

# Assessment of Calcium and Vitamin D Medications Adherence in Patients with Hypoparathyroidism After Thyroidectomy

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## Research Article

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# Abstract

**Summary:** In this study, we found that patients with hypoparathyroidism had a problem with calcium medication compliance, and this problem increased with the duration of the disease. We also showed that patients are concerned about the possible side effects of drugs.

**Introduction:** In this study, we aimed to evaluate adherence to active vitamin D and calcium replacement in patients with post surgical hypoparathyroidism.

**Methods:** To elucidate the medication adherence, we performed a questionnaire survey using the six item "Medication adherence questionnaire"(MAQ). The first, second and sixth questions reflect the motivation status of the patients whereas the third, fourth and sixth questions reflect the knowledge about the medication that is received. The responses are scored and patients are classified regarding their motivation to and knowledge about the particular drug.

**Results:** Totally 64 patients (Male:12/Female:52; mean age  $48.6 \pm 11.6$  years) who had postoperative hypoparathyroidism were included in our study. Median disease duration was 60 months (min-max; 12-295 months). We found that motivation score of calcium usage was significantly lower compared to vitamin D usage ( $p < 0.001$ ). The calcium motivation score was reversely correlated with disease duration ( $r = -0.256$  and  $p = 0.046$ ). The most common worry about calcium usage was nephrotoxicity, and the most common worries about calcitriol treatment were kidney damage and polyuria. One third of the patients were taking oral calcium and calcitriol less than the recommended dose.

**Conclusion:** One third of patients lack motivation to use calcium whereas half of the patients' experiences anxiety about drug related side effects. This is a preliminary study showing that vital calcium and active vitamin D intake may be interrupted due to side effect anxiety and motivation can be increased by frequent visits and acknowledging the patient about the deleterious effects of drug withdrawal.

## Introduction

Hypoparathyroidism (HypoPT) is defined as dysfunctional production and/or secretion of parathormone (PTH) by the parathyroid glands. It is characterized with hypocalcemia and hyperphosphatemia. The most common etiology is surgical removal of the parathyroid glands during thyroidectomy or other neck operations. After total thyroidectomy, the incidence of post-operative HypoPT ranges from 0.5–6.6% [1]. However, incidences as high as 20% have been reported depending on surgery extension and complexity. HypoPT is called as "persistent" or "chronic" if it lasts longer than 6 months to one year [2, 3]. All patients should be treated if their serum Calcium (Ca) is lower than 8 mg/dl [4, 5]. While treating the patients with hypoPT there are 6 applied principles used for monitoring. Those are as follows; 1) serum Ca should be slightly below normal 2) there should be no sign or symptom of hypocalcemia 3) Serum Calcium-Phosphorus (Ca-P) product to below  $55 \text{ mg}^2/\text{dL}^2$  (4.4 mmol/L); 4) to avoid hypercalciuria; 5) to avoid hypercalcemia; and 6) to avoid renal (nephrocalcinosis/nephrolithiasis) and other extra skeletal calcifications [4]. For the treatment of hypoPT, calcium and activated Vitamin D replacement are used.

The most common oral Ca with the highest percentage of elemental Ca is calcium carbonate (CaCO<sub>3</sub>). It should be taken with meals and its absorption depends on the gastric acidity. Particular food can increase or decrease absorption and bioavailability of the mineral. CaCO<sub>3</sub> can cause gastrointestinal side effects such as bloating or constipation [6]. Calcium citrate has greater absorption in the small intestine since it is not affected by gastric acid and can be taken with proton pump inhibitors. However, it is more expensive and requires greater number of tablets because of lower elemental Ca content. Activated 1 $\alpha$  hydroxylated vitamin D analogs are also essential for Ca absorption, with most commonly used forms 1,25 dihydroxy vitamin D (calcitriol) and 1 $\alpha$  calcidiol. The short half life of calcitriol mandates twice daily administration. Recombinant PTH (1-84) is another option in cases in whom clinical targets are not maintained despite high doses of calcium and active vitamin D supplements [6–9]. Optimizing the biochemical and clinical parameters without causing short- and long-term complications remain a challenge for endocrinologists. It is known that quality of life is significantly affected in individuals with chronic hypoPT. There are no objective clinical tools to measure and quantify the symptom burden of the patients. Reduced quality of life is closely related with calcium fluctuation. Compliance to that lifelong medical therapy is difficult in-patient terms. To our knowledge there is no data in the literature about the patient compliance to medical treatment in patients with post-surgical chronic hypoPT. In this study our aim was to demonstrate the motivation and acknowledgement status of patients about calcium and calcitriol treatment and reveal the factors that can affect compliance. This study is the first one in the literature performed in hypoPT patients.

## Material And Method

The patients who were admitted to our endocrinology outpatient clinics between May 2017 and January 2018 with the diagnosis of persistent postsurgical hypoPT were enrolled in this study. This study was designed as a single center prospective study and it was approved by the local ethics committee. Persistent or chronic hypoPT was defined as hypoparathyroidism lasting at least one year after operation. After recording medical history and making physical examination, the patients were requested to fill the form of “Medication Adherence Questionnaire” (MAQ) [11, 12]. The endocrinologist accompanied each patient while filling the form and explained each question one by one. MAQ was previously translated in our language by a professional then confirmed and validated by three separate researchers [13]. This questionnaire includes six questions. The first question asks if the patient forgets to take the medication. Second question asks if the patient takes the medication on time. Third question asks if the patient skips the medication when he/she feels well. Fourth question asks if the patient experiences adverse effects which he/she relates with the medication leading to non-compliance. Fifth question asks if the patient knows the benefits of the medication and lastly sixth question asks if the patient forgets to get prescriptions for the medication on time. The answer is either yes or no. The patients are scored regarding the response.” Yes” to question 2 and five is scored as 1 and “No” is scored as 0 point. Answer “Yes” to the remaining questions is scored as 0 whereas” No” is scored as 1 point. The first, second and sixth questions reflect the motivation status of the patients. If the score is above 1 to those mentioned questions, it is interpreted as “patient is motivated”. If the total score is less than one, it

is interpreted as “the patient is not motivated to the treatment”. The third, fourth and sixth questions reflect the knowledge about the medication that is received. If the total score of the responses to those questions are above 1, that means patient has adequate knowledge whereas score below 1 means the patient does not have adequate knowledge.

The patients were also questioned whether or not they experience drug related anxiety (calcium supplements and active vitamin D). It was also asked if they ever pause using the medications and frequency was questioned if the answer was “yes”.

The demographic data of the patients such as age, sex, education level, marital status, occupation and comorbid chronic conditions, duration of hypoparathyroidism, presence of thyroid malignancy, presence of neuropsychiatric disturbance, renal stone, concomitant thyroid malignancy, presence of disease related hospitalization or emergency admittance were recorded.

## Statistical Analysis

Statistical analyses were performed using SPSS version 17 (SPSS Inc. Chicago, IL, USA). Continuous variables were presented as mean  $\pm$  SD or median (min-max) where appropriate. Normality of distribution was tested by Shapiro Wilkins test. Descriptive analysis was presented as mean  $\pm$  SD or median (min-max) where appropriate. Categorical variables were demonstrated as percentage and numbers. The Mann Whitney U Test was used to compare differences between two independent groups for the continuous variables whereas Kruskal Wallis was used to compare more than two groups. Fisher's exact test or binomial test was used to determine if there were nonrandom associations between two categorical variables. Motivation and knowledge scores and drug compliance were compared with Wilcoxon signed rank test. The correlation of disease duration with knowledge and motivation scores were assessed by Spearman correlation test.  $P < 0.005$  was accepted as statistically significant.

## Results

A total of 64 patients were enrolled. Twelve patients were male, fifty-two were female and the mean age was  $48.6 \pm 11.6$  years. Median disease duration defined as the time interval between disease diagnosis and the last clinical visit was 60 months (min-max; 12-295 months). Mean elemental calcium replacement dosage was  $1388 \pm 897.92$  mg whereas mean calcitriol dosage was  $0.61 \pm 0.39$   $\mu$ g. Emergency admittance history due to hypocalcemia symptoms was present in 26.6% of the patients. The demographic data of the patients was shown on Table 1. Fifty nine percent ( $n=38$ ) of the patients reported anxiety due to possible side effects of calcium supplements. The percentage of patients who take time off the calcium treatment due to anxiety was 15.6% ( $n=10$ ). The percentage of patients who experience anxiety due to active vitamin D side effects was 13.3% ( $n=8$ ). Nobody gave a break to active vitamin D because of the side effect anxiety (Table 2). Education level did not affect the drug compliance (Table 3). Regarding to the histopathology reports, the patients with a concomitant thyroid malignancy had similar motivation and information scores for oral calcium and calcitriol compared to ones without concomitant

thyroid malignancy (Table 4). The median motivation score for calcium treatment was lower than calcitriol treatment ( $p < 0.001$ ) whereas distribution of patients in two different motivation groups were similar for calcium and calcitriol treatments. There was no difference regarding the drug acknowledgement scores /degrees for calcium and calcitriol ( $p = 0.097$  and  $0.007$ , respectively). The rate of drug incompliance was higher for calcium than it is for calcitriol ( $p = 0.002$ ) (Table 5). There was no significant correlation between emergency admittance and calcium/ calcitriol motivation scores and acknowledgement scores (Supp Table 1).

**Table1. Demographic and clinical data of the patients (n=64)**

<b>Age years (mean)</b>	48.6±11.6
<b>Sex</b>	
<i>Male</i>	12 (18.8%)
<i>Female</i>	52 (81.2%)
<b>Education level</b>	
<i>Primary</i>	35 (%54.7)
<i>Secondary</i>	7 (%10.9)
<i>High</i>	9 (%14.1)
<i>University</i>	13 (%20.3)
<b>Marital status</b>	
<i>Married</i>	53 (82.8)
<i>Single</i>	6 (%9.4)
<i>Widow</i>	5 (%7.8)
<b>Occupation</b>	
<i>Actively working</i>	13 (20.3%)
<i>Not working</i>	41 (64.1%)
<i>Retired</i>	10 (15.6%)
<b>HypoPT Duration (months)</b>	60 (7-395%)
<b>DM</b>	4 (6.3%)
<b>HT</b>	16 (25.0%)
<b>Neuropsychiatric disease</b>	13 (20.3%)
<b>Renal Stone</b>	13 (20.3%)
<b>Malignancy</b>	39 (60.9%)
<b>Hospitalization due to hypoPT</b>	1 (1.6%)
<b>Emergency admittance</b>	17 (26.6%)

DM: Diabetes Mellitus, HT: Hypertension, hypoPT: Hypoparathyroidism

Table 2  
Descriptives of drug anxiety and compliance status (n=64)

<b>Calcium side effect anxiety</b>	
<i>Present</i>	38 (59.4%)
<i>Not present</i>	26 (40.6%)
<b>Giving off the drug due to anxiety</b>	
<i>Yes</i>	10 (15.6%)
<i>No</i>	54 (84.4%)
<b>Frequency of giving off Calcium tablets</b>	
<i>Always</i>	3 (4.7%)
<i>Frequently</i>	3 (4.7%)
<i>Sometimes</i>	3 (4.7%)
<i>Rarely</i>	25 (39.1%)
<i>Never</i>	30 (46.9%)
<b>Active vitamin D side effect anxiety</b>	
<i>Present</i>	8 (13.3%)
<i>Not present</i>	52 (86.7%)
<b>Frequency of giving off active vitamin D tablets</b>	
<i>Frequently</i>	1 (1.5%)
<i>Sometimes</i>	16 (26.7%)
<i>Very rare</i>	43 (71.7%)
<b>Using the drugs lower than the recommended dosage</b>	
<i>Yes</i>	21 (32.8%)
<i>No</i>	43 (67.2%)

Table 3  
Ca and active vitamin D treatment motivation to and knowledge scores regarding to education levels of the patients (n=64)

	Primary	Secondary	High school	University	p-value
<b>Ca motivation score</b>	2 (0-3)	3 (1-3)	3 (2-3)	2 (0-3)	0,198†
<b>Ca motivation level</b>					0,151‡
<i>Low</i>	10 (30.3%)	2 (28.6%)	0 (0.0%)	4 (30.8%)	
<i>High</i>	23 (69.7%)	5 (71.4%)	8 (100.0%)	9 (69.2%)	
<b>Ca knowledge score</b>	2 (0-3)	2 (1-3)	2 (2-3)	2 (1-3)	0.314†
<b>Ca knowledge level</b>					0.178‡
<i>Low</i>	9 (27.3%)	1 (14.3%)	0 (0.0%)	2 (15.4%)	
<i>High</i>	24 (72.7%)	6 (85.7%)	8 (100.0%)	11 (84.6%)	
<b>Active Vitamin D motivation score</b>	3 (1-3)	3 (2-3)	3 (2-3)	3 (2-3)	0.109†
<b>Active Vitamin D motivation level</b>					0.056‡
<i>Low</i>	8 (24.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
<i>High</i>	25 (75.8%)	7 (100.0%)	9 (100.0%)	11 (100.0%)	
<b>Active Vitamin D knowledge score</b>	2 (0-3)	2 (2-3)	2 (2-3)	2 (2-3)	0,130†
<b>Active Vitamin D knowledge level</b>					
<i>Low</i>	4 (12.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0,171‡
<i>High</i>	29 (87.9%)	7 (100.0%)	9 (100.0%)	11 (100.0%)	
† Wilcoxon sign test, ‡ McNemar test, Ca: Calcium					

Table 4  
 Motivation and knowledge scores to/about Ca and active vitamin D treatments  
 regarding to concomittant thyroid malignancy (n=64)

	<b>Malignancy (-)</b>	<b>Malignancy (+)</b>	<b>p-value</b>
<b>Ca motivation score</b>	2 (0-3)	2 (0-3)	0.802†
<b>Ca motivation level</b>			
<i>low</i>	6 (25.0%)	10 (27.0%)	>0.999‡
<i>High</i>	18 (75.0%)	27 (73.0%)	
<b>Ca knowledge score</b>	0 (0-3)	2 (0-3)	0.597†
<b>Ca knowledge level</b>			
<i>Low</i>	5 (20.8%)	7 (18.9%)	>0.999¶
<i>High</i>	19 (79.2%)	30 (81.1%)	
<b>Active Vitamin D motivation score</b>	3 (1-3)	3 (1-3)	0.133†
<b>Active Vitamin D motivation level</b>			
<i>Low</i>	2 (8.7%)	6 (16.2%)	0.698¶
<i>High</i>	21 (91.3%)	31 (83.8%)	
<b>Active Vitamin D knowledge score</b>	2 (1-3)	2 (0-3)	0.955†
<b>Active Vitamin D knowledge level</b>			
<i>Low</i>	2 (8.7%)	2 (5.4%)	0.634¶
<i>High</i>	21 (91.3%)	35 (94.6%)	
† Wilcoxon sign test, ‡ McNemar test, Ca: Calcium			

Table 5  
Comparison of motivation/acknowledgement scores of Ca and Vitamin D

	CaCO <sub>3</sub>	Vitamin D	p-value
<b>Motivation score</b>	2 (0-3)	3 (1-3)	<b>&lt;0.001†</b>
<b>Motivation level</b>			0.070‡
<i>Low</i>	14 (24.6%)	8 (14.0%)	
<i>High</i>	43 (75.4%)	49 (86.0%)	
<b>Knowledge score</b>	2 (0-3)	2 (0-3)	0.097†
<b>Knowledge level</b>			0.070‡
<i>Low</i>	10 (17.5%)	4 (7.0%)	
<i>High</i>	47 (82.5%)	53 (93.0%)	
<b>Incompliance to the drug</b>			<b>0,002†</b>
<i>Always</i>	3 (%5,0)	-	
<i>Frequently</i>	2 (%3,3)	1 (%1,7)	
<i>Sometimes</i>	3 (%5,0)	-	
<i>Rarely</i>	23 (%38,3)	16 (%26,7)	
<i>Never</i>	29 (%48,3)	43 (%71,7)	
† Wilcoxon sign test, ‡ McNemar test, Ca: Calcium,			
Bold values denote statistical significance at the p < 0.05 level.			

The most common worry about calcium usage was nephrotoxicity that was present in 55.2% (n=21) of the patients. Anxiety about the gastrointestinal side effects of calcium was present in 26.3% (n=11). The most common worry about calcitriol reported by the patients were kidney damage and polyuria (50%). One third (33%) of the patients were taking oral calcium and calcitriol less than the prescribed and recommended dose whereas 67% were taking them as advised. The calcium motivation score was reversely correlated with disease duration (r= -0.256 and p=0.046). the 22 %(n=14) reported that calcium prepartate had a nice taste whereas 53% (n=43) reported a bitter taste. Sixteen patients (25%) reported a neutral taste.

## Discussion

Evaluation of adherence to oral medications in permanent hypoPT patients is extremely important for preventing hypocalcemia related symptoms without causing side effects such as nephrocalcinosis. There is no previous study in the literature evaluating the drug compliance and related factors in patients with

hypoPT. The quality of life evaluated with “Short Form 36 and Hospital Anxiety and Depression scale” was reported to be lower in hypoPT patients due to lifelong treatment burden of medications, need for hospitalizations or frequent visits and fluctuating serum Ca levels [14]. Post-surgical hypoPT was also found to be correlated with lower quality of life scores compared with other hypoPT subtypes in that study. Despite calcium and active vitamin D replacement, some patients may still experience physical and emotional symptoms regardless of the serum Ca level since parathyroid hormone receptors are distributed in central nervous system and muscle tissues [15].

In this study, the emergency admittance because of hypoPT or its complications was found 26.6% of the patients. In a previous study 42 of 120 patients (33%) had at least one hypoPT related emergency admittance after diagnosis [16]. The lower rate of disease related emergencies in our patient group may be related to younger age compared with the mentioned study. Most common hypo PT symptom was muscle weakness in the previous studies. Sikjaer et al reported that muscle functions are affected more severely in patients with concomitant hypothyroidism and hypo PT compared to hypo PT alone and control groups [17].

In this study prevalence of psychiatric diseases (depression and anxiety disorders) in hypo PT patients was 20.3%. Like our study, previous reports suggested more prevalent anxiety, phobia and depression compared to control group despite keeping the calcium levels in the normal range [18, 19]. In a cohort of patients in Denmark, hospitalization due to depression, bipolar disorder and infections were higher in hypoPT patients compared to controls [20]. In our study almost 60% of patients had worries about calcium carbonate side effects and 13.3% had worries about calcitriol adverse effects. The most common source of anxiety was giving harm to kidneys or gastrointestinal disturbances such as bloating and constipation. Twenty percent of our study group had history of nephrolithiasis.

To our knowledge there is scarce indeed no study in the literature evaluating drug compliance in post-surgical hypo PT patients. Compliance to calcium and vitamin D replacement was previously studied in patients with osteoporosis [21, 22]. But those patient populations are different from ours regarding the advanced age and significant female predominance. In a previous study, using Morisky-Green test, osteoporosis patients detected to have poor compliance to calcium and vitamin D. The major determinants of drug incompliance were reported to be memory problems and high costs [23]. In our patient group all patients had social health security covering the costs so the major reason of incompliance was thought to be side effects. In a study by Branco et al only two of every ten patients who received a prescription for Ca and vitamin D persisted and complied properly with the treatment 1 year after beginning it [24]. The possible explanations for incompliance included the presence of psychiatric disorders, cognitive impairment, provider-patient relationship, complexity of treatment, and barriers to care. Physician’s attitude was reported to be an important factor to increase the awareness of the patients about the benefits of the treatment and risks of giving drug holidays. In a previous study it was shown that specific activities aimed to strengthen motivation of the patients as scheduling periodic follow-up visits every 6 months seem ed to increase the adherence to calcium and vitamin D

supplementations after only 6 months [25]. In that study drug adherence was correlated with age as the younger had more compliance in contrast to our study result

In our study the motivation and knowledge about the drugs and adherence level was higher compared to previous ones conducted in different patient populations. That might be due to the highly selected group of individuals in this study who admitted to a tertiary endocrine center with postoperative hypoparathyroidism. The major determinant of non-compliance was disease duration which can be explained by patient exhaustion. We can't draw direct conclusions from the previous reports since they were conducted in osteoporotic patients in whom drug adherence is not as vital as in hypo PT. Motivation score is lower for calcium than calcitriol in this study possibly because of the larger and tablet sizes and the bitter taste.

Our study is the first one evaluating drug compliance and factors affecting it in post-surgical hypo PT. The limitation is the small number of patients and lack of laboratory data reflecting the disease control status.

In conclusion, one third of patients in our study lack motivation to use calcium whereas half of the patients' experiences anxiety about drug related side effects. Drug motivation further decrease as the disease duration increase. This is a preliminary study showing that vital calcium and active vitamin D intake may be interrupted due to side effect anxiety and motivation can be increased by frequent visits and acknowledging the patient about the deleterious effects of drug withdrawal.

## Declarations

**Funding** No funding was received for conducting this study.

**Conflict of interest** Muhammet Cuneyt Bilginer, Cevdet Aydin, Burcak Polat, Sevgul Faki, Oya Topaloglu, Reyhan Ersoy and Bekir Cakir declare that they have no conflict of interest. The authors declare no competing financial interests

**Ethical approval** The study protocol was approved Ankara Ataturk Education and Research Hospital and complied with the principles of the Declaration of Helsinki

**Consent for publication** Patients signed informed consent regarding publishing their data.

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