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RESEARCH ARTICLE

Cognitive performance in chronic postoperative hypoparathyroidism: A cross-sectional study

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ABSTRACT

Objective: To evaluate cognitive performance in patients with chronic postoperative hypoparathyroidism and to investigate its association with biochemical parameters.

Methods: This prospective, observational, cross-sectional study included 56 patients aged 40–65 years with chronic postoperative hypoparathyroidism, 28 post-thyroidectomy hypothyroid patients without hypoparathyroidism, and 28 healthy controls. Cognitive function was assessed using the Mini-Mental State Examination (MMSE). Biochemical parameters, including albumin-corrected serum calcium and intact parathyroid hormone (iPTH), were measured concurrently. Multivariable analyses were performed to identify independent determinants of cognitive performance.

Results: Although no significant differences were observed among the groups in terms of total MMSE scores, selective differences were detected in the registration and language subdomains in patients with chronic postoperative hypoparathyroidism. Albumin-corrected serum calcium levels and age independently predicted language performance. In addition, a positive correlation was identified between iPTH levels and registration memory scores.

Conclusion: Chronic postoperative hypoparathyroidism may be associated with mild, domain-specific cognitive alterations rather than global cognitive decline. The association of albumin-corrected serum calcium and age with language performance suggests a potential role of calcium homeostasis in cognitive function. Cognitive assessment may therefore be considered as part of long-term follow-up in these patients.

Keywords: hypoparathyroidism, calcium, mini-mental state examination, cognition

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INTRODUCTION

Hypoparathyroidism (hypoPT) is a rare disorder of mineral metabolism characterized by hypocalcemia and hyperphosphatemia resulting from absent or inappropriately low levels of parathyroid hormone (PTH) (1,2). The most common etiology is the iatrogenic form, which develops secondary to accidental removal or damage to the parathyroid glands during neck surgery (3). Clinically, hypoparathyroidism may present as a transient condition that resolves within the first months after surgery; however, persistence beyond 12 months is defined as chronic hypoPT (4). In high-volume centers with experienced endocrine surgeons, the reported rates of chronic hypoPT following thyroid surgery range between 0.9% and 1.6%. Although conventional treatment with calcium supplementation and active vitamin D analogs constitutes the cornerstone of management in chronic hypoPT, this approach does not fully restore physiological calcium homeostasis (5). HypoPT may lead to a spectrum of neurological, psychiatric, and cognitive disturbances. Patients frequently report muscle cramps, spasms, paresthesia, sleep disturbances, anxiety, depression, and reduced quality of life (6-10). Recent evidence also suggests that hypoPT may adversely affect cognitive function (5).

Cognitive functioning encompasses a broad range of mental processes, including learning, memory, reasoning, problem-solving, decision-making, and attention (11). Patients with hypoPT commonly describe symptoms such as slowed thinking, difficulty performing daily activities, and "brain fog." Although the underlying mechanisms remain incompletely understood, intracranial calcifications and hypocalcemia have been associated with impairments in attention, memory, and information-processing speed. Moreover, cognitive dysfunction has been reported in association with extrapyramidal symptoms in this population (12-16).

PTH receptors are expressed in multiple tissues, including the central nervous system. PTH has been shown to cross the blood–brain barrier and bind to PTH2 receptors expressed in the brain, where it may contribute to the regulation of intracellular calcium homeostasis (17,18). The PTH2 receptor has also been proposed to play a role in limbic, neuroendocrine, and sensory-protective functions (19). Calcium ions are fundamental to synaptic transmission and neuronal cell function (5). Furthermore, PTH may influence regional cerebral capillary blood flow, and alterations observed in hypoPT have been suggested to be associated with disturbances in neurovascular coupling (20).

Data regarding the objective assessment of cognitive function in patients with hypoPT are limited, and most available studies rely predominantly on patients' subjective evaluations of well-being. Therefore, in the present study, we aimed to evaluate the relationship between cognitive function and biochemical parameters in patients with chronic hypoPT using the Mini-Mental State Examination (MMSE).

MATERIALS AND METHODS

Study population

This study was designed as a prospective, observational, single-center study. A total of 112 individuals aged between 40 and 65 years who presented for routine follow-up at the Endocrinology Outpatient Clinic of Ankara Training and Research Hospital between January 2021 and July 2023 were enrolled. The postoperative hypoparathyroidism group (Po-hypoPT [+]) consisted of patients who had undergone total thyroidectomy at least 12 months prior to enrollment, had documented hypocalcemia accompanied by low or inappropriately normal PTH levels, and were receiving calcium supplementation and/or active vitamin D therapy (n = 56). The comparison group included patients with a history of total thyroidectomy who had hypothyroidism but did not develop hypoparathyroidism (Po-hypoPT [–]) (n = 28). The control group comprised healthy individuals aged 40–65 years with no history of thyroid surgery, no chronic medical conditions, and no regular medication use (n = 28). The exclusion criteria were as follows: pregnancy; incomplete or insufficient clinical data; history of parathyroidectomy due to primary, secondary, or tertiary hyperparathyroidism; follow-up duration of less than 12 months after total thyroidectomy; previously diagnosed psychiatric disease or cognitive impairment; use of psychotropic medications; severe renal insufficiency (glomerular filtration rate <30

mL/min); chronic liver disease; presence of diabetes mellitus or hypertension; inadequate thyroid hormone control under levothyroxine therapy; anemia; vitamin B12 or iron deficiency; serum 25-hydroxyvitamin D levels <20 ng/mL; other systemic diseases affecting calcium–phosphorus metabolism or PTH levels; use of medications that may pharmacologically interact with calcium; and any condition precluding administration of the Mini-Mental State Examination (e.g., illiteracy, refusal to undergo testing).

Study protocol

Demographic and clinical data, including age, sex, educational level, time since thyroidectomy, presence of hypocalcemia-related symptoms, and doses of calcium, calcitriol, and levothyroxine were recorded for all participants. Height and body weight were measured during physical examination, and body mass index (BMI) was calculated accordingly. Laboratory assessments included measurements of serum glucose, alanine aminotransferase (ALT), urea, creatinine, alkaline phosphatase (ALP), thyroid-stimulating hormone (TSH), free thyroxine (fT4), parathyroid hormone (PTH), total calcium, albumin, phosphorus, 25-hydroxyvitamin D [25(OH)D], complete blood count, ferritin, and vitamin B12 levels. Corrected serum calcium levels were calculated using the following formula: Corrected calcium (mg/dL) = Total serum calcium (mg/dL) + 0.8 × [4 – serum albumin (g/dL)]. In patients diagnosed with hypoparathyroidism, 24-hour urinary calcium and creatinine levels were additionally evaluated. For patients who had undergone cranial computed tomography (CT) within the previous two years, reports retrieved from the hospital's electronic medical record system were reviewed for the presence of calcifications in the basal ganglia. MMSE was administered to all participants on the day of clinical evaluation by the same physician to ensure standardization. Blood samples for biochemical analyses were obtained within one hour following completion of the cognitive assessment. This approach was adopted to ensure that biochemical parameters and neurocognitive performance reflected the participants' concurrent clinical status.

Mini-mental state examination

MMSE was first described by Folstein et al. (21). It is a brief (5–10 minutes), practical, and standardized screening instrument designed to provide a quantitative assessment of cognitive performance. The MMSE has been widely used across different cultural and ethnic populations worldwide and has been translated and culturally adapted from its original English version into Turkish, with established validity and reliability in the Turkish population (Supplementary Appendix 1) (22-25). To minimize inter-examiner variability, a standardized administration guideline has been developed (Supplementary Appendix 2) (23). The test consists of 11 items covering five cognitive domains: orientation (10 points), registration (3 points), attention and calculation (5 points), recall (3 points), and language (9 points), yielding a total possible score ranging from 0 to 30. Higher scores indicate better cognitive functioning (23). In standard administration, the total score is calculated as the sum of correct responses. However, this method may be misleading when participants refuse to answer specific items. In epidemiological studies, refusal to respond is often considered to reflect an inability to provide the correct answer (26). Therefore, in cases where participants did not complete all items, only the scores obtained from the completed items were included in the analysis.

In the Turkish population, the MMSE has demonstrated high sensitivity (0.91) and specificity (0.95) for the diagnosis of mild dementia using a cut-off value of 24, with positive and negative predictive values of 0.90 and 0.95, respectively (23,25). In the present study, consistent with the literature, a threshold value of 24 was adopted. MMSE scores were not used for diagnostic purposes; rather, they were evaluated as a screening indicator reflecting the participants' overall level of cognitive performance.

Statistical analysis

Statistical analyses were performed using SPSS software (version 26.0; IBM Corp., Armonk, NY, USA). The normality of data distribution was assessed using the Shapiro–Wilk test. Continuous variables were presented as mean ± standard deviation (SD)

when normally distributed and as median (minimum–maximum) when not normally distributed. Categorical variables were expressed as numbers and percentages. For comparisons between independent groups, parametric variables were analyzed using the Student's *t*-test (for two groups) or one-way analysis of variance (ANOVA) (for ≥3 groups), whereas non-parametric variables were analyzed using the Mann–Whitney *U* test (for two groups) or the Kruskal–Wallis test (for ≥2 groups). In post hoc analyses following ANOVA, Tukey's test was used when homogeneity of variances was confirmed, and the Games–Howell test was applied when the assumption of homogeneity was violated. For pairwise comparisons following the Kruskal–Wallis test, Bonferroni correction was employed. Associations between variables were evaluated using Pearson correlation analysis for parametric variables and Spearman correlation analysis for non-parametric variables. Independent risk factors predicting an MMSE score <24 were identified using logistic regression analysis. A *p-value* <0.05 was considered statistically significant. For post hoc analyses, a threshold of *p* <0.017 was applied.

Sample size calculation

The sample size was calculated using G*Power software (version 3.1.9.4). Based on a power of 90%, an effect size of 0.4, and a significance level (α) of 0.05, the minimum required sample size was determined to be 84 participants. To increase the statistical power of the study, a total of 112 participants were ultimately included: 56 in the Po-hypoPT (+) group, 28 in the Po-hypoPT (–) group, and 28 in the control group.

RESULTS

The demographic and clinical characteristics of the study population are presented in Table 1. No statistically significant differences were observed among the Po-hypoPT (+), Po-hypoPT (–), and control groups in terms of age, sex distribution, educational level, smoking status, or body mass index (BMI) (p > 0.05 for all comparisons). The laboratory findings of the study population are summarized in Table 2. Albumin-corrected serum calcium levels were significantly lower in the Po-hypoPT (+) group compared with both

Table 1. Demographic and clinical characteristics of the study population

Demographic and Clinical Characteristics	Po-hypoPT (+) (n=56)	Po-hypoPT (–) (n=28)	Control (n=28)	p value
Age, years	48.62 ± 7.12	51.32 ± 5.65	47.75 ± 5.68	0.093
Sex, Female, n (%)	53 (94.6%)	25 (89.3%)	25 (89.3%)	0.482
Education level, n (%)				0.873
Primary/secondary school	43 (76.8%)	21 (75%)	23 (82.1%)	
High school or higher	13 (23.2%)	7 (25%)	5 (17.9%)	
Smoking, n (%)	12 (21.4%)	6 (21.4%)	10 (35.7%)	0.155
BMI, kg/m²	28.62 ± 4.40	28.39 ± 4.83	30.61 ± 6.12	0.166
Time since thyroid surgery, years	14 (3–32)	14.5 (1–30)	–	N/A
Symptomatic hypocalcemia, n (%)	32 (57.1%)	–	–	N/A
Mean LT4 dose, µg/day	112.5 (50–200)	100 (75–175)	–	N/A
Mean calcitriol dose, µg/day	0.5 (0.25–2)	–	–	N/A
Mean calcium dose, g/day	2 (0–4)	–	–	N/A

Data are presented as n (%), mean ± standard deviation, or median (minimum–maximum). For comparisons between independent groups, Student's t-test (for two groups) and ANOVA (for ≥2 groups) were used for normally distributed variables. Categorical variables were compared using the chi-square (χ^2) test or Fisher's exact test. A p-value <0.05 was considered statistically significant. Statistically significant values ($p < 0.05$) were marked with an asterisk (*) and indicated in bold. p_a denotes comparisons between the Po-hypoPT (+) and Po-hypoPT (–) groups. For the time since thyroid surgery, p_a=0.902; for the mean daily LT4 dose, p_a=0.312.

Abbreviations: LT4, levothyroxine sodium; Po-hypoPT, postoperative hypoparathyroidism; BMI, body mass index.

the Po-hypoPT (–) and control groups (both $p < 0.001$). No significant difference was observed between the Po-hypoPT (–) and control groups ($p = 0.994$). Serum phosphorus levels were significantly higher in the Po-hypoPT (+) group compared with the other two groups ($p < 0.001$), whereas no significant difference was detected between the Po-hypoPT (–) and control groups ($p = 0.546$). Intact parathyroid hormone (iPTH) levels were markedly lower in the Po-hypoPT (+) group, while no significant difference was found between the Po-hypoPT (–) and control groups ($p = 0.851$). A comparative box-plot graph of cognitive assessment scores is shown in Figure 1. No statistically significant difference was observed among the Po-hypoPT (+), Po-hypoPT (–), and healthy control groups with respect to total Mini-Mental State Examination (MMSE) scores ($p = 0.115$). However, among the cognitive subdomains, significant differences were identified in the registration and language subscales ($p = 0.002$ and $p = 0.031$, respectively).

Correlation analysis

Correlation analyses were performed in the overall study population to examine the associations between registration and language subscale scores and participants' demographic, clinical, and laboratory parameters. A positive correlation was observed between the registration score and intact parathyroid hormone (iPTH) levels ($r = 0.257$, $p = 0.006$). The language score showed a negative correlation with age ($r = -0.230$, $p = 0.015$) and a positive correlation with albumin-corrected serum calcium (Alb-cCa) levels ($r = 0.204$, $p = 0.031$). The distribution of the study population according to total cognitive assessment scores is illustrated in Figure 2. When groups were compared based on the total MMSE score, the proportion of participants scoring <24 was 58.9% in the Po-hypoPT (+) group, 42.9% in the Po-hypoPT (–) group, and 25% in the control group. A statistically significant difference was found among the groups with respect to MMSE total score distribution ($p = 0.015$). In pairwise comparisons, the proportion of participants with MMSE scores <24 was significantly higher in the Po-hypoPT (+) group compared with the control group ($p = 0.003$). In contrast, no significant difference was observed between the Po-hypoPT (–) and control groups regarding MMSE total score distribution ($p > 0.05$). The comparison of participants' characteristics after categorization according to the MMSE total score cut-off value of 24 is presented in Table 3.

Table 2. Laboratory findings of the study population

Laboratory parameters	Po-hypoPT (+) (n=56)	Po-hypoPT (-) (n=28)	Control (n=28)	p value
FPG, mg/dl	91.75±9.62	96.89±8.76	94.57±8.99	0.053
Creatinine, mg/dl	0.74±0.12	0.73±0.13	0.71±0.13	0.723
TSH, µIU/L	1.49 (0.52-4.4)	1.56 (0.53-3.91)	1.71 (0.56-3.86)	0.623
Alb-cCa, mg/dl	8±0.62	9.08±0.47	9.07±0.27	**<0.001***
Phosphorus, mg/dl	4.45±0.76	3.73±0.47	3.61±0.39	**<0.001***
25 (OH) Vitamin D, µg/L	34.95 (21-56)	32.9 (22.6-71.8)	29.7 (22.5-46)	**0.006***
iPTH, ng/L	11.56±6.1	43.05±16.18	44.96±9.23	**<0.001***
24 h urinary Ca, mg/day	167.5 (11-687)	-	-	N/A

Data are presented as n (%), mean ± standard deviation, or median (minimum–maximum). For comparisons among independent groups, one-way ANOVA was used for normally distributed variables and the Kruskal–Wallis test for non-normally distributed variables. Post hoc analyses were performed using the Tukey test when variances were homogeneous and the Games–Howell test when variances were not homogeneous; Bonferroni correction was applied after the Kruskal–Wallis test. Categorical variables were compared using the chi-square (χ^2) test or Fisher's exact test, as appropriate. A p-value <0.05 was considered statistically significant; for post hoc comparisons, p <0.017 was considered significant. Statistically significant values are indicated with an asterisk (*).pa denotes comparisons between the Po-hypoPT (+) and Po-hypoPT (–) groups, pb denotes comparisons between the Po-hypoPT (+) and Control groups, and pc denotes comparisons between the Po-hypoPT (–) and Control groups. For Alb-cCa, pa<0.001, pb<0.001, and pc=0.994; for phosphorus, pa<0.001, pb<0.001, and pc=0.546; for 25(OH) vitamin D, pa=0.377, pb=0.001, and pc=0.073; for iPTH, pa<0.001, pb<0.001, and pc=0.851.

Alb-cCa: Albumin-corrected serum calcium, ALP: Alkaline phosphatase, FPG: Fasting plasma glucose, Ca: Calcium; h: Hour; iPTH: Intact parathyroid hormone, Po-hypoPT: Postoperative hypoparathyroidism, TSH: Thyroid-stimulating hormone.

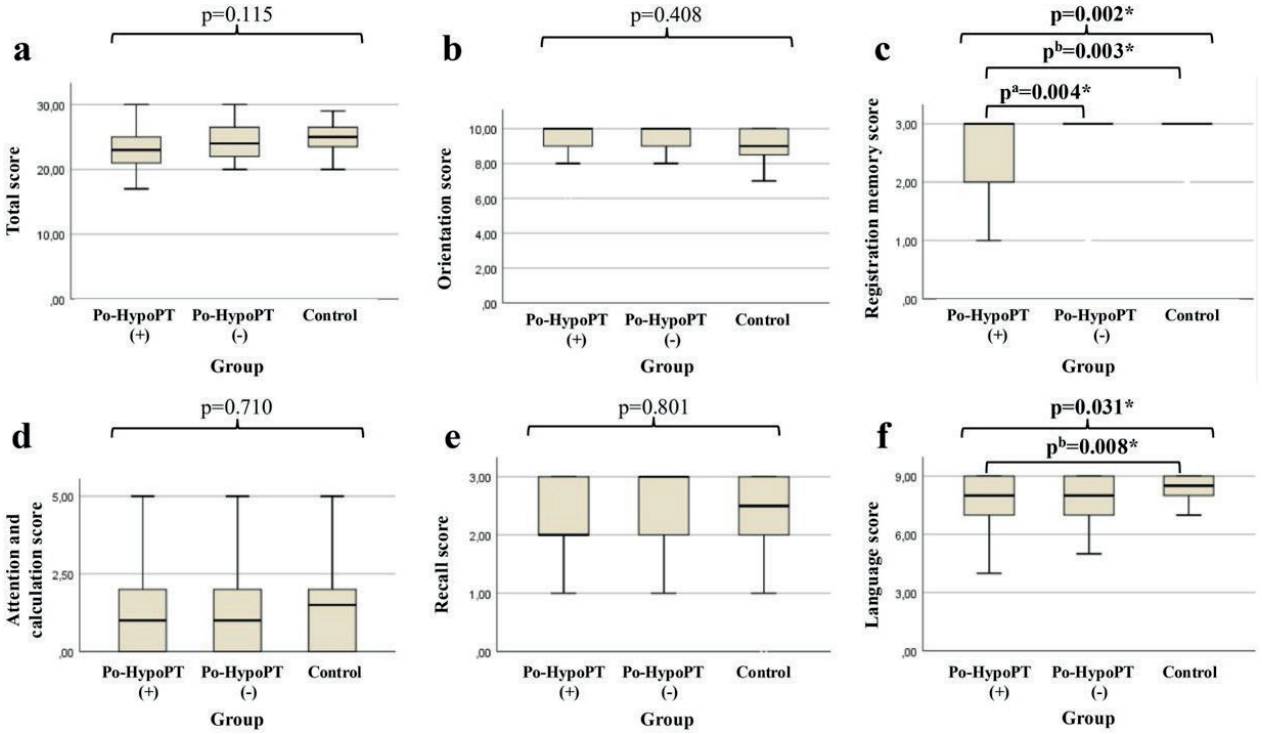

Figure 1. Comparative box plots of cognitive assessment scores among the study groups. The figure presents the following subdomains: (a) Total score, (b) Orientation, (c) Registration memory, (d) Attention and calculation, (e) Recall, and (f) Language. Comparisons among the independent groups were performed using one-way analysis of variance (ANOVA) for normally distributed variables and the Kruskal–Wallis test for non-normally distributed variables. For post hoc analyses, Tukey's test was applied following ANOVA when the assumption of homogeneity of variances was met, whereas the Games–Howell test was used when variances were unequal. Following the Kruskal–Wallis test, pairwise comparisons were performed using the Bonferroni correction. A two-sided p value <0.05 was considered statistically significant; however, for post hoc pairwise comparisons, p<0.017 was regarded as statistically significant. Statistically significant differences (p<0.05) are indicated by an asterisk (*) and shown in bold. . pa indicates the comparison between the Po-HypoPT (+) and Po-HypoPT (–) groups, whereas pb indicates the comparison between the Po-HypoPT (+) and control groups.

DISCUSSION

In the present study, although no significant difference was observed among the groups in terms of total MMSE scores, selective cognitive involvement was noted in patients with hypoparathyroidism, particularly in the domains of registration and language. These findings suggest that domain-specific cognitive alterations may be present even when global cognitive performance appears to be preserved.

Early detection of cognitive dysfunction is important for identifying patients at risk and planning appropriate intervention strategies. However, comprehensive neuropsychological assessments may be time-consuming and costly in routine clinical practice. Therefore, easily applicable screening tools may be useful in detecting early cognitive changes, particularly in high-risk patient populations (14). The Mini-Mental State Examination can be considered a practical, time-efficient, and cost-effective screening instrument for the preliminary evaluation of cognitive function (23).

In recent years, the relationship between PTH and cognitive function has attracted increasing attention. Several studies have reported that elevated PTH levels may be associated with cognitive decline and an increased risk of dementia (27-29). However,

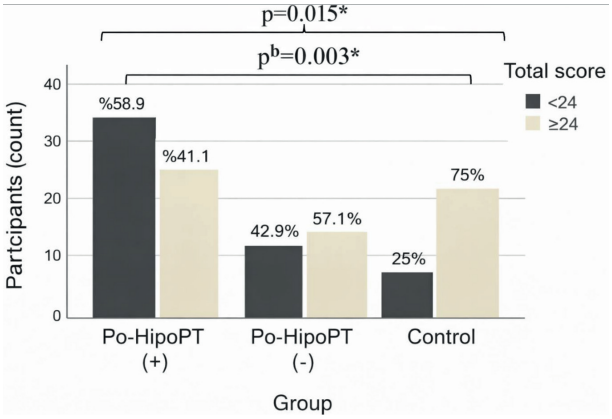

Figure 2. Distribution of the study population according to total cognitive assessment scores. Participants were categorized into two groups based on the Mini-Mental State Examination (MMSE) cut-off score of 24 as <24 and ≥24. Comparisons of categorical variables were performed using the chi-square (χ^2) test or Fisher's exact test, as appropriate. A two-sided p value <0.05 was considered statistically significant. Statistically significant differences ($p<0.05$) are indicated by an asterisk (*) and shown in bold. pb indicates the comparison between the Po-HypoPT (+) and control groups.

evidence also suggests that the low PTH levels and hypocalcemia observed in hypoparathyroidism may likewise be linked to adverse cognitive outcomes (15,30). These findings imply that the effects of PTH and calcium homeostasis on cognitive processes may be bidirectional and complex. Hypoparathyroidism is a rare disorder, and the available evidence regarding its association with cognitive dysfunction remains limited. In the majority of published studies, cognitive status has been assessed using self-reported measures of quality of life rather than objective, performance-based cognitive tests. Instruments such as the Short Form Health Survey (SF-36) have been widely used for this purpose. This reliance on subjective assessments creates uncertainty regarding the extent to which the reported cognitive impairment in hypoPT is objectively measurable and clinically meaningful (31). Abnormal PTH levels have been hypothesized to affect cognitive function through mechanisms such as neuronal calcium imbalance, cerebral hypoperfusion, and impaired neuronal signaling. However, a systematic review conducted within this framework did not demonstrate a significant association between PTH levels and cognitive dysfunction, suggesting that cognitive impairment may be more closely related to disturbances in calcium metabolism rather than PTH itself (17). In a web-based survey including 374 patients with hypoPT, the majority of participants reported fatigue, emotional disturbances, and cognitive complaints (12). In contrast, another study evaluating 19 patients—18 of whom had postoperative hypoPT—reported possible cognitive impairment in 68% of patients based on global cognitive scores and in 32% when premorbid-adjusted fluid cognition scores were used. Processing speed was identified as the most frequently affected cognitive domain, and impairment in this domain was associated with lower serum calcium and higher serum phosphate levels (31). In a study conducted by Aggarwal et al. involving 62 patients with idiopathic hypoPT and employing comprehensive neuropsychological testing, neuropsychological dysfunction characterized by reduced inhibitory control, visuospatial impairment, and psychomotor slowing was identified in 32% of patients. Poor cognitive performance was associated with longer disease duration, increased serum calcium–phosphorus product, and lower total serum calcium levels. An important limitation of this study was the exclusion of patients with postoperative hypoPT (15). Similarly, in a study by Saponaro et al., which evaluated 33 patients with postoperative hypoPT receiving conventional therapy using standardized neuropsychological tests, no overt global cognitive impairment was detected. However, visuospatial attention, executive function, and semantic memory were found to be modulated by (Alb-cCa) levels, with lower Alb-cCa levels associated with poorer performance in these domains (20). The variability in the reported prevalence of cognitive impairment in the literature may be related to heterogeneity in the etiopathogenesis of hypoPT (idiopathic versus postoperative), differences in disease duration, variability in neurocognitive assessment methods, and patient age.

In our study, 58.9% of patients with chronic postoperative hypoparathyroidism had an MMSE total score <24, and this proportion was significantly higher compared with the control group. These findings

Table 3. Comparison of participants' characteristics after categorization according to the total score cut-off value of 24

Demographic and Clinical Characteristics	Total score <24 (n=52)	Total score ≥24 (n=60)	p value
Group, n (%)			0.015*
Po-hypoPT (+)	33 (63.5%)	23 (38.3%)	
Po-hypoPT (–)	12 (23.1%)	16 (26.7%)	
Control	7 (13.5%)	21 (35%)	
Age, years	50.09 ± 6.38	48.26 ± 6.57	0.126
Sex, Female, n (%)	50 (48.5%)	53 (51.5%)	0.172
Education level, n (%)			0.042*
Primary/secondary school	45 (86.5%)	42 (70%)	
High school or higher	7 (13.5%)	18 (30%)	
Smoking, n (%)	16 (26.7%)	10 (19.2%)	0.379
BMI, kg/m²	29.04 ± 4.22	29.08 ± 5.66	0.969
Laboratory parameters			
FPG, mg/dL	91.26 ± 9.21	95.88 ± 9.15	0.009*
Creatinine, mg/dL	0.72 ± 0.11	0.74 ± 0.13	0.522
TSH, IU/L	1.21 (0.52–4.31)	1.71 (0.56–4.4)	0.208
Ca, mg/dL	8.9 ± 0.73	9.08 ± 0.72	0.197
Alb-cCa, mg/dL	8.39 ± 0.73	8.66 ± 0.74	0.052
Phosphorus, mg/dL	4.16 ± 0.74	3.98 ± 0.71	0.208
25(OH) Vitamin D, ng/mL	33.25 (22.2–50)	33.95 (21–71.8)	0.809
iPTH, ng/L	24.11 ± 18.58	30.97 ± 19.32	0.059

Data are presented as n (%), mean ± standard deviation, or median (minimum–maximum). For comparisons between independent groups, Student's *t*-test was used for normally distributed variables and the Mann–Whitney *U* test for non-normally distributed variables. Categorical variables were compared using the chi-square (χ^2) test or Fisher's exact test. A p-value <0.05 was considered statistically significant. Statistically significant values ($p < 0.05$) are indicated with an asterisk (*) and shown in bold. p_a denotes comparisons between the Po-hypoPT (+) and Po-hypoPT (–) groups; p_β denotes comparisons between the Po-hypoPT (+) and Control groups; *pc* denotes comparisons between the Po-hypoPT (–) and Control groups. For Group: p_a=0.164, p_β=0.003, *pc*=0.158 For Education level: p_a=0.015, p_β=0.057, *pc*=0.518

Abbreviations: FPG, fasting plasma glucose; Alb-cCa, albumin-corrected serum calcium; Ca, calcium; TSH, thyroid-stimulating hormone; ALP, alkaline phosphatase; iPTH, intact parathyroid hormone; Po-hypoPT, postoperative hypoparathyroidism.

suggest that cognitive impairment in this patient population should not be overlooked.

Statistically significant between-group differences were observed only in the registration and language subdomains of the cognitive assessment. The positive correlation identified between registration scores and iPTH levels may be related to the effects of PTH on cerebral blood flow and its regulatory role in calcium–phosphate homeostasis. This finding suggests potential neurophysiological effects of PTH on the central nervous system. Sikjaer et al. reported reduced long-term memory performance in patients with chronic hypoparathyroidism and demonstrated that disease duration may influence thalamic volume, highlighting a possible link between cognitive symptoms and structural brain alterations (32). In contrast, Berisha et al., in a study comparing 30 patients with chronic hypoparathyroidism to healthy controls, found no significant differences in verbal learning, memory, or executive function domains (5). Language emerged as another cognitive domain exhibiting significant

between-group differences. Language scores showed a negative correlation with age and a positive correlation with albumin-corrected serum calcium levels. Age-related cognitive change is a well-established physiological process, and language function is among the domains known to be sensitive to aging. Language represents a multidimensional and complex cognitive construct; visual confrontation naming performance has been reported to remain relatively stable until approximately 70 years of age, followed by a gradual decline. Similarly, verbal fluency—the ability to generate words within a specific category over a defined time interval—tends to decrease with advancing age (33). The observed negative association between language scores and age therefore appears consistent with expected physiological cognitive aging. Cognitive impairment in hypoparathyroidism has most frequently been described in the domains of attention/processing speed and executive function. Dysfunction in these areas may indirectly influence language-related tasks such as verbal fluency and naming (5). Given the central role of calcium in synaptic transmission and neuronal excitability, transient slowing of processing speed during hypocalcemia has been reported (20,31). This mechanism may partly explain the association observed between lower serum calcium levels and reduced language performance.

Neurological manifestations in hypoparathyroidism have been suggested to be associated with intracranial calcifications. These calcifications may impair cognitive function by altering cerebral blood flow and disrupting neurotransmission (34). Kowdley et al. reported cognitive impairment in 65% of individuals with hypoparathyroidism and attributed this finding to the presence of intracranial calcifications (30). In the present study, the absence of basal ganglia calcifications may be explained by the inclusion of patients with postoperative hypoparathyroidism who were treated at an early stage of the disease.

No significant sex-related differences were observed in cognitive function scores in the present study. In contrast, Aggarwal et al. reported a higher prevalence of neurocognitive dysfunction in women compared with men among patients with idiopathic hypoparathyroidism, suggesting that socioeconomic and cultural factors might contribute to this disparity (15). Thyroid dysfunction, particularly hypothyroidism, is considered an important confounding factor in cognitive assessment and has been associated with adverse effects on attention, memory, and psychomotor speed (35). In our cohort, no significant differences in MMSE scores were observed between patients who developed hypoparathyroidism after thyroidectomy and those who did not. Because all post-thyroidectomy patients had adequate thyroid hormone replacement and were biochemically euthyroid, the observed findings are unlikely to be attributable to differences in thyroid function. This finding suggests that maintenance of euthyroidism through appropriate thyroid hormone replacement may largely mitigate cognitive effects attributable to hypothyroidism. Furthermore, the absence of significant differences in MMSE scores between groups supports the notion that the observed cognitive changes may be more closely related to hypoparathyroidism-specific mechanisms rather than thyroid function per se. Nevertheless, given that the MMSE is a screening instrument designed primarily to assess global cognitive function, its sensitivity in detecting subtle, domain-specific cognitive differences may be limited.

In the present study, cognitive assessment in patients with hypoparathyroidism was conducted using a screening and classification tool intended to reflect overall cognitive performance rather than for diagnostic purposes. The absence of comprehensive, performance-based neuropsychological test batteries represents an important limitation of the study. In addition, the relatively small sample size and the cross-sectional design restrict the ability to draw causal inferences. The lack of longitudinal follow-up data examining the relationship between improvements in biochemical parameters and changes in MMSE scores constitutes another limitation. Furthermore, basal ganglia calcifications were evaluated only in patients who had previously undergone cranial computed tomography, and systematic neuroimaging was not performed in all participants.

CONCLUSION

The findings of this study suggest that cognitive function may be adversely affected in patients with hypoparathyroidism. The independent association of

albumin-corrected serum calcium levels and age with language performance supports the potential impact of chronic hypocalcemia and aging on language-related cognitive domains. These results indicate that postoperative hypoparathyroidism should be considered not merely as a biochemical disorder but also as a clinical condition potentially associated with domain-specific cognitive alterations. Accordingly, a comprehensive approach incorporating the assessment of cognitive function alongside biochemical parameters may be warranted during the long-term follow-up of patients with hypoparathyroidism.

Ethical approval

The study was approved by the Ethics Committee of Ankara Training and Research Hospital (Approved date and number: October 27, 2021; No. E-21-784). It was conducted in accordance with the principles of the Declaration of Helsinki.

Author contribution

Conceptualised and supervised the study: PG, TO; Concept: PG, CÇ, TO; Design: ŞED, ÇEÖ, IT; Data Collection or Processing: PG, ŞED; Analysis or Interpretation: PG, ÇEO, CÇ; Literature Search: PG, TO; Writing: PG, IT. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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