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ORIGINAL ARTICLE

Assessment of calcium and vitamin D medications adherence in patients with hypoparathyroidism after thyroidectomy

Muhammet Cuneyt Bilginer[1] · Cevdet Aydin[2] · Burcak Polat[2] · Sevgul Faki[3] · Oya Topaloglu[2] · Reyhan Ersoy[2] · Bekir Cakir[2]

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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 fifth 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±11.6 years) who had post-operative hypoparathyroidism were included in our study. Median disease durance 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.

Keywords Hypoparathyroidism · Calcium · Vitamin D · Medications adherence · Patient compliance

✉ Muhammet Cuneyt Bilginer
cuneytbilginer@hotmail.com

Cevdet Aydin
cevdetaydin68@hotmail.com

Burcak Polat
burcakugurlu@gmail.com

Sevgul Faki
black_snowtr@yahoo.com

Oya Topaloglu
oyasude@gmail.com

Reyhan Ersoy
reyhanersoy@yahoo.com

Bekir Cakir
drcakir@yahoo.com

[1] Faculty of Medicine, Department of Endocrinology and Metabolism, Karadeniz Technical University, Trabzon, Turkey

[2] Faculty of Medicine, Department of Endocrinology and Metabolism, Ankara Yıldırım Beyazıt University, Ankara, Turkey

[3] Department of Endocrinology and Metabolism, University of Health Sciences Turkey, Ankara City Hospital, Ankara, Turkey

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Introduction

Hypoparathyroidism (HypoPT) is defined as dysfunctional production and/or secretion of parathormone (PTH) by the parathyroid glands. It is characterized by 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 to 6.6% [1]. However, incidences as high as 20% have been reported depending on surgery extension and complexity. HypoPT is called "persistent" or "chronic" if it lasts longer than 6 months to 1 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 mg^2/dL^2 (4.4 mmol/L); (4) to avoid hypercalciuria; (5) to avoid hypercalcemia; and (6) to avoid renal (nephrocalcinosis/nephrolithiasis) and other extraskeletal 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 ($CaCO_3$). It should be taken with meals and its absorption depends on gastric acidity. Particular food can increase or decrease absorption and bioavailability of the mineral. $CaCO_3$ can cause gastrointestinal side effects such as bloating or constipation [6]. Calcium citrate is more expensive and requires a greater number of tablets because of its lower elemental Ca content. Activated 1 α hydroxylated vitamin D analogs are also essential for Ca absorption, with most commonly used forms 1,25 dihydroxy vitamin D (calcitriol) and 1α calcidiol. The short half-life of calcitriol mandates twice-daily administration. Recombinant PTH (1-84) is another option in cases in which 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 to calcium fluctuation. Compliance with that lifelong medical therapy is difficult in-patient terms. To our knowledge, there is no data in the literature about 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 post-surgical 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 1 year after operation. After recording medical history and making physical examination, the patients were requested to fill the form of "Medication Adherence Questionnaire" (MAQ) [11–13]. The endocrinologist accompanied each patient while filling out the form and explained each question one by one. MAQ was previously translated into our language by a professional then confirmed and validated by three separate researchers [14]. This questionnaire includes six questions. The first question asks if the patient forgets to take the medication. The second question asks if the patient takes the medication on time. The third question asks if the patient skips the medication when he/she feels well. The fourth question asks if the patient experiences adverse effects which he/she relates with the medication leading to incompliance. The fifth question asks if the patient knows the benefits of the medication, and lastly, the 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 questions 2 and five is scored as 1 and "No" is scored as 0 point. The 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 fifth questions reflect the knowledge about the medication that is received. If the total score of the responses to those questions is above 1, that means the patient has adequate knowledge, whereas the 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). They were 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, durance 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). The data for continuous variables were expressed as mean ± SD or as ranges. Normality of distribution was tested by the Saphira Wilkins test. Descriptive analysis was presented as mean ±SD or median (min–max) where appropriate. Categorical variables were demonstrated as the percentage and numbers. The Mann–Whitney *U* test was used to compare differences between two independent groups for the continuous variables whereas the Kruskal–Wallis was used to compare more than two groups. Fisher's exact test or binominal 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's signed-rank test. The correlation of disease durance with knowledge and motivation scores was assessed by Spearman's 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± 11.6 years. Median disease durance defined as the time interval between disease diagnosis and the last clinical visit was 60 months (min–max: 12–295 months). The mean elemental calcium replacement dosage was 1388± 897.92 mg, whereas the mean calcitriol dosage was 0.61± 0.39 µg. Emergency admittance history due to hypocalcemia symptoms was present in 26.6% of the patients. The percentage of the patients who were admitted to the ER due to symptoms of hypocalcemia and needed parenteral calcium infusion was 26.6% whereas 1.6% of those could not be discharged from ER and needed prolonged hospitalization in the endocrinology ward. The demographic data of the patients is shown in 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 the histopathology reports, the patients with a concomitant thyroid malignancy had similar motivation and information scores for oral calcium and calcitriol compared to the ones without concomitant thyroid malignancy (Table 4). The median motivation score for calcium treatment was lower than calcitriol treatment (p<0.001), whereas the distribution of patients in two different motivation groups was 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).

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 was 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).

Table 1 Demographic and clinical data of the patients (n=64)

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

DM diabetes mellitus, *HT* hypertension, *HypoPT* hypoparathyroidism

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

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

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 drug compliance and related factors in patients with HypoPT. The quality of life evaluated with the "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 [15]. 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 the central nervous system and muscle tissues [16].

In this study, the emergency admittance because of HypoPT or its complications was found in 26.6% of the patients. In a previous study, 42 of 120 patients (33%) had at least one HypoPT-related emergency admittance after diagnosis [17]. The lower rate of disease-related emergencies in our patient group may be related to younger age compared with the mentioned study. The most common HypoPT symptom was muscle weakness in the previous studies. Sikjaer et al. [18] reported that muscle functions are affected more severely in patients with concomitant hypothyroidism and HypoPT compared to HypoPT alone and control groups.

In this study, the prevalence of psychiatric diseases (depression and anxiety disorders) in HypoPT patients was 20.3%. Like our study, previous reports suggested more prevalent anxiety, phobia, and depression compared to the

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

	Primary	Secondary	High school	University	*p*-value
Ca motivation score	2 (0–3)	3 (1–3)	3 (2–3)	2 (0–3)	0.198†
Ca motivation level					0.151‡
Low	10 (30.3%)	2 (28.6%)	0 (0.0%)	4 (30.8%)	
High	23 (69.7%)	5 (71.4%)	8 (100.0%)	9 (69.2%)	
Ca knowledge score	2 (0–3)	2 (1–3)	2 (2–3)	2 (1–3)	0.314†
Ca knowledge level					0.178‡
Low	9 (27.3%)	1 (14.3%)	0 (0.0%)	2 (15.4%)	
High	24 (72.7%)	6 (85.7%)	8 (100.0%)	11 (84.6%)	
Active vitamin D motivation score	3 (1–3)	3 (2–3)	3 (2–3)	3 (2–3)	0.109†
Active vitamin D motivation level					0.056‡
Low	8 (24.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
High	25 (75.8%)	7 (100.0%)	9 (100.0%)	11 (100.0%)	
Active vitamin D knowledge score	2 (0–3)	2 (2–3)	2 (2–3)	2 (2–3)	0.130†
Active vitamin D knowledge level					
Low	4 (12.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.171‡
High	29 (87.9%)	7 (100.0%)	9 (100.0%)	11 (100.0%)	

†Wilcoxon's signed-rank test; ‡McNemar's test; *Ca* calcium

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

	Malignancy (-)	Malignancy (+)	*p*-value
Ca motivation score	2 (0–3)	2 (0–3)	0.802†
Ca motivation level			
Low	6 (25.0%)	10 (27.0%)	>0.999‡
High	18 (75.0%)	27 (73.0%)	
Ca knowledge score	0 (0–3)	2 (0–3)	0.597†
Ca knowledge level			
Low	5 (20.8%)	7 (18.9%)	>0.999¶
High	19 (79.2%)	30 (81.1%)	
Active vitamin D motivation score	3 (1–3)	3 (1–3)	0.133†
Active vitamin D motivation level			
Low	2 (8.7%)	6 (16.2%)	0.698¶
High	21 (91.3%)	31 (83.8%)	
Active vitamin D knowledge score	2 (1–3)	2 (0–3)	0.955†
Active vitamin D knowledge level			
Low	2 (8.7%)	2 (5.4%)	0.634¶
High	21 (91.3%)	35 (94.6%)	

†Wilcoxon's signed-rank test; ‡McNemar's test; *Ca* calcium

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

	$CaCO_3$	Vitamin D	*p*-value
Motivation score	2 (0–3)	3 (1–3)	**<0.001**†
Motivation level			0.070‡
Low	14 (24.6%)	8 (14.0%)	
High	43 (75.4%)	49 (86.0%)	
Knowledge score	2 (0–3)	2 (0–3)	0.097†
Knowledge level			0.070‡
Low	10 (17.5%)	4 (7.0%)	
High	47 (82.5%)	53 (93.0%)	
Incompliance to the drug			**0.002**†
Always	3 (5.0%)	-	
Frequently	2 (3.3%)	1 (1.7%)	
Sometimes	3 (5.0%)	-	
Rarely	23 (38.3%)	16 (26.7%)	
Never	29 (48.3%)	43 (71.7%)	

†Wilcoxon's signed-rank test; ‡McNemar's test; *Ca* calcium

Bold values denote statistical significance at the $p < 0.05$ level

control group despite keeping the calcium levels in the normal range [19, 20]. In a cohort of patients in Denmark, hospitalization due to depression, bipolar disorder, and infections was higher in HypoPT patients compared to controls [21]. 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 a history of nephrolithiasis.

To our knowledge, there is scarce to no study in the literature evaluating drug compliance in post-surgical HypoPT patients. Compliance with calcium and vitamin D replacement was previously studied in patients with osteoporosis [22, 23]. But those patient populations are different from ours regarding the advanced age and significant female predominance. In a previous study, using the Morisky–Green test, osteoporosis patients were 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 [24]. In our patient group, all patients had social health security covering the costs so the major reason for incompliance was thought to be side effects. In a study by Castelo-Branco et al. [24], 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. 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 the motivation of the patients as scheduling periodic follow-up visits every 6 months seemed to increase the adherence to calcium and vitamin D supplementations after only 6 months [26]. In that study, drug adherence was correlated with age as the youngers had more compliance in contrast to our study result.

In our study, the motivation and knowledge about the drugs and adherence level were 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 were admitted to a tertiary endocrine center with post-operative hypoparathyroidism. The major determinant of incompliance was disease duration which can be explained by patient exhaustion. We cannot draw direct conclusions from the previous reports since they were conducted in osteoporotic patients in whom drug adherence is not as vital as in HypoPT. 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 HypoPT. The main limitation is the small number of patients and lack of laboratory data reflecting the disease control status. Another limitation is that social desirability response bias may impact the results because the questionnaire was administered in the presence of the treating physician.

In conclusion, one-third of patients in our study lack the motivation to use calcium, whereas half of the patients experiences anxiety about drug-related side effects. Drug motivation further decreases 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. In the light of those findings, we suggest that motivation can be increased by frequent visits and acknowledging and assuring the patient about the safety and benefit of those medications and the deleterious effects of drug withdrawal.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11657-022-01066-0.

Declarations

Ethical approval The study protocol was approved by 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.

Conflicts of interest None.

References

1. Bilezikian JP, Khan A, Potts JT Jr (2009) Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the Third International Workshop. J Clin Endocrinol Metab. 94:335–339. https://doi.org/10.1210/jc.2008-1763
2. Powers J, Joy K, Ruscio A, Lagast H (2013) Prevalence and incidence of hypoparathyroidism in the United States using a large claims database. J Bone Miner Res. 28(12):2570–6. https://doi.org/10.1002/jbmr.2004
3. Marx SJ (2000) Hyperparathyroid and hypoparathyroid disorders. New Engl J Med. 343:1863–1875. https://doi.org/10.1056/NEJM200012213432508
4. Brandi ML, Bilezikian JP, Shoback D, Bouillon R, Clarke BL, Thakker RV, Khan AA, Potts JT Jr (2016) Management of hypoparathyroidism: summary statement and guidelines. J Clin Endocrinol Metab. 101(6):2273–83. https://doi.org/10.1210/jc.2015-3907
5. Bollerslev J, Rejnmark L, Marcocci C, Shoback DM, Sitges-Serra A, van Biesen W, Dekkers OM (2015). European Society of Endocrinology. European Society of Endocrinology Clinical Guideline: Treatment of chronic hypoparathyroidism in adults. Eur J Endocrinol. 173(2):G1–G20 https://doi.org/10.1530/EJE-15-0628
6. Bilezikian JP, Brandi ML, Cusano NE, Mannstadt M, Rejnmark L, Rizzoli R, Rubin MR, Winer KK, Liberman UA, Potts JT Jr (2016) Management of hypoparathyroidism: present and future. J Clin Endocrinol Metab. 101(6):2313–24. https://doi.org/10.1210/jc.2015-3910
7. Lakatos P, Bajnok L, Lagast H, Valkusz Z (2016) An open-label extensıon study of parathyroid hormone rhPTH(1–84) in adults with hypoparathyroidism. Endocr Pract. 22(5):523–32. https://doi.org/10.4158/EP15936.OR
8. Winer KK, Yanovski JA, Cutler GB Jr (1996) Synthetic human-parathyroid hormone 1–34 vs calcitriol and calcium in the treatment of hypoparathyroidism. JAMA. 276:631–636
9. Mitchell DB, Regan S, Cooley MR, Lauter KB, VrlaMc Becker CB, Burnett-Bowie SAM, Mannstadt M (2012) Long-term follow-up of patients with hypoparathyroidism. J Clin Endocrinol Metab. 97:4507–4514. https://doi.org/10.1210/jc.2012-1808
10. Case Management Society of America (CMSA) (2006) CMAG: Case management adherence guidelines. Guidelines from the Case Management Society of America for improving patient adherence to medication therapies. Version 2.0. Available at: http://www.cmsa.org/portals/0/pdf/ CMAG2. pdf. Accessed Dec 16, 2016
11. Morisky DE, Green LW, Levine DM (1986) Concurrent and predictive validity of a self-reported measure of medication adherence. Med Care. 24(1):67–74
12. Morisky DE, Levine DM, Green LW, Shapiro S, Russell RP, Smith CR (1983) Five-year blood pressure control and mortality following health education for hypertensive patients. Am J Public Health. 73(2):153–162
13. Son NE, Taskiran B, Yorulmaz G, Son O, Kokoglu B, Bilgin M, Bilge U (2017) Relationship between the 6-item Morisky Medication Adherence Scale (MMAS-6) score and glycemic control in a Turkish population with type 2 diabetes mellitus. Acta Med Mediterr. 33(6):921–928
14. Vural B, Teberru Acar Ö, Topsever P, Filiz TM (2012) Modifiye Morisky Ölçeğinin Türkçe geçerlilik güvenilirlik çalışması. Turk Fam Physician. 3(4):17–20
15. Astor MC, Løvås K, Debowska A, Eriksen EF, Evang JA, Fossum C, Fougner KJ, Holte SE, Lima K, Moe RB, Myhre AG, Kemp EH, Nedrebø BG, Svartberg J, Husebye ES (2016) Epidemiology and health-related quality of life in hypoparathyroidism in Norway. J Clin Endocrinol Metab. 101(8):3045–53. https://doi.org/10.1210/jc.2016-1477
16 Büttner M, Musholt TJ, Singer S (2017) Quality of life in patients with hypoparathyroidism receiving standard treatment: a systematic review. Endocrine. 58(1):14–20. https://doi.org/10.1007/s12020-017-1377-3
17 Mitchell DM, Regan S, Cooley MR, Lauter KB, Vrla MC, Becker CB, Burnett-Bowie SA, Mannstadt M (2012) Long-term follow-up of patients with hypoparathyroidism. J Clin Endocrinol Metab. 97(12):4507–14. https://doi.org/10.1210/jc.2012-1808
18 Sikjaer T, Moser E, Rolighed L, Underbjerg L, Bislev LS, Mosekilde L, Rejnmark L (2016) Concurrent hypoparathyroidism ıs associated with ımpaired physical functionand quality of life in hypothyroidism. J Bone MinerRes. 31(7):1440–8. https://doi.org/10.1002/jbmr.2812

19. Arlt W, Fremerey C, Callies F, Reincke M, Schneider P, Timmermann W, Allolio B (2002) Well-being, mood and calcium homeostasis in patients with hypoparathyroidism receiving standard treatment with calcium and vitamin D. Eur J Endocrinol. 146(2):215–22. https://doi.org/10.1530/eje.0.1460215
20. Khan AA, Koch C, Van Uum SHM et al (2018) Standards of care for hypoparathyroidism in adults. Eur J Endocrinol. 180(3):P1–P22. https://doi.org/10.1530/EJE-18-0609
21 Underbjerg L, Sikjaer T, Mosekilde L, Rejnmark L (2014) Postsurgical hypoparathyroidism–risk of fractures, psychiatric diseases, cancer, cataract, and infections. J Bone Miner Res. 29(11):2504–10. https://doi.org/10.1002/jbmr.2273
22. Touskova T, Vytrisalova M, Palicka V, Hendrychova T, Chen YT, Fuksa L (2016) Patterns of non-adherence to supplementation with calcium and vitamin D in persistent postmenopausal women are similar at start and 1 year later: a qualitative longitudinal study. Front Pharmacol. 7:339. https://doi.org/10.3389/fphar.2016.00339
23. Maksimovic Marina, Jurisic Vladimir, Erdeljan Biljana, Dojcinovic Dragana (2017) The evaluation of the adherence to calcium, vitamin D and drugs for osteoporosis in patients with low bone mineral density. Srp Arh Celok Lek. 145:41–41. https://doi.org/10.2298/SARH160524041M
24 Castelo-Branco C, Cortés X, Ferrer M, UNICAD study investigators, (2010) Treatment persistence and compliance with a combination of calcium and vitamin D. Climacteric. 13(6):578–84. https://doi.org/10.3109/13697130903452804
25. Conti F, Piscitelli P, Italiano G, Parma A, Caffetti MC, Giolli L, Di Tanna GL, Guazzini A, Brandi ML (2012) Adherence to calcium and vitamin d supplementations: results from the ADVICE Survey. Clin Cases Miner Bone Metab. 9(3):157–60
26 Kothawala P, Badamgarav E, Ryu S, Miller RM, Halbert RJ (2007) Systematic review and meta-analysis of real-world adherence to drug therapy for osteoporosis. Mayo Clin Proc. 82(12):1493–501. https://doi.org/10.1016/S0025-6196(11)61093-8