Research Article

The Relationship Between Depressive Symptoms and Treatment Adherence in Patients With Hypoparathyroidism

Kronik Hipoparatiroidizm hastalarında depresif belirtiler ve tedaviye uyum arasındaki ilişki

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ABSTRACT

Aims: Hypoparathyroidism (HPT) is a chronic disease characterized by low calcium levels and significant psychological and physical complications. The aim of this study was to investigate the relationship between depressive symptoms and treatment adherence in patients with HPT.

Materials and Methods: This cross-sectional, observational study included patients with chronic HPT from the endocrinology clinic of a tertiary care hospital. Adults receiving oral calcium and active vitamin D therapy, who volunteered to complete the Beck Depression Inventory (BDI), and who did not have any mental disability or concomitant chronic serious disease were included. Biochemical and complication data were collected, and treatment adherence was assessed on the basis of self-reported medication use.

Results: Of the 33 patients (mean age 53.7 ± 12.7 years; 78.8% female), 54.5% were non-adherent to treatment. Depressive symptoms ranged from minimal to severe, with 24.3% experiencing moderate to severe symptoms. A significant association was found between HPT etiology and depressive symptom severity ($p = 0.011$), with moderate symptoms more common in post-operative patients (34.8% vs. 0% in non-surgical cases). A weak negative correlation was observed between depressive symptom scores and highest calcium levels ($r = -0.359$, $p = 0.04$). Conclusions: This study emphasizes the importance of treatment goals by demonstrating the negative correlation between Ca levels and BDI scores. The high prevalence of depressive symptoms and non-adherence in patients with HPT underlines the need for tailored mental health and adherence interventions.

Keywords: Hypoparathyroidism, depression, hypocalcemia.

ÖZ

Amaç: Hipoparatiroidizm (HPT), düşük kalsiyum seviyeleri ve önemli psikolojik ve fiziksel komplikasyonlarla karakterize kronik bir durumdur. Bu çalışma, HPT hastalarında depresif belirtiler ile tedaviye uyum arasındaki ilişkiyi araştırmayı amaçlamıştır.

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Gereç ve Yöntemler: Bu kesitsel, gözlemsel çalışmaya, Haydarpaşa Numune Eğitim ve Araştırma Hastanesi Endokrinoloji Kliniği'nden kronik HPT'li hastalar dahil edilmiştir. Oral kalsiyum ve aktif D vitamini tedavisi alan, Beck Depresyon Ölçeği'ni (BDÖ) doldurmayı gönüllü olarak kabul eden, zihinsel engeli veya ciddi eşlik eden kronik hastalığı olmayan yetişkinler çalışmaya alınmıştır. Biyokimyasal ve komplikasyon verileri toplanmış, tedaviye uyum hastaların ilaç kullanımını kendi bildirimlerine dayalı olarak değerlendirilmiştir.

Bulgular: Otuz üç hastanın (ortalama yaş 53,7 ± 12,7 yıl; %78,8 kadın) %54,5'inde tedaviye uyumsuzluk tespit edilmiştir. Depresif belirtiler minimalden şiddetliye kadar değişiklik göstermiş, %24,3'ü orta ila şiddetli belirtiler yaşamıştır. Depresif belirti skorları ile en yüksek kalsiyum seviyeleri arasında zayıf bir negatif korelasyon bulunmuştur (r = -0,359, p = 0,04).

Sonuç: Bu çalışma, kalsiyum seviyeleri ile BDÖ skorları arasındaki negatif korelasyonu ortaya koyarak tedavi hedeflerinin önemini vurgulamaktadır. HPT hastalarında depresif belirtilerin ve tedaviye uyumsuzluğun yüksek prevalansı, ruh sağlığı ve tedavi uyumuna yönelik özel müdahalelere ihtiyaç olduğunu ortaya koymaktadır.

Anahtar Kelimeler: Hipoparatiroidizm, depresyon, tedavi uyumu.

INTRODUCTION

Hypoarathyroidism (HPT) is a rare disease characterized by low serum calcium (Ca) levels and relatively high phosphorus (P) levels due to parathormone (PTH) deficiency(1). Chronic HPT has findings that persist for more than 6 months (2). The most common cause is post-surgical HPT caused by damage to parathyroid tissue following to neck surgery, usually after thyroidectomy. Genetic mutations and autoimmune diseases are also less common causes. Chronic HPT is mostly observed in adults aged 55 years and older and is three times more common in women than in men (3).

The clinical manifestations of HPT are mostly due to hypocalcemia and most commonly include increased neuromuscular excitability (tetany) and calcification of the kidneys, brain and vascular structures. In addition to physical symptoms such as fatigue, pain, muscle spasms, and paresthesia, there may be cognitive symptoms such as "brain fog" and emotional symptoms that affect quality of life such as depression and anxiety disorders. The relationship between depression and HPT is complex and likely involving the chronic stress of disease management, neurochemical changes due to hypocalcemia, and the psychological distress of persistent physical symptoms, all of which can lead to depression (4–6).

Chronic HPT treatment is a long-term therapy. Even active vitamin D and calcium therapies included in standard replacement therapy may not be sufficient to achieve ideal serum calcium and phosphorus levels. In these patient groups, recombinant PTH therapies have emerged as an as an alternative solution (7-8). Effective management of HPT requires lifelong adherence to therapy. However, adherence is particularly challenging in these patients due to the high medication burden, frequent gastrointestinal side effects, and the long-term nature of the treatment. These factors can lead to fatigue with daily regimens and reduced motivation to maintain adherence over time. Non-adherence to

treatment increases complications, may worsen psychological outcomes (9). This study examines the relationship between depressive symptoms and treatment adherence in patients with HPT, with a focus on achieving optimal biochemical control.

MATERIALS AND METHODS

Study Design and Participants

This cross-sectional, observational study was conducted at the endocrinology clinic of a tertiary care hospital in Istanbul between March 2018 and March 2021. Adults (≥18 years) diagnosed with chronic HPT and receiving conventional treatment (oral calcium carbonate supplementation at dose of 1 to 2 g/day and calcitriol at dose of 0.25 to 1.0 mcg/day) were eligible. All patients received standardized medication counselling from the same physician throughout the study period to ensure consistency in treatment explanations and adherence guidance. Patients with significant comorbidities or those receiving recombinant PTH therapy were excluded. Patients with a previously diagnosed psychiatric disorder or those using psychiatric medications or supplements (such as antidepressants, anxiolytics, mood stabilizers, or herbal supplements with psychoactive effects) were also excluded from the study to minimize potential confounding effects on depression scores. Ethical approval (decision number: 2018-KAEK-4/37) and written informed consent were obtained from all participants.

Data Collection

Demographic characteristics, level of education,body mass index (BMI), and duration of disease were recorded. The etiology of HPT was categorized into two main groups: post-surgical HPT and other causes. Post-surgical HPT included patients who developed the condition following thyroidectomy, parathyroidectomy, or other neck surgeries. The other causes group included patients with autoimmune, genetic, idiopathic, or other non-surgical forms of HPT. Classification was based on patient history and medical records. Biochemical parameters: Ca, corrected Ca, P, magnesium (Mg), 25-OH vitamin D3, creatinine and alkaline phosphatase (ALP), collected during patients' clinical visits approximately every 3 to 6 months. To assess treatment response and variability, the lowest serum Ca and highest serum P levels observed during the entire treatment period were recorded and included in the analysis. These values were considered potential indicators of treatment failure. Blood samples were taken by venipuncture in the morning after fasting. Measurements were performed using standard autoanalyzer devices in our laboratory.

Urine was collected for 24 hours to assess urinary calcium excretion. 24-hour urine collection was performed. The first-morning urine was discarded. All subsequent urine collected over the next 24 hours in a designated container. Urinary calcium levels was measured by using atomic absorption spectrophotometry. Creatinine clearance was calculated, and the results were corrected for urine volume. Hypercalciuria was defined as urinary calcium excretion >300 mg/day (or >4 mg/kg/day for weight-based assessment). The reference ranges are as follows: Serum Ca: 8.4-10.2 mg/dL, serum P: 2.5-4.5 mg/dL, serum Mg: 1.6-2.6 mg/dL, PTH: 15-65 pg/mL, 25-OH vitamin D: 20-50 ng/mL, and creatinine: 0.6-1.2 mg/dL. Estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) equation.

HPT complications (e.g., nephrolithiasis, cataracts, fractures, etc.) were obtained from medical records. Various imaging modalities were used to assess complications associated with HPT, based on clinical indications and patient history. Renal complications, including nephrolithiasis and nephrocalcinosis, were evaluated using renal ultrasound (USG) and, if necessary, non-contrast computed tomography (CT). Skeletal complications, such as osteopenia, osteoporosis, and pathological fractures, were assessed by using dual-energy X-ray

absorptiometry (DEXA) and plain radiographs of relevant skeletal regions. Intracranial calcifications, in particular basal ganglia calcifications (BGC), were assessed by computed tomography of the brain. Extrapyramidal signs, parkinsonism or seizures were evaluated by a neurologist and considered to be cerebrovascular complications of HPT unless an alternative cause was identified. Cardiovascular complications, including vascular calcifications, were evaluated using echocardiography and vascular Doppler ultrasound when clinically indicated. Arrythmia or prolonged QT interval was noted if seen on electrocardiography. Cataract was assessed by ophthalmic examination performed by an ophthalmologist.

Assessment Tools

Treatment adherence was defined as consistent use of prescribed medication, with "non-adherence" defined as more than one missed dose per week. This definition is based on standard adherence criteria commonly used in chronic disease management, where multiple missed doses have been associated with suboptimal outcomes. This definition consistent with adherence criteria in chronic disease management (10). Depressive symptoms were assessed using the Beck Depression Inventory (BDI), a validated 21-item self-report tool (11). For patients who were illiterate or suspected of having limited intellectual capacity, the survey was administered by a physician to ensure comprehension and accurate responses. This approach aimed to minimize response bias and improve the reliability of the depression assessment. The version developed by Hisli for Turkish population was used (12). BDI scores were categorized as minimal (0-9), mild (10-16), moderate (17-29), and severe (30-63).

Statistical Analysis

A post-hoc power analysis was performed using GPower version 3.1.9.7 to assess whether the study's sample size was sufficient to detect significant differences. Power calculations were performed for parametric (Student's t-test) and non-parametric (Mann-Whitney U, Kruskal-Wallis) tests based on an expected moderate effect size (Cohen's d = 0.5 for t-tests, r = 0.3 for Mann-Whitney U, and η^2 = 0.06 for Kruskal-Wallis), a significance level of α = 0.05, and a target power of 80%.

All statistical analyses were performed using SPSS version 26 (IBM Corp., Armonk, NY, USA). Continuous variables were tested for normality using the Kolmogorov-Smirnov test. Variables with normal distribution were presented as mean ± standard deviation (SD), while non-normally distributed variables were presented as median (minimum-maximum). Categorical variables were expressed as numbers (percentages).

Comparison of treatment adherence groups (adherent vs. non-adherent) was performed using Student's t-test for normally distributed continuous variables, Mann-Whitney U test for non-normally distributed continuous variables, Fisher's exact test for categorical variables. Comparison of depressive symptom severity groups (minimal, mild, moderate, severe) based on the BDI scores was performed using: Kruskal-Wallis test for continuous variables, chi-square or linear-by-linear association test was dused to assess trends across ordered categories.

Correlations between biochemical parameters and depressive symptom scores were assessed using Spearman's rank correlation coefficient.A p-value <0.05 was considered statistically significant.

RESULTS

Power Analysis

The post-hoc power analysis showed that the study had sufficient power to detect medium-to-large effect sizes, especially for comparisons using t-tests. However, for non-parametric analyses (Mann-Whitney U, Kruskal-Wallis), the sample size may have limited the ability to detect small effect sizes.

Patient Characteristics

The study included 33 patients (mean age 53.7 ± 12.7 years; 78.8% female). The median disease duration was 9 years (IQR: 1-41), and the mean BMI was 29.3 kg/m² (range: 19.8-48.8). Treatment non-adherence was observed in 54.5% of patients, and 39.4% had at least one complication. The majority of participants were female (78.8%), and most had a primary school education level (48.5%). The proportion of illiterate patients was 21.2% (Table 1).

Table 1. Patient characteristics and biochemical profiles

Total number of patients, n		33
Age, mean (±SD)		53.70±12.72
Sex, n (%)	Female	26 (78.8)
	Male	7 (21.2)
Education, n (%)	Illiterate	7 (21.2)
	Primary	16 (48.5)
	High School	6 (18.2)
	Higher Education	4 (12.1)
BMI (kg/m^2), median (min-max)		29.3 (19.8-48.8)
Disease duration (years), median (min-max)		9 (1-41)
Etiology, n(%)	post-surgical	23 (69.7)
	other	10 (30.3)
Presence of complications, n (%)	yes	13 (39.4)
	no	20 (60.6)
Treatment adherence, n (%)	yes	15 (45.5)
	no	18 (54.5)
Serum calcium (mg/dl), mean (±SD)		8.15±0.82
	Lowest Ca	6.38±1.03
	Highest Ca**	9.4 (7.9-11.9)
Serum phosphorus (mg/dl), mean (±SD)		4.94±0.68
	Lowest P	4.09±0.67
	Highest P**	5.8 (4.3-9.6)
CaxP (mg^2/ml^2), mean (±SD)		39.17±6.08
Creatinine (mg/dl), median (min-max)		0.9 (0.6-2)
eGFR (mL/min/1.73m²), mean (±SD)		74.6 (±18.9)
Mg (mg/dl), mean (±SD)		1.74±0.17
PTH (pg/ml), median (min-max)		4.30 (0-33)
Serum 25-OH vitamin D (ng/ml), mean (±SD)		27.18±11.71
24-hour urinary Ca (mg/day), median (min-max)		159.6 (25-478)
ALP (U/l), mean (±SD)		66.27±17.73

ALP; alkalin phosphatase, **BMI**; body mass index, **eGFR**; estimated glomerular filtration rate, **PTH**; parathormone

Biochemical Data

Mean serum Ca levels were 8.15 ± 0.82 mg/dL, with a median peak of 9.4 mg/dL (range: 7.9-11.9 mg/dL). P levels showed a median peak of 5.8 mg/dL (range: 4.3-9.6 mg/dL). Patients had a mean serum Mg level of 1.74 ± 0.17 mg/dL, and a median serum PTH levels of 4.3 pg/mL (range: 0-33 pg/mL). Median 24-hour urinary calcium excretion was 159.6 mg/day (range: 25–478 mg/day). Hypercalciuria was observed in two patients (6.1%) (Table 1).

Complications

Of the patients, 60.6% reported no complications. However, 39.4% experienced one or more complications, including nephrolithiasis (18.2%), cataracts (18.2%), and infections (12.1%) (Figure 1). Cardiovascular and cerebrovascular complications were less common (9.1% and 3%, respectively).

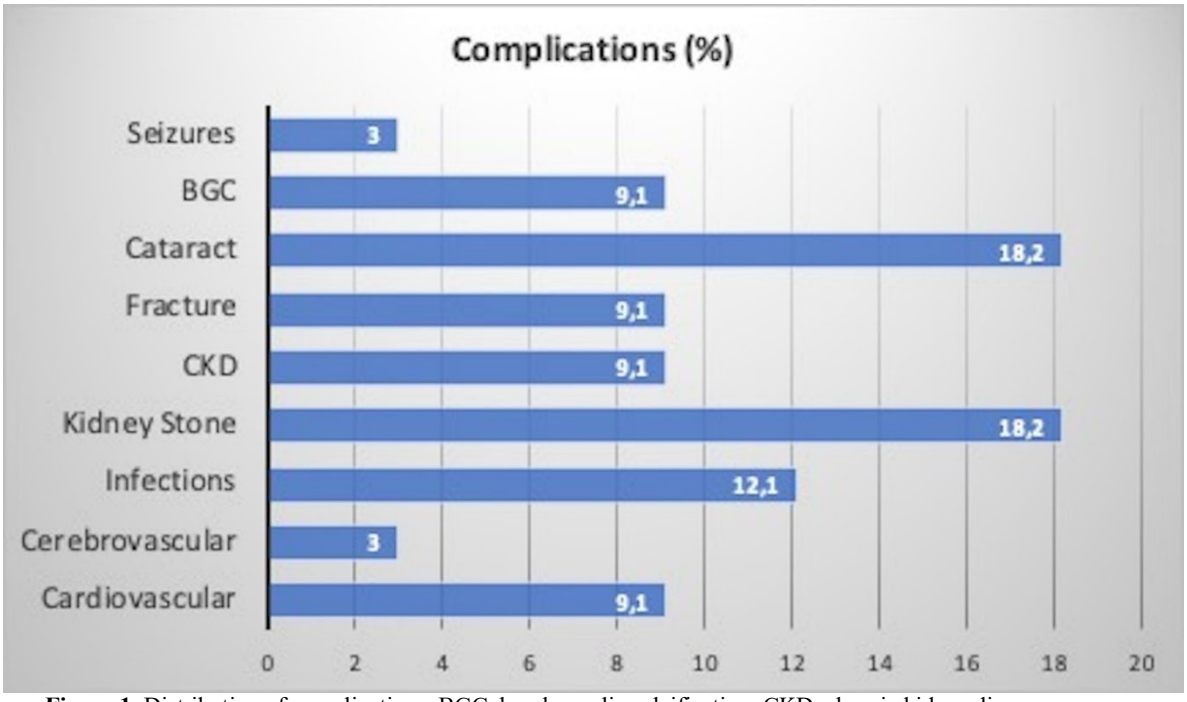

Figure 1. Distribution of complications. BGC, basal ganglia calcification; CKD, chronic kidney disease

Depressive Symptoms

The BDI scores indicated that 39.4% of patients had minimal depressive symptoms, 36.4% had mild symptoms, and 24.2% had experienced moderate to severe symptoms. Severe depressive symptoms were combined with the moderate group for statistical analysis due to the small sample size in the severe category (Figure 2).

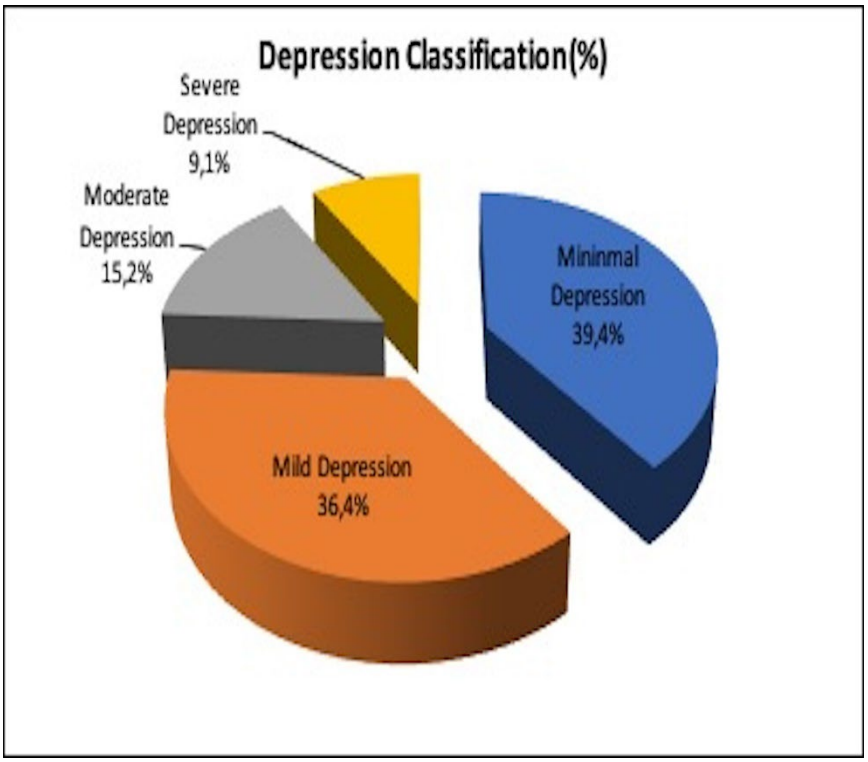

Figure 2. Depressive symptom severity classification of patients according to Beck Depression Inventory (BDI) scores

Patients with moderate-to-severe depressive symptoms (as indicated by BDI scores) were referred to a psychiatrist for further assessment. However, the effect of psychiatric interventions was not assessed in this study. No significant differences were observed between the minimal, mild, and moderate depressive symptoms groups, except for HPT etiology (Table 2).

Table 2. Comparison of patient characteristics, biochemical parameters, and presence of complications between treatment-adherent and non-adherent groups, as well as among different depressive symptom severity groups based on Beck Depression Inventory (BDI) scores [mean (standard deviation) or number (percentage)]

	Treatment Adherence		p	**BDI Score Severity**			p
	Yes (n=15)	**No (n=18)**		**Minimal (n=13)**	**Mild (n=12)**	**Moderate (n=8)**	
Age (years), mean (±SD)	56.4±7.6	51.3±15.6	[a]0.328	56.4±10.2	53.08±14.1	50.13±14.6	[c]0.385
Female, n (%)	12(80.0)	15 (83.3)	[b]1.000	9 (69.2)	10 (83.3)	8 (100)	[c]0.109
Male, n (%)	3(20.0)	3(16.7)		4 (30.8)	2 (16.7)	0 (0)	
BMI, mean (±SD)	28.98±5.7	30.63±8.6	[a]0.731	30.82±8.3	28.69±4.4	30.13±9.74	[c]0.959
Post-surgical, n (%)	11 (73.3)	12 (66.7)	[b]0.722	6 (46.1)	9 (75.0)	8 (100)	[c]0.009
Other etiology, n (%)	4 (26.6)	6 (33.3)		7 (53.9)	3 (25.0)	0 (0)	
Disease duration (years), mean (±SD)	13.40±13.8	10.11±8.3	[a]0.841	13.69±11.8	9.92±11.8	10.75±9.3	[c]0.554
Ca (mg/dl), mean (±SD)	8.14±0.70	8.17±0.93	[a]0.928	8.21±0.85	7.95±0.76	8.38±0.90	[c]0.473
P (mg/dl), mean (±SD)	4.83±0.66	5.03±0.70	[a]0.393	5.05±0.63	4.66±0.64	5.19±0.75	[c]0.133
Corrected Ca (mg/dl), mean (±SD)	8.10±0.96	7.82±0.74	[a]0.346	8.13±0.67	7.78±1.05	7.89±0.80	[c]0.471
CaxP (mg^2/dl^2), mean (±SD)	389.93±60.26	393.17±63.07	[a]0.882	407.69±39.83	362.75±68.12	409.13±68.28	[c]0.167
Creatinine (mg/dL), mean (±SD)	0.94±0.21	0.87±0.301	[a]0.480	0.99±0.36	0.86±0.08	0.81±0.26	[c]0.150
eGFR (mL/min/1.73m^2), mean (±SD)	73.4±15.9	75.8±20.7	[d]0.083	69.8±24.0	72.4±9.4	95.2±11.5	[c]0.190
Albumin (g/l), mean (±SD)	42.60±2.41	43.62±3.75	[a]0.370	42.17±3.47	44.08±2.64	43.38±3.46	[c]0.404
Mg (mg/dl), mean (±SD)	1.73±0.20	1.75±0.15	[a]0.686	1.78±0.13	1.69±0.22	1.76±0.15	[c]0.509
PTH (pg/ml), mean (±SD)	2.13±4.02	6.11±10.02	[a]0.137	4.23±9.05	4.17±5.92	4.63±9.96	[c]0.836
25-OH Vitamin D (ng/ml), mean (±SD)	26.80±8.46	27.50±14.10	[a]0.862	30.38±12.67	25.68±9.97	24.24±12.74	[c]0.475
ALP (U/l), mean (±SD)	67.93±21.6	64.89±14.24	[a]0.644	65.15±13.5	71.33±21.77	60.50±17.17	[c]0.529
Lowest Ca (mg/dl), mean (±SD)	6.35±1.28	6.40±0.81	[a]0.885	6.34±1.23	6.55±0.84	6.18±1.04	[c]0.785
Highest Ca (mg/dl), mean (±SD)	9.65±1.01	9.58±0.84	[a]0.832	9.95±0.96	9.58±0.83	9.10±0.76	[c]0.187
Lowest P (mg/dl), mean (±SD)	5.93±1.26	5.86±0.84	[a]0.058	4.38±0.58	3.73±0.76	4.19±0.39	[c]0.060
Highest P (mg/dl), mean (±SD)	3.85±0.70	4.29±0.59	[a]0.847	6.18±0.64	5.40±0.87	6.15±1.53	[c]0.072
24-h urinary Ca (mg/day), mean (±SD)	174±128	146±82	[d]0.725	162±68	174±136	102±68	[c]0.568
Presence of complications, n (%)	9 (60.0)	11 (61.1)	[b]1.000	10 (50.0)	7 (35.0)	3 (15.0)	[c]0.075
BDI score, medium (min-max)	11 (1-31)	8 (0-35)	[d]0.717	4 (0-6)	11 (10-14)	21 (18-35)	[c] <0.001
Treatment adherent, n (%)				4 (30.7)	8 (66.7)	3 (60.0)	[c]0.576
Treatment non-adherent, n(%)				9 (69.2)	3 (33.3)	5 (40.0)	

[a]Student T Test [b] Fischer's Exact Test [c] Kruskal Wallis Test, [d] Mann-Whitney U test [e] Linear-by-Linear Association

ALP; alkalin phosphatase, **BDI;** Beck Depression Inventory, **BMI**; body mass index, **eGFR**: estimated GFR**; PTH**; parathormone

A significant association was found between the severity of depression and the etiology of HPT ($p = 0.011$). Patients with post-surgical HPT had a higher proportion of moderate depressive symptoms category (34.8%), whereas none of the patients in the non-surgical group had moderate depressive symptoms. In contrast, minimal depressive symptoms were more evenly distributed between the two groups (26.1% vs. 70%). The distribution of depressive symptom levels was not significantly different between the adherent and non-adherent groups, suggesting that treatment adherence was not a major determinant of depressive symptom severity in this study population.

Adherence vs. Non-Adherence

Patients in the adherent group had a slightly longer median disease duration than those in the non-adherent group (13.4 vs. 10.1 years). There were no statistically significant differences in serum calcium, phosphorus, PTH levels or BDI scores between the adherent and non-adherent groups. Similarly, the prevalence of complications was comparable between the two groups (Table 2).

Correlations

Although no biochemical differences were observed between the groups according to BDI scores, correlation analysis between BDI scores and biochemical parameters, revealed a weak negative correlation between BDI scores and the highest recorded Ca levels ($r = -0.359$, $p = 0.04$), suggesting that lower calcium levels may be associated with higher depressive symptom scores (Figure 3).

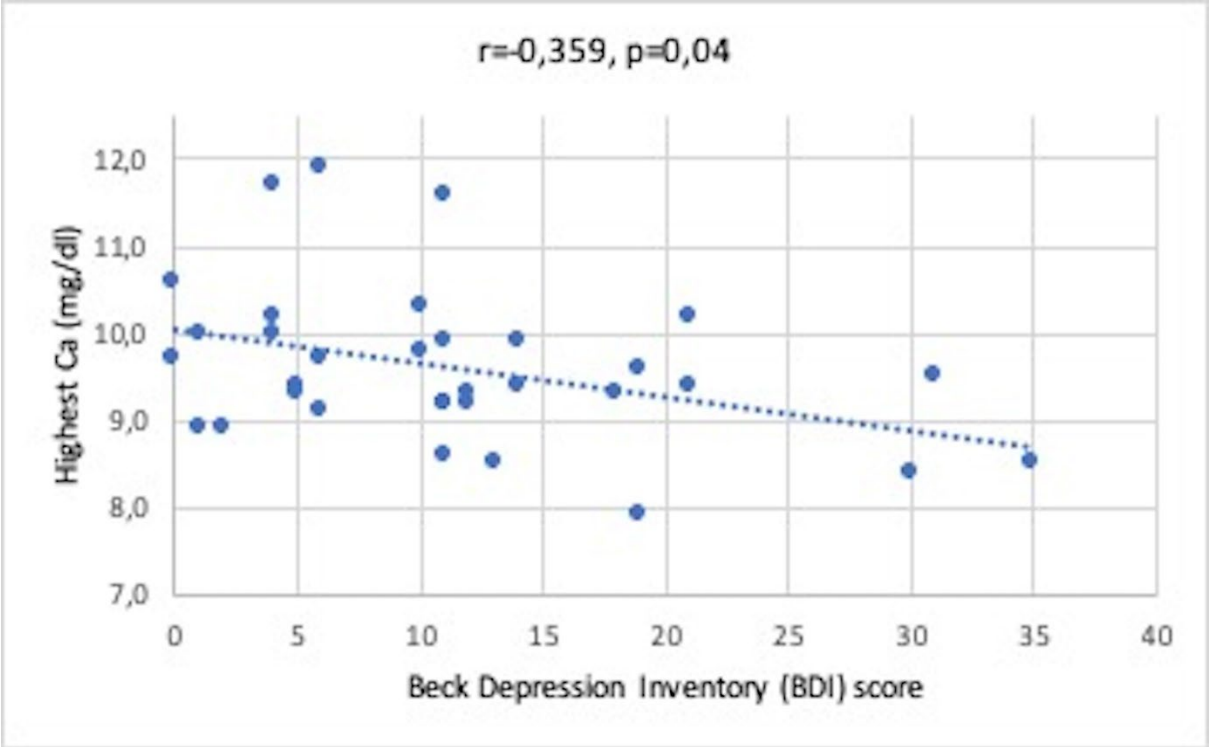

Figure 3. Negative Spearman correlation graph between Beck Depression Inventory (BDI) score and highest measured Ca value (rho=-0.359, p=0.04)

DISCUSSION

(HPT) is a chronic disease that requires long-term treatment, and its management is complicated by various factors, including patient adherence and psychological well-being. Although treatment adherence is important in achieving calcium and phosphorus target levels, Hadker et al. reported that 72% of patients had more than 10 a symptoms of hypocalcemia, despite one year of treatment (13). Anaforoğlu et al. found no difference in biochemical data and complications between HPT patient groups with and without treatment adherence (9). In our study, the complication rate was 32.4% and there was no difference in complications between the adherent and non-adherent groups.

Despite the expectations that treatment adherence would influence biochemical parameters and complication rates, no statistically significant differences were observed between the adherent and non-adherent groups. This finding may be due to the relatively small sample size of the study, the short follow-up period, and lpossible compensatory physiological mechanisms. Also, patients classified as non-adherent may have had partial adherence rather than complete treatment discontinuation. In addition, patients with severe non-adherence may have also missed follow-up visits, resulting in under-representation of true non-adherence underrepresentation of true non-adherence-related complications. This could lead to selection bias, with only partially adherent patients remaining in the study, potentially underestimating the true impact of poor adherence.

Treatment non-adherence was found to be 39.3% in the study by Anaforoglu et al. and 54.5% in our study. However, in our study, treatment non-adherence was defined as missing more than one medication per week and interview tools such as the Brief Medication Questionnaire (BMQ) and the Medication Adherence Rating Scale (MARS) which are used to assess non-adherence, were not used in this study (14-15). However, as discussed by Lieber et al. rather than using the same questionnaires for all chronic diseases to assess adherence, we suggest that the development of specific questionnaires tailored to HPT may better reveal behavioural tendencies and improve adherence assessment in future studies (10).

Patients with HPT are known to haveIt e difficulties in adhering to treatment compliance due to multiple drug use and gastrointestinal side effects (16). In addition, Büttner et al. have shown that patients diagnosed with HPT have an unmet information gap on many issues, particularly the long-term effects of the disease and treatment side effects (17). Comprehensive patient education at diagnosis and follow-up may improve adherence, although this requires further validation in prospective randomized trials. In our study all patients with HPT were treated with conventional therapies (calcium, vitamin D and active vitamin D metabolites). Recombinant PTH (1-84) therapy was introduced for the treatment of HPT after the REPLACE phase 3 trial in 2017 (18). When used in patients who do not respond to standard treatments and cannot use these treatments due to side effects, it is known to reduce the required doses of calcium and active vitamin D and improve quality of life (16).

In a multicentre study designed to evaluate the long-term effects of recombinant PTH (1-84) given as an adjunct to standard treatment for 24 weeks, Vokes et al compared quality of life measures using the Short Form-36 with a control group receiving placebo in addition to standard treatment. Although no statistically significant difference was found between the groups, the group receiving recombinant PTH showed statistically significant improvements compared to their baseline. In addition, in August 2024, the U.S Food and Drug Administration (FDA) approved the use of

palopegteriparatide, an extended-release PTH (1-34) prodrug, for chronic HPT (8). In a phase 3 trial, palopegteriparatide demonstrated maintenance of normocalcemia without conventional therapy, reduced urinary calcium, improved renal function, and quality of life in patients with chronic HPT (19). Based on these considerations, we believe that new trials on the use of PTH treatment alone should focus on its efficacy on neuropsychiatric outcome in addition to quality of life.

The exact mechanisms underlying the association between HPT and depressive symptoms remain unclear, but there are several hypotheses. One possible pathway involves the effect of hypocalcemia on neurotransmission. Calcium plays a crucial role in neuronal excitability and synaptic transmission (6). Severe hypocalcemia can disrupt these processes, potentially leading to alterations in brain function and mood regulation and contributing to depressive symptoms (20). The observed improvements in cognitive function and potentially depressive symptoms with calcium restoration in several studies support this hypothesis (5-21). Calcifications in brain regions involved in mood regulation could disrupt neuronal activity and lead to depressive symptoms (22).

Several studies have directly linked HPT to an increased prevalence of depression and other mood disorders. In a large cohort study including 688 non-malignant HPT patients and 2064 controls, Underbjerg et al. showed an increased risk of depression and bipolar disorder in HPT patients with an HR (hazard ratio) of 1.99 (23). A nationwide cohort study in Korea showed a significantly higher incidence of depression, especially bipolar depression, HPT patients compared to controls (24). Specifically, 21.0% of patients with nonsurgical HPT had depression and bipolar disorder, compared to 12.4% in the control group. This study also found that patients with nonsurgical HPT had a significantly increased risk of depression and bipolar disease, with a hazard ratio of 1.82 (95% CI, 1.30–2.56) compared to controls. Hillary et al. also, found that patients with post-surgical HPT reported more fatigue and loss of energy compared to controls, but overall quality of life was not significantly different (25).

In our study, the observed association between hypoparathyroidism etiology and depression severity suggests that post-surgical patients may be at higher risk for moderate depressive symptoms. This may be due to differences in disease perception, post-operative complications, or psychological adjustment after surgery. Interestingly, none of the patients with non-surgical hypoparathyroidism had exhibited moderate depression. Overall, 24.2% of the patients in our study were found to have moderate to severe depressive symptoms based on BDI scores. This highlights the significant psychiatric burden associated with HPT, as reported in many previous studies (26–28). The clinical presentation of depression in the context of HPT can vary. Some studies report cases where depression is a prominent symptom (29-30). In addition, some studies suggest that patients with HPT have higher scores on validated questionnaires measuring anxiety and depression, suggesting a clinically relevant association (9-26). The study by Anaforoglu et al. showed a statistically significant difference in BDI scores between the groups with and without treatment adherence and significant negative correlations were also observed between anxiety/depression scores and serum Ca and Mg levels. Our study found a weak negative correlation between depression severity and Ca levels (rho=-0.359, p=0.04), suggesting that as Ca levels decrease, depression severity may increase. While this finding suggests a possible association, the weak correlation suggests caution in interpreting these results. In their 2013 study, Aggarwal et al. found neuropsychological dysfunction in approximately one third of idiopathic HPT patients and showed that this was correlated with female

gender, Ca levels, and CaxP products (31). The fact that 78.8% of the HPT patients included in our study were female may have influenced the results. The increase in BDI scores with decreasing patient Ca levels is consistent with the study by Aggarwal et al. However, as self-reporte scales likesuch as the BDI were used, future studies incorporating structured psychiatric evaluations are needed to establish causality and assess changes over time. For example, the Hypoparathyroid Patient Questionnaire (HPQ) specifically identified depression and anxiety as significant scales in assessing the impact of the disease on patients' lives (32). This highlights the need for comprehensive assessment tools that include mental health measures.

This study has several limitations. First, all patients with HPT were treated with conventional therapies (oral Ca and active vitamin D metabolites), and no patients received recombinant PTH (1-84) or palopegteriparatide therapy, limiting comparisons between treatment modalities. Second, treatment non-adherence was defined as missing more than one medication per week, but no standardized adherence assessment tools were used, which may have limited the comprehensiveness of the adherence assessment. In addition, clinical findings related to HPT were not systematically recorded, preventing a detailed correlation between treatment adherence and clinical outcomes. Another limitation is that patients underwent multiple dose adjustments during follow-up, leading to variability in treatment regimens. As a result, dosing data were not included in the final analysis, which may have influenced the interpretation of adherence-related biochemical and clinical outcomes. In addition, depressive symptoms were assessed using self-report scales (BDI) without structured psychiatric assessment or longitudinal follow-up, which limits causal inference. Finally, the study population had a high proportion of female participants (78.8%), which may have influenced the results, as gender differences may play a role in both treatment adherence and depression severity. Overall, despite the small sample size, observed effect sizes suggest clinically meaningful associations, highlighting the need for further research with larger cohorts and longer follow-up period.

CONCLUSIONS

HPT is a rare chronic disease that leads to alterations in the metabolism of minerals such as Ca, P, and Mg, resulting in various long-term cardiovascular, neurological, and psychiatric complications. In addition to demonstrating an increased frequency of depressive symptoms in patients diagnosed with HPT, this study highlights the importance of treatment goals by revealing the negative correlation between Ca levels and BDI scores. Furthermore, our findings suggest that disease etiology may influence neuropsychiatric symptoms, emphasizing the need for tailored management strategies for different patient subgroups. Given the complex interplay between biochemical stability and psychological health in HPT, a more disease-specific approach to neuropsychiatric assessment is warranted, particularly in light of emerging treatment options. The development and validation of targeted assessment tools could provide a better understanding of the psychological burden of HPT and help to refine individualized therapeutic strategies for these patients.

Informed Consent:

Written informed consent was obtained from each participant.

Authorship Contributions

Concept: Z.E.D., S.T. Design: Z.E.D., S.T. Data Collection or Processing: Z.E.D., S.T. Analysis or Interpretation: Z.E.D., S.T. Literature Search: Z.E.D Writing: Z.E.D.

Conflict of Interest:

No conflict of interest was declared by the authors.

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