Original Article

DOI: 10.4274/tjem.2591

Type 2 Diabetes Mellitus and Functional Hypoparathyroidism

Tip 2 Diyabetes Mellitus ve Fonksiyonel Hipoparatiroidi

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Abstract

Purpose: The present study aims to investigate the effect of blood sugar regulation and vitamin D levels on calcium metabolism and parathormone levels in patients with type 2 diabetes mellitus.

Material and Method: We included 132 patients with type 2 diabetes mellitus who presented to our outpatient clinic for regular check up between August 2013 and October 2013. Fasting blood glucose, HbA1c, calcium, phosphorus, magnesium, albumin, creatinine, parathormone, 25-Hydroxy vitamin D [25(OH)D], spot urinary calcium and creatinine levels were studied for each patient.

Results: Vitamin D levels were below 30 ng/mL in 96.9% (n=128) and below 20 ng/mL in 78.7% (n=102) of the patients included in the study. Patients with impaired blood sugar regulation (HbA1c >10%) had lower levels of PTH, albumin and 25(OH)D levels and higher phosphorus levels compared to patients with HbA1c levels below 10% (p=0.018, p=0.043, p=0.002, p=0.01, respectively). The rates of functional hypoparathyroidism (parathormone <65 ng/mL) in patients with vitamin D levels below 30 ng/mL and 20 ng/mL were 63.2% and 59.6%, respectively. Among the diabetic patients with vitamin D levels <30 ng/mL, magnesium levels were significantly lower in those with functional hypoparathyroidism (parathormone <65 ng/mL) compared to those with secondary hyperparathyroidism (p=0.015). Comparative statistical analysis of patients with HbA1c levels above and below 10% demonstrated higher proportion of patients with functional hypoparathyroidism in the group with impaired blood sugar regulation (p=0.035 for patients with vitamin levels below 30 ng/mL, and p=0.031 for patients with vitamin levels below 20 ng/mL).

Discussion: Impaired blood sugar regulation leads to functional hypoparathyroidism with secondary hypomagnesemia in type 2 diabetes mellitus, as was previously described for subjects with type 1 diabetes mellitus. *Turk Jem 2014; 18: 116-120*

Key words: Type 2 diabetes mellitus, hypoparathyroidism, vitamin D deficiency

Conflict of interest: The authors reported no conflict of interest related to this article.

Özet

Amaç: Bu çalışmada tip 2 diabetli hastalarda kan şekeri regülasyonu ve D vitamini düzeyinin, kalsiyum metabolizması ve parathormon düzeyi üzerine olan etkisinin araştırması amaçlandı.

Gereç ve Yöntem: Çalışmaya Ağustos 2013-Ekim 2013 tarihleri arasında kontrol amacı ile polikiniğimize başvuran 132 tip 2 diabetes mellituslu olgu dahil edildi. Olguların açlık kan glukozu, HbA1c, kalsiyum, fosfor, magnezyum, albümin, kreatinin, parathorrmon, 25 (OH) vitamin D, spot idrar kalsiyum ve kreatinin düzeyleri çalışıldı.

Bulgular: Olguların %96,9'unda (128) D vitamin düzeyi 30 ng/mL'nin, %78,7'sinde (102) ise 20 ng/mL'nin altında saptandı. Kan şeker regülasyonu bozuk (HbA1c >%10) olan diabet hastalarında, HbA1c'si %10'un altında olan hastalara kıyasla PTH, Albümin ve 25 (OH) vitamin D düzeyi düşük, fosfor düzeyi ise yüksekti (sırası ile p değeri; p=0,018, p=0,43, p=0,002, p=0,01). D vitamin düzeyi 30 ng/mL ve 20 ng/mL'nin altında olan olgularımızda fonksiyonel hipoparatiroidi (parathormon <65 ng/mL) sıklığı sırası ile %63,2 ve %59,6 olarak saptandı. HbA1c düzeyi 10'un üstünde olan olgular ile %10'un altında olan olguların karşılaştırmalı istatistiğinde, fonksiyonel hipoparatiroidili olgu sayısı kan şeker regülasyonu bozuk olan grupta yüksekti (D vitamin düzeyi 30 ng/mL altında olan olgular için p değeri: 0,035, 20 ng/mL'nin altında olanlar için p değeri 0,031).

Tartışma: Tip 1 diabetes mellituslu olgularda tanımlandığı gibi; tip 2 diabetes mellitusta kan şeker regülasyon bozukluğu neden olduğu hipomagnezemi ile fonksiyonel hipoparatiroidiye neden olmaktadır. *Turk Jem 2014; 18: 116-120*

Anahtar kelimeler: Tip 2 diabetes mellitus, hipoparatiroidi, D vitamin eksikliği

Çıkar çatışması: Yazarlar bu makale ile ilgili olarak herhangi bir çıkar çatışması bildirmemişlerdir.

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Introduction

Vitamin D is a hormone derived from cholesterol in the skin with the effect of ultraviolet rays (1). Vitamin D deficiency is a common condition today, due to life indoors and use of sunscreens (2,3,4,5). While the effects of low levels of vitamin D on osteomalacia, rachitis and osteoporosis are known, many recent studies have demonstrated the association of low vitamin D levels with malignancies, fracture risk, inflammation, cardiovascular disorders and diabetes (6). The relationship between vitamin D deficiency and diabetes mellitus, both type 1 and 2, has been shown by several studies (7,8,9). Measurement of hydroxy vitamin D [25(OH) D] is acknowledged to provide an indicator of vitamin D status of an individual patient (10). In addition, low serum calcium and phosphorus levels, increased serum alkaline phosphatase and parathormone levels and reduced urinary calcium elimination may also suggest vitamin D deficiency. Diabetic patients, particularly poorly controlled ones, may have further alterations in their calcium metabolism in addition to vitamin D deficiency. Osmotic diuresis secondary to glycosuria in patients with type 1 and type 2 diabetes mellitus has been shown to increase urinary calcium and phosphorus elimination (11,12). Vitamin D deficiency leads to secondary hyperparathyroidism by increasing parathormone release. In type 1 diabetic patients with vitamin D deficiency, however, it was shown that parathormone levels did not elevate adequately, resulting in functional hypoparathyroidism. The mechanism held responsible for this is hypomagnesemia resulting from osmotic diuresis (13,14). The association of poorly-controlled type 2 diabetes mellitus with functional hypoparathyroidism has not been established (11). The present study aims to investigate the extent of vitamin deficiency and its effect on calcium metabolism in patients with type 2 diabetes mellitus.

Materials and Methods

The study was conducted in the endocrinology outpatient clinic at Van Yüzüncü Yıl University Medical Faculty. Patients with type 2 diabetes mellitus who presented to the endocrinology outpatient clinic for regular check-up between August 2013 and October 2013 were included in the study. The study protocol was carried out in accordance with the Helsinki Declaration as revised in 2000. The study protocol was approved by the local ethics committee, and informed consent was obtained from each subject.

Fasting blood glucose, HbA1c, calcium, phosphorus, magnesium, albumin, creatinine, parathormone, 25(OH)D, spot urine calcium and creatinine levels were studied for each patient. Biochemical assays were performed with Cobus Integra® 800, parathormone levels were measured by Architec® i4000 and 25(OH)D levels were evaluated by HPLC with HP Agilent® 1200 using commercial kits.

Patients with chronic renal failure, chronic hepatic disease, primary hyperparathyroidism and those with conditions that may impair calcium and Vitamin D metabolism including conditions requiring diuretic use and patients with type 2 diabetes mellitus receiving calcium and/or vitamin D for osteoporosis were excluded.

A total of 132 patients meeting the inclusion criteria were grouped according to 25(OH)D levels as <30 ng/mL and <20 ng/mL, according to parathormone levels as below and above 65 ng/mL, and according to HbA1c levels as below and above 10%.

The results were analyzed using the SPSS 16 statistics software. Two groups comparisons were performed with the Unpaired t-test. Chi-square test was used to determine the relationships between categorical variables. Pearson's test was used for correlation analysis. The results were expressed as mean ± standard deviation and statistical significance was set at $p<0.05$.

Results

The study included 132 patients with type 2 diabetes mellitus. Of these, 53% were females and 47% were males, and their average age was 54.7 years. Vitamin D levels below 30 ng/mL were detected in 96.9% (n=128) and vitamin D levels below 20 ng/mL in 78.7% (n=102). Descriptive statistics of the patients included in the study are provided in Table 1.

Of the 128 patients with 25(OH)D levels below 30 ng/mL, the percentages of those with HbA1c levels above and below 10% were 42% and 58%, respectively. The patients with impaired blood sugar regulation (HbA1c >10%) had lower levels of PTH, albumin and 25 (OH) vitamin D and higher levels of phosphorus compared to those with HbA1c levels below 10% ($p=0.018$, $p=0.043$, $p=0.002$, $p=0.01$, respectively) (Table 2).

HbA1c levels in 74 patients were below 10%. Of these, 56.75% (n=42) were female, 43.25% (n=32) were male. HbA1c levels in 54 patients were above 10%. Of these, 57.4% (n=31) were female, 42,60% (n=23) were male. Only 25(OH)D levels were significantly lower in females compared to that in males in subgroup analysis according to gender ($p<0.001$ for both groups).

The frequencies of functional hypoparathyroidism (parathormone <65 ng/mL) in patients with vitamin D level <30 ng/mL and <20 ng/mL were 63.2% and 59.6%, respectively. The distribution of patients with functional hypoparathyroidism among those with HbA1c levels above and below 10% is shown in Figure 1. The number of patients with functional hypoparathyroidism in the subset of patients with HbA1c >10% was markedly higher

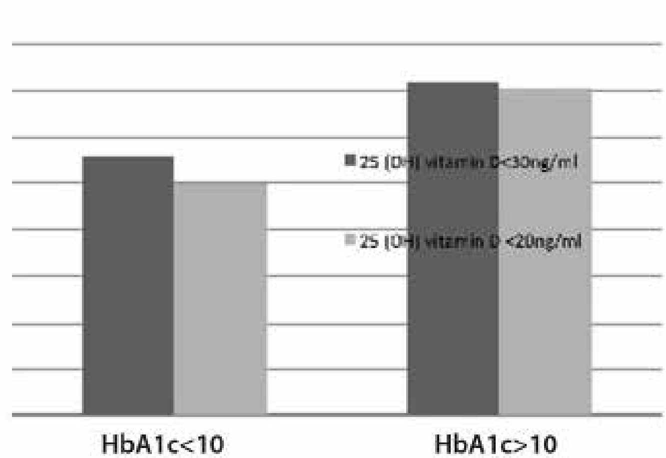

Figure 1. Distribution (%) of patients with functional hypoparathyroidism among those with HbA1c levels above and below 10%

(p=0.035 and p=0.031 for patients with vitamin D levels below 30 ng/mL and below 20 ng/mL, respectively).

Comparison of cases with parathormone levels below and above 65 ng/mL in diabetic patients with vitamin D levels <30 ng/mL is shown in Table 3. The number of patients with parathormone levels below and above 65 ng/mL was 81 and 47, respectively. Phosphorus and urine calcium/creatinine levels were higher and magnesium levels were significantly lower in those with functional hypoparathyroidism (parathormone <65 ng/mL) compared to those with secondary hyperparathyroidism (p=0.009, p=0.001, p=0.015, respectively).

Parathormone levels in 81 patients were below 65 ng/mL. Of these, 50.6% (n=41) were female, 49.4% (n=40) were male. Parathormone levels in 47 patients were above 65 ng/mL. Of these, 68.08% (n=32) were female, 31.02% (n=15) were male. Only 25(OH)D levels were significantly lower in females compared with males in subgroup analysis according to gender (p<0.001 and p=0.012 for patients with parathormone levels below 65 ng/mL and above 65 ng/mL, respectively).

With Pearson's correlation analysis of patients with vitamin D deficiency, PTH was positively correlated with alkaline phosphatase and negatively correlated with urine calcium creatinine (r=0.462, p<0.001; r=-0.346, p<0.001, respectively). Calcium was negatively correlated with HbA1c and positively correlated with vitamin D (r=-0.215, p=0.016; r=0.206, p=0.021, respectively). Phosphorus was negatively correlated with vitamin D (r=-0,194, p=0.033). Vitamin D was negatively correlated with ALP and HbA1c (r=-0,235, p=0.019; r=-0,295, p=0.001, respectively).

Discussion

In our study, 96.9% of the patients with type 2 diabetes mellitus had vitamin D levels below 30 ng/mL and 78.7% below 20 ng/mL. In poorly-controlled diabetic patients (HbA1c >10), vitamin D levels were lower than in those with HbA1c <10% (p=0.002). There was a corresponding negative correlation between vitamin D and HbA1c levels (p=0.001). This correlation was probably associated with the effect of vitamin D on insulin secretion. Presence of vitamin D receptors in pancreatic beta cells was demonstrated previously, and vitamin D supplementation given to type 2 diabetic patients with vitamin D deficiency has been shown to improve insulin release and diminish insulin resistance by several studies (15,16,17,18).

In our poorly-controlled diabetic patients (HbA1c >10), parathormone levels as well as vitamin D levels were lower compared to those with HbA1c levels <10% (p=0.018). This was probably associated with the effect of hyperglycemia and/or glycosuria on calcium metabolism. Sugimoto et al. demonstrated that glucose at high concentrations inhibited parathormone secretion in bovine parathyroid cell culture (19). This in vitro evidence was later supported by several clinical studies. For example, Polymeris et al. reported parathormone reduction, which was negatively correlated with increases in blood glucose levels, during oral glucose tolerance test in non-diabetic postmenopausal women (20). There are also similar studies with comparable results in patients with type 1 diabetes mellitus. In one of these, Thalasinos et al. demonstrated elevated parathormone levels following blood sugar regulation in patients with poorly-controlled type 1 diabetes mellitus (11). McNair et al. also reported that low serum immunoreactive parathroid hormone levels were correlated with high glycosuria and long duration of diabetes mellitus in patients with type 1 diabetes mellitus (21). Besides impaired blood sugar regulation, magnesium loss developing during osmotic diuresis secondary to glycosuria is another mechanism held responsible for impaired parathormone secretion in patients with type 1 diabetes mellitus. As such, chronic magnesium deficiency impairs parathormone release, resulting in functional hypoparathyroidism (22). In a study by Sagesse et al. in patients with type 1 diabetes mellitus, magnesium replacement resulted in increased parathormone levels, which is supportive

Table 1. Descriptive statistics of the patients included in the study

	n	Normal referans	Minimum	Maximum	Mean	Standard Deviation
Parathyroid Hormone	132	10-65 pg/mL	10	354	65.65	45.39
Calcium	132	8.5-10.5 mg/dL	7.5	10.5	9.43	0.60
Phosphorus	132	2.6-4.5 mg/dL	2.1	5.4	3.72	0.52
Corrected Calcium	132	8.5-10.5 mg/dL	7.88	10.36	9.20	0.47
Urinary Ca/Creatinin	132	0.09-0.16	0.01	0.47	0.12	0.09
Magnesium	132	1.6-2.6 mg/dL	1.20	2.69	1.96	0.32
Albumin	132	3.5-5 g/dL	3.6	5.1	4.28	0.49
Alkaline Phosphatase	132	38-155 U/L	97	705	221.68	88.85
Glucose	132	80-100 mg/dL	56	743	226.95	118.16
HbA1c	132	4.5-5.5%	5.1	17.8	9.62	2.71
25 (OH) Vitamin D	132	30-80 ng/mL	4.0	33.6	14.72	6.30

Table 2. Comparison of cases with HbA1c levels below and above 10% in diabetic patients with vitamin D levels <30 ng/mL

	HBa1c (%)	n	Mean	Standard Deviation	p
Parathyroid Hormone (pg/mL)	HbA1c <10	74	73.73	53.85	.018
	HbA1c >10	54	54.14	27.62	
Calcium (mg/dL)	HbA1c <10	74	9.50	0.58	.083
	HbA1c >10	54	9.31	0.64	
Corrected Calcium (mg/dL)	HbA1c <10	74	9.22	0.40	.613
	HbA1c >10	54	9.18	0.56	
Phosphorus (mg/dL)	HbA1c <10	74	3.62	0.58	.010
	HbA1c >10	54	3.86	0.41	
Alkaline Phosphatase (U/L)	HbA1c <10	74	211.83	77.20	.189
	HbA1c >10	54	235.80	102.58	
Magnesium (mg/dL)	HbA1c <10	74	1.91	0.31	.155
	HbA1c >10	54	2.07	0.34	
Albumin (g/dL)	HbA1c <10	74	4.36	0.53	.043
	HbA1c >10	54	4.17	0.45	
25 (OH) Vitamin D (ng/mL)	HbA1c <10	74	15.49	5.70	.002
	HbA1c >10	54	12.41	5.01	
Urinary Calcium/ Creatinin	HbA1c <10	74	0.11	0.08	.072
	HbA1c >10	54	0.14	0.11	

of the above evidence (14). Similarly, Paula et al. demonstrated blunted parathormone responses to hypocalcemia induced by EDTA infusion in most type 1 diabetes mellitus patients with poor metabolic control. This study also determined low serum magnesium levels in poorly-controlled diabetic patients compared to controls (23). However, there is a very limited number of studies in the literature investigating the effect of poorly-controlled type 2 diabetes mellitus on parathormone secretion and the results conflict with those obtained with subjects with type 1 diabetes mellitus. In their study comparing subjects with type 1 and type 2 diabetes mellitus, Thalassinoss et al. reported that parathormone secretion was maintained in subjects with type 2 diabetes mellitus (11). The study was limited due to the limited number of type 2 diabetic subjects enrolled (37) and the lack of analysis on vitamin D levels. Similarly, there are published data demonstrating reduced parathormone levels following blood sugar regulation and lack of a relationship between blood glucose levels and parathormone in poorly-controlled type 2 diabetes mellitus patients as opposed to the findings obtained with type 1 diabetes mellitus patients (12,24). Likewise,

Table 3. Comparison of cases with parathormone levels below and above 65 ng/mL in diabetic patients with vitamin D levels <30 ng/mL

	Parathormon	n	Mean	Standard Deviation	p
Total Calcium (mg/dL)	PTH <65	81	9.399	.5979	0.547
	PTH >65	47	9.468	.6434	
Corrected Calcium (mg/dL)	PTH <65	81	9.1752	.51672	0.429
	PTH >65	47	9.2465	.40469	
Phosphorus (mg/dL)	PTH <65	81	3.817	.4578	0.009
	PTH >65	47	3.562	.5982	
Alkaline Phosphatase (U/L)	PTH <65	81	217.38	91.858	0.418
	PTH >65	47	232.75	87.681	
Magnesium (mg/dL)	PTH <65	81	1.8355	.28064	0.015
	PTH >65	47	2.0648	.32543	
Albumin (g/dL)	PTH <65	81	4.285	.4223	0.795
	PTH >65	47	4.260	.6265	
25 (OH) Vitamin D (ng/mL)	PTH <65	81	14.825	5.5361	0.094
	PTH >65	47	13.098	5.6369	
Urinary Calcium/ Creatinin	PTH <65	81	.1455	.10426	0.001
	PTH >65	47	.0793	.07521	
HbA1C (%)	PTH <65	81	9.854	2.8096	0.226
	PTH >65	47	9.239	2.6076	
Glucose (mg/dL)	PTH <65	81	243.40	127.764	0.054
	PTH >65	47	200.70	100.779	

vitamin D levels were not investigated in these studies. Vitamin D deficiency is associated with an increase in parathormone levels. Absence of elevated parathormone levels in vitamin D deficiency is defined as functional hypoparathyroidism (24). In our study, the frequency of functional hypoparathyroidism was higher in patients with impaired blood sugar regulation (HbA1c >10). Magnesium levels were also lower in these patients with functional hypoparathyroidism. This finding was consistent with functional hypoparathyroidism resulting from osmotic diuresis due to glycosuria in patients with type 1 diabetes.

In conclusion, our study is important in that it is the first to demonstrate the increased frequency of functional hypoparathyroidism in patients with type 2 diabetes mellitus with impaired blood sugar regulation, which was described previously for patients with type 1 diabetes mellitus. This should be evaluated by further studies to investigate the effects on bone loss and fragility in patients with type 2 diabetes mellitus.

Conflicts of Interest

There are no conflicts of interest.

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