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Could diabetes mellitus be a risk factor for postoperative hypoparathyroidism?

Diabetes mellitus postoperatif hipoparatiroidizm için bir risk faktörü olabilir mi?

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ABSTRACT

Aim: Postoperative hypoparathyroidism (postop hypoPT) is usually seen after aggressive neck surgery, and can be fatal if left untreated. To the best our knowledge there is no study in literature that directly investigates the association between diabetes mellitus (DM) and postop hypoPT. In this study, we aimed to determine whether DM increases the risk of permanent postop hypoPT.

Materials and Methods: Patients presenting to endocrinology outpatient clinic with a diagnosis of permanent postoperative hypoparathyroidism, were studied retrospectively. Patients older than 18 years of age were included in the study if one year had passed after the neck operation.

Results: The average age of 131 patients who met the inclusion criteria was 49 ± 12. 93.9% of the patients were women and the patients were generally obese or overweight (mean body mass index= 30±5.29 kg/m^2). While 14.5% of the patients were diabetic and 32.8% prediabetic (47.3% had impaired carbohydrate tolerance), 52.7% had normal glucose metabolism.

Conclusion: The rate of DM / prediabetes (preDM) in patients diagnosed with postop hypoPT and the prevalence of DM / preDM in Turkish population were similar. Even though DM is associated with endothelial dysfunction, our findings suggest that DM is not a risk factor for postop hypoPT.

Keywords: Postoperative hypoparathyroidism, permanent hypoparathyroidism, diabetes mellitus, prediabetes.

ÖZ

Amaç: *Postoperatif hipoparatiroidizm (postop hipoPT) genellikle agresif boyun cerrahisinden sonra görülür ve tedavi edilmezse ölümcül olabilir. Bildiğimiz kadarıyla literatürde diabetes mellitus (DM) ile postop hipoPT arasındaki ilişkiyi doğrudan araştıran bir çalışma bulunmamaktadır. Bu çalışmada DM'nin kalıcı postop hipoPT riskini artırıp artırmadığını belirlemeyi amaçladık.*

Gereç ve Yöntem: *Endokrinoloji polikliniğine postoperatif kalıcı hipoparatiroidizm tanısı ile başvuran hastalar retrospektif olarak incelendi. Boyun ameliyatının üzerinden en az bir yıl geçmiş olan 18 yaş üstü hastalar çalışmaya dâhil edildi.*

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Bulgular: *Dâhil edilme kriterlerine uyan 131 hastanın yaş ortalaması 49 ± 12 idi. Hastaların %93,9'u kadındı ve hastalar genel olarak obez veya fazla kiloluydu (ortalama vücut kitle indeksi= 30±5,29 kg/m^2). Hastaların %14,5'i diyabetik ve %32,8'i prediyabetik (%47,3'ü bozulmuş karbonhidrat toleransına sahipti), %52,7'si normal glukoz metabolizmasına sahipti.*

Sonuç: *Postop hipoPT tanısı alan hastalarda DM / prediyabet (preDM) sıklığı ile Türk popülasyonunda DM / preDM prevalansı benzerdi. Diyabet, endotel disfonksiyonu ile ilişkili olmasına rağmen, çalışmamızdaki bulgular DM'nin postop hipoPT için bir risk faktörü olmadığını düşündürmektedir.*

Anahtar Sözcükler: *Postoperatif hipoparatiroidizm, kalıcı hipoparatiroidizm, diabetes mellitus, prediyabet.*

INTRODUCTION

Postoperative hypoparathyroidism (postop hypoPT) is a common complication of neck surgery. Development of 'permanent hypoparathyroidism' is especially significant, as it can be fatal when left untreated. Permanent hypoPT, which requires long-term close monitoring, is a cumbersome complication both for the patient and the physician. If patients at risk for postop hypoPT can be identified, necessary supportive measures can be provided and morbidity may be reduced (1).

Known risk factors for postop hypoPT include surgery for thyroid malignancy, bilateral central neck dissection, inexperience of the surgeon, recurrent surgery, substernal goiter, vitamin D deficiency, surgery for parathyroid hyperplasia, pregnancy, lactation, female gender, autoimmune thyroid disease, and malabsorptive conditions such as previous gastric bypass surgery (2, 3).

Parathyroid glands are fragile organs with a rich in blood supply. In addition to the above-mentioned risk factors, 'endothelial dysfunction', which causes impaired blood flow to the parathyroid glands, may also play a critical role in the development of postop hypoPT. Studies have shown that diabetes, a cardiovascular disease equivalent, is associated with endothelial dysfunction. (4-6). Diabetes mellitus (DM) also affects angiogenesis and delays the wound healing (7). DM may hence be related to postoperative parathyroid gland dysfunction.

To the best knowledge of the authors, there is no study in literature that directly investigates the association between DM and postop hypoPT. In this study, we aimed to determine whether DM increases the risk of permanent postop hypoPT.

MATERIALS and METHODS

Patients who presented to the endocrinology outpatient clinic of a tertiary hospital with a diagnosis of permanent postop hypoPT between April 2015 and March 2020, were evaluated retrospectively.

Patients older than 18 years of age were included in the study if one year had passed after the neck operation. Patients with metabolic bone disease that could affect serum calcium and phosphorus levels, patients diagnosed with idiopathic hypoparathyroidism, pregnant or breastfeeding women, patients on dialysis, and patients with known active malignancy were excluded. The data on whether the patients were diabetic or prediabetic in the preoperative period were based on their anamnesis or preoperative laboratory data, if available. The patients who had not reliable data were not recruited to study.

Body mass index (BMI) was calculated as weight (kg) divided by height in meters squared (m²). Total cholesterol and triglycerides were measured by enzymatic color test. Calcium, phosphorus, magnesium and albumin were tested by photometric method. LDL and HDL cholesterol were studied with enzymatic color + immuno-inhibition test, FPG enzymatic UV test (HK G6P-DH) and creatinine kinetic color test (AU5800 auto analyzer, Beckman Coulter Inc., Brea, CA, USA). Serum TSH was studied in Beckmann-Coulter DXI-800 immunoassay device by chemiluminescence immunoassay (CLIA) method. Parathyroid hormone (PTH) and 25 (OH) vitamin D were measured using the chemiluminescence method on the Cobas E-801 analyzer (Roche Diagnostics GmbH, Mannheim, Germany).

Those with impaired fasting glucose and / or impaired glucose tolerance were considered preDM. American Diabetes Association criteria were used for the diagnosis of DM (8). Those with a body mass index (BMI) ≥30 kg/m^2 were defined as obese, while those with a BMI = 25 - <30 kg/m^2 were defined as overweight. A PTH level below 15 one year after surgery was considered permanent hypoPT. The study was

approved by the institutional review board (2017/E-17-1274).

Statistical analyzes were performed using IBM SPSS for Windows Version 24.0 package program. Numerical variables were summarized by mean ± standard deviation or median [minimum-maximum]. Categorical variables were shown with numbers and percentages. Whether there was a difference between the groups in terms of categorical variables was investigated by chi-square test or Fisher's exact test. Whether numerical variables showed normal distribution or not was examined by Kolmogorov Smirnov test, and homogeneity of variances was examined by Levene test. Differences between two independent groups in terms of numerical variables; In case the parametric test assumptions were met, independent groups were analyzed by t-test. If the parametric test assumptions were not provided, the Mann Whitney U test was used. The significance level was taken as $p < 0.05$.

RESULTS

One hundred and thirty-one patients who met the inclusion criteria were included in the study. The average age of the patients was 49±12 years, and the mean time after the operation was 9 (min-max: 1-44) years (Table-1). 93.9% of the patients were women and the patients were generally obese or overweight (body mass index 'BMI' 30 ± 5.29 kg/m^2). When those with impaired fasting glucose and / or impaired glucose tolerance were evaluated as preDM, 32.8% of the patients who developed postop hypoPT were prediabetic and 14.5% had diabetes. In other words, while 47.3% of the patients had impaired carbohydrate tolerance, 52.7% had normal glucose metabolism (Table-1).

The current laboratory data of patients are shown in Table-2. Treatment regimens of patients and the daily treatment doses are presented in Table-3. The doses of daily calcitriol did not differ significantly between the group with impaired glucose metabolism (DM + preDM) and the group with normal glucose tolerance (Table-4).

Table-1. Descriptive data of the patients.

Parameter	Value / result
Age (year)	49.47 ± 12.14
Gender (F/M) (n)	123 / 8
(%)	(%93.9) / (%6.1)
Body mass index (BMI) (kg/m^2)	30 ± 5.29
Mean time after surgery (years) (min-max)	9 (1-44)
Thyroid malignancy n (%)	36 (27.5)
Recurrent operation n (%)	12 (9.2)
Lymph node dissection n (%)	16 (12.2)
Hypertension n (%)	33 (25.2)
Cardiovascular disease n (%)	12 (9.2)
Preop DM + pre DM n (%)	22 (16.8)
Postop carbohydrate metabolism situation:	
• **DM (+)** n (%)	19 (14.5)
• **Pre DM** n (%)	43 (32.8)
• **Normal glucose tolerance** n (%)	69 (52.7)
Postop DM + Pre DM	61 (47.3)

DM: Diabetes mellitus, Pre DM: Pre-diabetes, Preop: Preoperative, Postop: Postoperative

Table-2. Current laboratory data of patients.

Parameter	Value
PTH (pg/ml)	6.73 ± 4.49
25-OH vitamin D3 (ng/ml)	22.61 ± 9.19
Ca (mg/dl)	8,7 (5.5-10.3)
P (mg/dl)	4.47 ± 0.23
Mg (mg/dl)	1.87 ± 0.20
Fasting plasma glucose (mg/dl)	95 (70-338)
HbA1c (%)	6 (5.3-14.5)
Creatinine (mg/dl)	0.85 ± 0.22
Triglyceride (mg/dl)	142.64 ± 94.35
Total cholesterol (mg/dl)	205.07 ± 36.24
LDL-cholesterol (mg/dl)	122.63 ± 29.84
HDL-cholesterol (mg/dl)	53.23 ± 12.54
Vitamin B12 (ng/L)	237 (53-518)
Uric acid (mg/dl)	4.87 ± 1.40

PTH: Parathyroid hormone, Ca: Calcium, P: Phosphorus, Mg: Magnesium,

HbA1c: Glycated hemoglobin, LDL: Low-density lipoprotein, HDL: High-density lipoprotein

Table-3. Medications and their daily doses.

Medication	Daily dose of medication
Calcitriol (mcg/day)	0.5 (0.25-2)
Levothyroxine (mcg/day)	125 (25-350)
Calcium (mg/day)	1709.49 ± 779.47

Table-4. Comparison of the patients with impaired glucose metabolism (DM + Pre DM) and normal glucose tolerance in terms of calcitriol treatment doses.

	Patients with normal glucose metabolism (n=69)	Patients with DM + pre DM (n=62)	p value
Calcitriol dose (mcg/day)	0.70 ± 0.415 (0.25-2)	0.55 ± 0.265 (0.25-1)	0.063
Patients with serum 'Ca' in the target range (n)	14 (20.3)	13 (21)	0.886
Patients with serum 'P' in the target range (n)	41 (59.4)	29 (46.8)	0.278

DM: Diabetes mellitus, Pre DM: Pre-diabetes

DISCUSSION

We found that the prevalence of DM / preDM in patients who developed permanent hypoPT after neck surgery was similar to the general prevalence of DM / preDM in our country (9, 10).

Postop hypoPT is the most common complication of neck surgery (2). It is usually seen after aggressive thyroid surgery and can be fatal if left untreated. Quality of life is seriously impaired, especially if 'permanent hypoparathyroidism' develops. It is important to identify patients at risk of postop hypoPT, so that necessary supportive measures can be taken to reduce the risk.

Postop hypoPT may be transient or permenant. Transient hypoPT usually resolves within 6 months postoperatively, while permanent hypoPT continues beyond 6 months (even up to a year) after surgery (11, 12). Parathyroid hormone (PTH) has a short half-life (3-5 minutes) and disruption of arterial supply during surgical manipulation can result in temporary low PTH levels (<15 pg/ml) in the circulation. If PTH levels continue to remain below 15 pg/ml for more than 6-12 months, calcitriol and calcium replacement therapy are usually required along with close monitoring. Long-term consequences of hypoPT include basal ganglia / ectopic soft tissue calcification, cataracts, imperfections in bone metabolism, nephrolithiasis, and even end stage renal failure (3). In addition to increased morbidity and mortality, permanent hypoPT have a serious impact on quality of life (3, 13). Postop hypoPT mandates lifetime follow-up, which is difficult for both the patient and the physician, not to mention the financial burden. In our study, despite close monitoring, patients with serum calcium levels in the target range (8-8.5 mg/dl) (14, 15) constituted only 1/5 of the total patients.

Most of the risk factors for postop hypoPT are associated with trauma and devascularization of the parathyroid glands (11, 12). Risk factors other than the extent of the surgical intervention and the experience of the surgeon are particularly associated with transient postop hypoPT. Other risk factors such as vitamin D deficiency have little role in the development of postop hypoPT (12, 14, 16-19). In the present study, extensive surgical procedures such as thyroid malignancy / neck lymph node dissection and recurrent operations were frequent, in accordance with the literature (2, 3, 12).

The current vitamin D3 levels of patients have been obtained 9 years after surgery, on average. Hence, we lack information regarding the preoperative 25-OH vitamin D3 levels. However, the fact that the patients still had vitamin D deficiency despite the routine use of 25-OH vitamin D3 replacement suggested that deficiency was probably present in the preoperative period as well. Vitamin D deficiency causes postoperative transient hypoparathyroidism (1) as 25-OH vitamin D3 increases intestinal calcium and phosphate absorption. PTH levels are increased in patients with low 25-OH vitamin D3 (secondary hyperparathyroidism), thus 1-hydroxylation is activated in the kidneys and 1,25-dihydroxy-vitamin D3 (calcitriol) production is stimulated (20, 21). The normal production rate of calcitriol is 0.5-1 µg per day (22). The calcitriol requirement of the patients in our study was between 0.25 and 2 mcg/day, which is in accordance with the literature. A possible explanation for the transient hypoPT seen in vitamin D3 deficiency may be that vitamin D deficiency leads to secondary hyperparathyroidism, which in turn increases the oxygen consumption of the parathyroid glands. However, in order to prove this possible mechanism, radiological studies showing an increased blood supply to the parathyroid glands are needed.

There are contradictory publications in the literature regarding the relationship between age and postoperative hypoPT development. Younger patients may require aggressive surgery for malignancy (23, 24). On the other hand, aging is thought to increase the risk of hypoPT due to impaired blood supply of the parathyroid glands and low vitamin D levels (1, 20). The average age of our study participants was 50 and the results were obtained approximately 9 years after surgery. Thus, in the present study, postop hypoPT was observed in adults around the age of 40. The study was conducted in a tertiary reference hospital, where aggressive surgery for malignancy is more common, which might explain the relatively young age of hypoPT patients.

In line with literature, we found that postop hypoPT was more common in women. This may be due to lower 25-OH D3 levels in women and other hormonal factors. The high risk of postop hypoPT in young women has also been attributed to the anti-osteoclastic effect of estrogen (25).

In addition to the above-mentioned risk factors for postop hypoPT, ‘endothelial dysfunction’ may cause an impairment in the blood supply of the parathyroid glands. The parathyroid glands are vulnerable organs, and a rich blood supply is required for its proper functioning. Approximately 30% of a normal parathyroid gland is composed of capillary cells, and interruption of the blood supply of this fragile gland leads to hypoPT (26). Studies have shown that diabetes, a disease equivalent to cardiovascular disease, is associated with endothelial dysfunction (4-6). In addition, diabetes mellitus negatively affects angiogenesis and delays the wound healing process (7). Thus, we hypothesized that the

blood flow to the parathyroid glands would be jeopardized in diabetic patients undergoing surgery. However, we did not find any significant difference in the prevalence of diabetes / prediabetes between patients who developed permanent hypoPT after neck surgery and the Turkish population in general. According to the TURDEP-II (Turkish Diabetes Epidemiology Study, n = 26499) study, the prevalence of DM in our country is 13.7%, and the prevalence of prediabetes (isolated impaired fasting glucose and/or impaired glucose tolerance) is 30.8% (9). The prevalence of DM and preDM in the patients included in our study were similar to the general Turkish population (14.5% and 32.8%, respectively). According to PURE study (an international Prospective Urban Rural Epidemiology Study, n=4056 participants [female: 60.7%, mean age: 50±9.1 years]) the prevalence of DM increased from 13.7% in 2008 to 21% in 2015 (10). In literature, we found only one study about the relationship between diabetes and the speed of postop PTH recovery. Al-Dhahri et al emphasized that DM is one of the risk factors affecting the speed of recovery (27). However, it was not about the association between diabetes and postop hypoPT risk.

Our retrospective study has several limitations worth mentioning. First of all, the sample size was small. A higher sample size could have revealed a statistically significant difference. Moreover, the operations were performed in different centers across the city and the patients were referred to the hospital where the study was conducted. Hence, pathology reports and preoperative laboratory data of some of the patients were missing, and we did not have sufficient data about the surgeons' experience or the indications of neck surgery in some patients. Finally, the results of the study cannot be generalized to the whole population.

CONCLUSION

In conclusion, to the best of our knowledge, this is the first study to directly investigate the association between DM / preDM and postop hypoPT. Our results suggest that diabetes mellitus is not a risk factor for postoperative hypoparathyroidism. Although there are many risk factors for the development of postop hypoPT, permanent hypoPT is mainly caused by the devascularization of parathyroid glands during the surgical procedure.

Conflicts of interest: The authors declare that they have no conflict of interest, and all authors have read and approved of the manuscript being submitted.

Ethics approval: The study was approved by the institutional review board (2017/E-17-1274).

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