Lack of Definite Association of Vitamin D Deficiency with Diabetic Neuropathy. Investigation in Greek and in Bangladeshi Patients

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Abstract. *Aim: Determination of the 25(OH) vitamin D levels in Greek-born and in Bangladeshi immigrant patients in Greece with diabetes with and without polyneuropathy. Materials and Methods: The method for the detection and staging of polyneuropathy proposed by Dyck, 1988 was used. Results: A total of 111 Bangladeshi immigrants and 101 Greek diabetic patients took part in the study. Vitamin D levels were significantly lower in Bangladeshi than in Greek diabetic patients, and were significantly lower in Greek patients with small-fiber neuropathy. In Bangladeshi patients, there was no statistically significant difference in the subgroup of patients with polyneuropathy in comparison to those without polyneuropathy. Conclusion: The association of vitamin D deficiency only with a small number of Greek patients with exclusively small-fiber neuropathy does not allow us to draw a definite conclusion on the role of vitamin D in the pathogenesis of diabetic neuropathy.*

Diabetic distal sensorimotor neuropathy (DSPN) is the most frequent type of polyneuropathy and the most frequent complication of diabetes affecting up to 50% of patients (1, 2). In several European studies, large-fiber neuropathy (LFN) and small-fiber neuropathy (SFN) seem to be less prevalent in Asian than in European patients with diabetes and this is attributed to their lower height, less smoking, and better skin microvascularization (3, 4). Vitamin D deficiency has also

been recently implicated in the pathogenesis of diabetic neuropathy (DN) (5-7).

In a previous study, we showed that vitamin D levels were lower in Bangladeshi immigrants with diabetes in Greece compared to indigenous Greek patients with diabetes (8). In this study, we investigated the 25 (OH) vitamin D level in patients with diabetes with and without polyneuropathy in both ethnic groups.

Materials and Methods

The study sample consisted of Greek and Bangladeshi patients recruited from the outpatient diabetic clinic of a general hospital and were matched as to age, sex and diabetes duration. This sample is part of that previously described (8). The following clinical and diabetes related factors were taken into consideration: Age, sex, type of diabetes, age at diabetes diagnosis, duration of diabetes, diabetes treatment, episodes of hypoglycemia, body mass index (BMI), glycated hemoglobin (HbA1c) and 25(OH) vitamin D levels. Patients treated for vitamin D deficiency, those taking vitamin D supplements and those treated with medicines known to affect bone metabolism were excluded from this study. The patients were recruited between January 2012 and December 2014, over a period of time that included all seasons. Serum 25(OH) vitamin D levels were measured using an assay kit from Roche Diagnostics GmbH (Mannheim, Germany) and the measurement was performed once, at the first appointment.

All patients gave their written consent and the study was approved by our local Ethics Committee (approval number 445/30-11-2011).

The electrophysiological study for the detection and staging of polyneuropathy has been described elsewhere (9): The diagnosis of polyneuropathy required the combination of abnormal findings from the Neuropathy Symptoms Score (NSS), Neuropathy Disability Score (NDS), nerve conduction velocities (NCV) and Quantitative Sensory Tests (QST). The classification proposed by Dyck for patients with diabetes was used (10).

Student's *t*-test analysis was used to assess the statistical significance of the differences between groups. A value of $p < 0.05$ was considered significant.

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Table I. 25(OH) Vitamin D (VitD) levels in 101 Greek and in 111 Bangladeshi patients with diabetes according to polyneuropathy (PN).

Variable	Greek		Bangladeshi	
	VitD (ng/dl)	p-Value	VitD (ng/dl)	p-Value
No PN	23±12.4		12.4±5.9	<0.01*
PN				
Exclusively LFN	20.25±12.9	NS**	10.7±5.9	NS**
Exclusively SFN	18.5±11	<0.05**	11.4±4.7	NS**

Data are the mean±SD. LFN: Large-fiber neuropathy, SFN: small-fiber neuropathy, NS: non significant. *Between ethnicities, **compared with the no polyneuropathy group.

Results

One hundred and eleven Bangladeshi immigrants (97 men and 14 women, mean age=47.35 years) and 101 consecutive Greek patients with diabetes (82 men and 19 women, mean age=49.18 years) were included in the study. The demographic characteristics of the two groups, the clinical and laboratory data of patients and diabetes complications and polyneuropathy have been described elsewhere (9).

Vitamin D levels were significantly lower in Bangladeshi than in Greek patients with diabetes without polyneuropathy (12.4±5.9 vs. 23±12.4 ng/ml, *t*-test: *p*<0.01). Table I shows 25(OH) vitamin D levels in groups of Greek and Bangladeshi patients with and without polyneuropathy. In Greek patients, the levels of vitamin D were significantly lower in those with SFN compared with those of the group without polyneuropathy (seven patients), but not in those with LFN (53 patients). In Bangladeshi patients, there was no statistically significant difference in the subgroup of patients with polyneuropathy in comparison with those without polyneuropathy (*t*-test, *p*>0.05).

Discussion

In this study, vitamin D levels were lower in the group of Greek patients with diabetes and with SFN compared to the group without polyneuropathy, but not in that of the patients with LFN. There were, however, only 7 patients with SFN (6.9%), while there were 53 patients with LFN (52.5%).

In previous studies an association of low vitamin D levels with DN was found (5-7, 11-13). The method followed for the diagnosis of polyneuropathy was not uniform in these studies. Some authors used symptoms alone (5) or signs (11) of polyneuropathy, while others used nerve conduction studies only (7, 13), Shehab *et al.* used NSS, NDS and nerve conduction studies (6). We did not find any study to have used QST for the detection of SFN and separating LFN and SFN. Soderstrom *et al.* conceded that the incidence of DN had probably been underestimated in their sample (5). In our study the diagnosis of DN was achieved through a strict combination

of NSS, NDS, NCV and QST. The guidelines for the diagnosis of DSPN of the American Association of Electrodiagnostic medicine (AAEM) state that the most accurate diagnosis of DSPN requires the combination of neuropathic signs, symptoms and abnormal electrophysiological findings, and that symptoms alone have poor diagnostic accuracy (14).

The pathogenesis of DN is not clearly understood. Vitamin D has been shown to have a neuroprotective effect (15) and to be implicated in the pathogenesis of diabetes mellitus (13, 16) and a low level of vitamin D in patients with DN may simply indicate its insufficiency in patients with diabetes.

Levels of vitamin D differ in different seasons and our sample was recruited over a period of time that included all seasons. In Bangladeshis, we did not find any difference in 25(OH) vitamin D level in the subgroups of patients with DN. The levels of vitamin D in these patients were in any case very low. Bangladeshis mostly have type V skin (as defined on the Fitzpatrick scale) which protects against the sun, but also reduces absorption of ultraviolet B sunlight that is needed to produce vitamin D by the skin. Additionally, traditional Asian diets are not rich in vitamin D-containing foods. On the contrary, fair-skinned individuals synthesize more vitamin D when exposed to the same radiation regime (17). Bangladesh is one of the countries with the highest number of patients with diabetes mellitus (18), with a prevalence approximating 20% (3). It is also known that Asians develop diabetes at an earlier age than Europeans (19). The high incidence of DN in Bangladeshi might also in part be attributed to the low levels of 25(OH) vitamin D.

We can postulate that vitamin D insufficiency is implicated in the pathogenesis and the high incidence of diabetes mellitus, but we cannot state this for DN.

In conclusion, the findings of vitamin D deficiency in a small number of Greek patients with exclusively SFN, but not in those with exclusively LFN, and the absence of such an association in Bangladeshis found in this study does not allow us to draw a definite conclusion on the role of vitamin D in the pathogenesis of DN.

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