatinine levels > 1.2 mg/dL, liver or heart failure, malignancies, infectious diseases, previous gastrointestinal surgery, gastrointestinal

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diseases such as ulcerative colitis, Crohn's disease, coeliac disease, pancreatitis, and taking any medications that affect vitamin D levels (corticosteroids, calcium and/or vitamin D supplements and anti-epileptics). All of the patients and control subjects had similar clothing habits and were evaluated in the same season in terms of vitamin D levels.

All patients were examined by the same ophthalmologist to detect diabetic retinopathy. Spot urine samples were used for microalbuminuria measurements. A diagnosis of microalbuminuria was established when the ratio of urinary albumin to creatinine was 30–300 mg/dL, whereas macroalbuminuria was diagnosed when the same ratio was > 300 mg/dL. Normoalbuminuria was identified if the ratio was < 30 mg/dL. Diabetic neuropathy was evaluated using neuropathy symptom score [NSS] (13) and a detailed physical examination.

Serum inorganic phosphorus (normal range 2.5–4.6 mg/dL) and calcium (normal range 8.4–10.6 mg/dL) levels were assayed photometrically on AU5800 analyzer (Beckman Coulter, USA). A latex agglutination inhibition assay on AU5800 analyzer (Beckman Coulter, USA) was used to measure glycated haemoglobin (HbA_{1c}) level. The values of parathyroid hormone (PTH; normal range 1.6–6.9 pmol/L) were determined by Elecsys 1010 System (Roche, Manheim, Germany). Serum 25-hydroxyvitamin D (25-OH-vitamin D) levels (normal range 25–80 ng/mL) were quantified by liquid chromatography mass spectrometry (LC-MS/MS) on water analyzers (Acquity UPLC and Quattro Premier XE Micromass spectrometry, USA).

Statistical analysis was performed using the IBM SPSS 20.0 (IBM Inc, Chicago, IL, USA) programme. The suitability of the normal distribution of the data was performed with Shapiro-Wilk test. To compare the groups for quantitative variables, two independent samples, t-test and Mann-Whitney U tests, were used. Chi-square test was used for qualitative variables. Data are expressed as frequency and percentage, mean and standard error mean. $P < 0.05$ was considered as statistically significant.

RESULTS

Among the 203 patients with diabetes, 80 were female and 123 were male with a mean age of 51.2 ± 0.5 years; the control group consisted of 43 females and 38 males with a mean age of 54.7 ± 1.3 years. Clinical characteristics of diabetic patients with and without microvascular complications and the healthy group are summarized in Table 1. The Figure shows the distribution of microvascular complications in the diabetic group with microvascular compli-
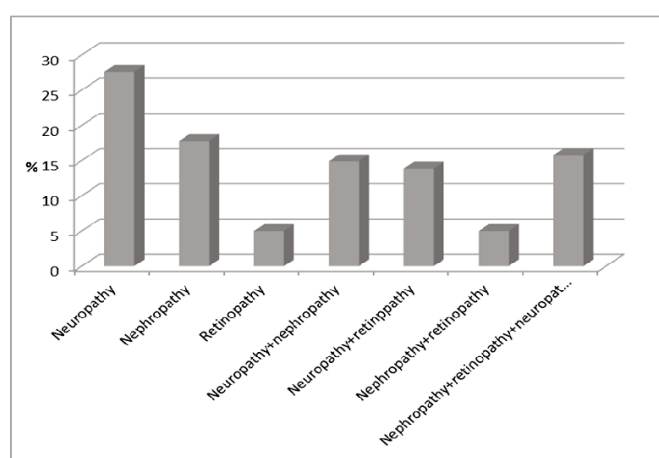

Figure: Percentiles of microvascular complications in the group with microvascular complication.

Table 1: Clinical characteristics of the groups

Characteristics	Patients without microvascular complications	Patients with microvascular complications	Healthy subjects
Gender (female/male)	39/63	41/60	43/38
Age (year)	51.1 ± 0.8	51.4 ± 0.6	54.7 ± 1.3
Duration of diabetes mellitus (year)	5.0 ± 0.4	8.0 ± 0.6	
Body mass index (kg/m²)	31.05 ± 0.6	32.8 ± 0.8	29.8 ± 0.7

Table 2: Comparison of biochemical variables between the two diabetic groups

Variables	Patients without microvascular complications	Patients with microvascular complications	P-value
HbA_{1c} (%)	7.3 ± 0.2	$8,9 \pm 0.2$	< 0.001
Microalbuminuria (mg/day)	10.5 ± 0.6	237.6 ± 83.6	< 0.001
Creatinine (mg/dL)	0.7 ± 0.1	0.7 ± 0.1	0.33
25-OH-vitamin D (ng/mL)	15.6 ± 1.9	14.0 ± 0.8	0.76
Total calcium (8.4–10.6 mg/dL)	9.5 ± 0.0	9.4 ± 0.0	0.10
Phosphorus (2.5–4.6 mg/dL)	3.5 ± 0.0	3.6 ± 0.0	0.17
PTH (1.6–6.9 pmol/L)	5.1 ± 0.1	4.5 ± 0.2	0.22

HbA_{1c}–glycated haemoglobin; PTH–parathyroid hormone

cations. There were no statistically significant differences between the patients with and without microvascular complications with respect to plasma 25-OH-vitamin D ($p = 0.76$), calcium, phosphorus and PTH levels (Table 2). Vitamin D levels were below the normal range in both groups. When we compared the vitamin D levels among the subgroups of those with microvascular complications, we did not detect any differences ($p > 0.05$). No correlation was identified between HbA_{1c} and vitamin D levels (p: 0.57, r: 0.40). There were no statistically significant differences between the diabetic and healthy groups in terms of plasma calcium, phosphorus and PTH levels. However, the healthy group had higher vitamin D levels than both diabetic groups ($p < 0.001$). Importantly, the healthy group also had low vitamin D levels (19 ng/dL) according to normal reference values of the commercial kit.

DISCUSSION

In the present study, we did not ascertain an association between vitamin D levels and microvascular complications of Type 2 diabetes mellitus. However, we demonstrated that vitamin D levels were below the normal range in all diabetic patients, and the healthy group had higher vitamin D levels than the diabetic groups; these findings are similar to the results of previous studies (8, 9, 14).

Vitamin D deficiency is a widespread disorder which is present in approximately 30% to 50% of the general population (15, 16). It is generally due to a lack of adequate sunlight exposure and/or nutritional vitamin D intake (17). There is no consensus on optimal serum levels of 25-OH-vitamin D. According to most experts, a level of < 20 ng/mL is defined as a certain deficiency, a level between 20 and 30 ng/mL is insufficiency, and a level of ≥ 30 ng/mL is normal (18). Hekimsoy *et al* researched the vitamin D status of a Turkish population that lived in a region of the country that gets a lot of sunlight and found a high prevalence of vitamin D deficiency (74.9%) and insufficiency [13.8%] (19). Our healthy group also had low vitamin D levels which may be associated with the high prevalence of vitamin D deficiency in the Turkish population.

Several studies suggesting the role of vitamin D in the pathogenesis of diabetes mellitus have been published. A study by Gedik and Akalin revealed that vitamin D supplementation increased insulin secretion from the pancreas (20). Additionally, vitamin D replacement in patients with impaired glucose tolerance has been shown to decrease insulin resistance (21). In our study, we did not detect any association between HbA_{1c} and vitamin D levels in Type 2 diabetic patients. However, diabetic patients had lower vitamin D levels than the healthy group.

A link between hypovitaminosis D and microvascular complications in Type 2 diabetic patients has been proposed. Albert *et al* demonstrated that calcitriol, the active metabolite of vitamin D, inhibits retinal revascularization and plays a protective role in the development of retinopathy (22).

Vitamin D also prevents diabetic retinopathy by regulating blood glucose levels and blood pressure (23, 24). A negative correlation between vitamin D levels and blood pressure has been shown previously (25). Vitamin D provides a cardio-protective effect by suppression of the renin-angiotensin system (26), inhibition of cardiac myocyte hypertrophy (27), reduction in the formation of vascular calcification and atherosclerosis, and has an anti-inflammatory effect (28). Agarwal *et al* showed that vitamin D replacement therapy reduces levels of albuminuria (29). In another study, vitamin D levels in diabetic patients were found to be lower in patients with nephropathy compared to the ones without nephropathy (30).

Diabetic neuropathy is the most common microvascular complication of diabetes mellitus. In the study carried out by Lee *et al*, an association was detected between hypovitaminosis D and diabetic neuropathy. Researchers indicated that neuropathic pain decreased after vitamin D replacement therapy (16). Another study demonstrated a link between hypovitaminosis D and neuropathy (13). In contrast, in our study we did not find any differences in vitamin D levels between diabetic patients with and without microvascular complications. Our study was cross-sectional and, thus, a cause-effect relationship could not be assessed. This was the major limitation of the study.

In conclusion, vitamin D deficiency is more common in patients with Type 2 diabetes mellitus than healthy subjects. Although vitamin D deficiency has been shown to be related to microvascular complications of diabetes in previous studies, this relationship could not be ascertained in our study. Further studies are needed to assess the role of vitamin D replacement therapy in the treatment of diabetes mellitus and prevention of microvascular complications.

AUTHORS' NOTE
The authors declare no conflict of interests.

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