



Neuropsychological Changes and Health-related Quality of Life in Patients with Asymptomatic Primary Hyperparathyroidism

Asemptomatik Primer Hiperparatiroidizmi Olan Hastalarda Nöropsikolojik Değişiklikler ve Yaşam Kalitesi

Banu Aktaş Yılmaz, Füsün Baloş Törüner*, Ceyla Konca Değertekin**, Özlem Turhan İyidir***, Burhaneddin Kaya****, Nuri Çakır*

Yüksek İhtisas University Faculty of Medicine, Department of Endocrinology and Metabolism, Ankara, Turkey

*Gazi University Faculty of Medicine, Department of Endocrinology and Metabolism, Ankara, Turkey

**Ufuk University Faculty of Medicine, Endocrinology and Metabolism, Ankara, Turkey

***Başkent University Faculty of Medicine, Department of Endocrinology and Metabolism, Ankara, Turkey

****Gazi University Faculty of Medicine, Department of Psychiatry, Ankara, Turkey

Abstract

Purpose: Data about neuropsychological impairment and health-related quality of life (HRQOL) in patients with asymptomatic primary hyperparathyroidism (APHPT) is limited. We aimed to investigate the HRQOL, neuropsychological impairment, including depression, anxiety in patients with APHPT who have mildly elevated serum calcium (Ca) levels.

Material and Method: Thirty-seven patients with APHPT and 37 controls were included. The Beck Depression Inventory (BDI), Spielberger State-Trait Anxiety Inventory (STAI), and the General Health Questionnaire were administered in all patients, HRQOL was investigated using the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36).

Results: Serum levels of Ca and parathyroid hormone (PTH) were significantly higher in patients than in controls [(10.92±0.66 vs. 9.49±0.66, p=0.016, and 133 (34-736) vs. 52.95 (25-75.50), p<0.001), respectively]. The levels of serum vitamin D were lower in patients than in controls [12.85 (4.0-62.50) vs. 20.30 (5.90-55.00), p=0.041]. The patient group had higher BDI scores than controls (12.49±10.34 vs. 7.46±5.33, p=0.011). Patients with APHPT showed lower scores in SF-36 mental health (60.55±20.75 vs. 69.62±14.31, p=0.034), SF-36 physical functioning (55.83±27.30 vs. 75.67±24.18, p=0.002), SF-36 social functioning (66.32±27.69 vs. 82.08±14.89, p=0.003), and SF-36 emotional role functioning (42.55±37.85 vs. 69.30±35.43, p=0.003). The patients showed higher STAI-1 scores (39.95±11.52 vs. 34.70±8.01, p=0.026). We observed that STAI-1 score positively correlated with serum Ca level (r=0.391; p=0.018); and PTH (r=0.341; p=0.042).

Discussion: Our study demonstrated that patients with APHPT have more depressive and anxiety symptoms and lower HRQOL. Our results suggest that HRQOL and neuropsychological changes should also be considered during the clinical follow-up of patients with APHT.

Keywords: Asymptomatic primary hyperparathyroidism, health-related quality of life, depression, anxiety, general health questionnaire

Öz

Amaç: Asemptomatik primer hiperparatiroidizmi (APHPT) olan hastalardaki yaşam kalitesi ve nöropsikolojik değişiklikler ile ilgili bilgilerimiz kısıtlıdır. Bu çalışmadaki amacımız serum kalsiyum (Ca) düzeyi orta derecede yüksek olan APHPT hastalarını yaşam kalitesi ve nöropsikolojik değişiklikler yönünden incelemektir.

Gereç ve Yöntem: Çalışmaya APHPT tanısı olan 37 hasta ve 37 kişilik kontrol grubu dahil edilmiştir. Olguların depresyon, kaygı düzeylerini ve yaşam kalitelerini değerlendirmek amacıyla Beck Depresyon Envanteri (BDE), Genel Sağlık Anketi, Durumluk-Süreklilik Kaygı Envanteri (STAI), Kısa Form (SF-36) ölçekleri kullanılmıştır.

Bulgular: Serum Ca ve paratiroid hormon (PTH) düzeyleri hasta grubunda anlamlı olarak daha yüksekti (10,92±0,66 karşılık 9,49±0,66; p=0,016; ve 133 (34-736) karşılık 52,95 (25-75,50), p<0,001). Serum vitamin D düzeyleri hasta grubunda daha düşüktü [12,85 (4,0-62,50) karşılık 20,30 (5,90-55,00), p=0,041]. BDE puanı hasta grubunda anlamlı olarak daha yüksekti (12,49±10,34 karşılık 7,46±5,33; p=0,011). SF-36 ölçeği ile değerlendirilen yaşam kalitesinin bazı bileşenlerinin puanlarının hasta grubunda istatistiksel anlamlı olarak daha düşüktü. Sırasıyla: SF-36 mental sağlık (60,55±20,75 karşılık 69,62±14,31; p=0,034), SF-36 fiziksel fonksiyon (55,83±27,30 karşılık 75,67±24,18; p=0,002), SF-36 sosyal fonksiyon (66,32±27,69 karşılık 82,08±14,89; p=0,003), SF-36 emosyonel rol kısıtlaması (42,55±37,85 karşılık 69,30±35,43; p=0,003). Durumluk kaygı envanteri (STAI-1) puanı hasta grubunda anlamlı olarak daha yüksekti (39,95±11,52 karşılık 34,70±8,01; p=0,026). STAI-1 puanı ile serum Ca düzeyi (r=0,391; p=0,018); ve serum PTH düzeyi (r=0,341; p=0,042) arasında pozitif korelasyon olduğu tespit edildi.

Tartışma: Çalışmamız APHT hastalarında depresif ve kaygı semptomlarının olduğunu, yaşam kalitesinin de olumsuz etkilendiğini göstermiştir. Çalışmamızın sonuçları, APHT hasta grubunun yaşam kalitesi ve nöropsikolojik değişiklikler açılarından da takip edilmesi gerektiğini göstermektedir.

Anahtar kelimeler: Asemptomatik primer hiperparatiroidizm, yaşam kalitesi, depresyon, kaygı, genel sağlık anketi

Introduction

The widespread use of multichannel autoanalyzer has transformed the clinical presentation of the classic primary hyperparathyroidism (PHPT) into the asymptomatic form of the PHPT. The classic symptoms of severe bone pain, nephrolithiasis, and obvious neuropsychological impairment are seen in only minority of patients who present with PHPT. Parathyroidectomy is the only curative method for symptomatic and asymptomatic PHPT. Parathyroidectomy improves biochemical properties of the disease and bone mineral density in patients with asymptomatic PHPT, however, the limited data showed that patients with asymptomatic PHPT have a long and stable clinical course (1,2). Indications for parathyroidectomy for patients with asymptomatic PHPT include a serum calcium (Ca) level of >1 mg/dL, which is upper limit of the normal, osteoporosis, vertebral fracture, reduced creatinine (Cr) clearance (<60 cc/min), hypercalciuria, increased stone risk, presence of nephrolithiasis or nephrocalcinosis, and age younger than 50 years (3).

Many patients with asymptomatic PHPT report nonspecific complaints including weakness, fatigue, depression and anxiety, and decreased memory and concentration (4,5,6). Moreover, these nonspecific complaints decrease after parathyroidectomy in some patients diagnosed with PHPT (5,7,8,9,10,11,12,13). On the other hand, a randomized prospective study stated that reduced health-related quality of life (HRQOL), and increased neuropsychological symptoms did not improve after parathyroidectomy in patients with asymptomatic PHPT (4).

Whether there is a relationship between neuropsychological impairment and biochemical properties of the hyperparathyroidism is not clear. A number of studies showed no correlation between the biochemical properties of PHPT, such as higher serum Ca and parathyroid hormone (PTH) levels, and neuropsychological impairment in patients with mildly elevated serum Ca levels (5,6,9,11,12). Some of these studies had no healthy control groups (2,14,15), the other studies used patients who had thyroid or orthopedic surgery as the control groups to rule out the placebo effect of the surgery (12,16,17). Some of these studies included both patients with symptomatic and asymptomatic PHPT (6,14,16).

We investigated HRQOL and neuropsychological impairment including depression and anxiety in patients with asymptomatic PHPT who had mildly elevated serum Ca levels and who might be observed without parathyroidectomy for a long time, and we compared the results with age-, sex- and co-morbid conditions-matched control group. Data on left ventricular structure and functions in a subgroup of our patients have previously been reported (18).

Materials and Methods

Thirty-seven patients with asymptomatic PHPT and 37 sex- and age-matched control subjects were included in this study. The principles of the declaration of Helsinki were followed and informed consent was obtained from all participants, and the study was approved by the Ethics Committee of Gazi University Medical Faculty (approval date and number: 23.03.2011/44, by the Chairman Prof. Dr. Canan Ulubay).

The diagnosis of asymptomatic PHPT was established by hypercalcemia and inappropriately high normal or elevated plasma

intact PTH levels. None of the patients had classical PHPT findings, such as osteitis fibrosa cystica, bone fractures, and renal stones. None of the participants were on antidepressant medication or lithium. Demographic data and medical history were obtained from the participants. None of the participants had coronary artery disease or diabetes mellitus.

Biochemical Assays

Fasting samples for serum Ca, Cr, phosphorus and lipid parameters were measured by an automated chemistry analyzer (Architect c16000, Abbott Diagnostic Systems, Illinois, USA). Serum 25-hydroxyvitamin D was measured with commercial kits (ImmuChrom GmbH, Tiergartenstr 7, Heppenheim, Germany) using the high performance liquid chromatography method (Shimadzu LC-20AT Prominence Liquid Chromatography, Japan). Serum PTH was measured by immunochemiluminometric assay for intact PTH by an automated immunoassay analyzer (Siemens- ADVIACentaur® XP Immunoassay System, Siemens Healthcare Diagnostics Inc., USA) using the commercial kits (Siemens Healthcare Diagnostics Inc, Tarrytown, NY, USA).

Health-Related Quality of Life

HRQOL was assessed using the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) that has been validated for the Turkish population (19). The SF-36 measures eight domains: vitality (assesses whether the respondent feel energetic or tired and worn out), physical functioning (what extent the health limits physical activities, such as self-care, walking, climbing stairs, bending, and moderate and vigorous exercises), bodily pain (assesses intensity of pain and effect of pain on normal work, both inside and outside of the home), general health perceptions (assesses personal evaluation of health, including current health, health outlook, and resistance to the illness), physical role functioning (what extent physical health interferes with work or other daily activities, including accomplishing less than wanted, limitations in the kind of activities, or difficulty in performing activities), emotional role functioning (what extent emotional problems interfere with work or other daily activities, including decreased time spent on activities, accomplishing less, and not working as carefully as usual), social functioning (whether physical health or emotional problems interfere with normal social activities) and mental health (assesses general mental health, including depression, anxiety, behavioral-emotional control, general positive affect). The weighted sum of the each scale is transformed to range from 0 where the respondent has the worst possible health to 100 where the respondent is in the best possible health.

Depression

Beck Depression Inventory (BDI) is a 21-item self-report measure of depression symptom severity (20). The validity and reliability of the Turkish version of the BDI was first performed by Hisli (21) in 1988. Higher scores indicate more severe depressive symptoms. Cut off score for the diagnosis of depression was determined as 17 for the Turkish population.

The Spielberger State-Trait Anxiety Inventory

The Spielberger State-Trait Anxiety Inventory (STAI) measures anxiety and consists of two 20-item scales measuring state anxiety (how the respondent feels at a particular moment in time) and trait anxiety

(how the respondent generally feels) (22). Higher scores indicate higher levels of anxiety. This test shows good validity and reliability in assessing anxiety states, and has been validated for the Turkish population (23).

General Health Questionnaire

The General Health Questionnaire (GHQ) is used to assess well-being in a person, and targets two areas; the inability to carry out normal functions and the appearance of new and distressing phenomena. The GHQ-12 (12 items) was used in our study (24). GHQ shows negative correlation with the global quality of life (QoL) scale; which means that there is an inverse relationship with an increase in distress leading to a decrease in QoL (25).

Statistical Analysis

Statistical analysis was performed with SPSS for Windows statistical package 15.0 (SPSS Inc., Chicago, IL, USA). Data with parametric distribution were expressed as mean \pm standard deviation; whereas data with non-parametric distribution were expressed via median. The independent samples t-test was performed to compare parametric distributed continuous variables, and Mann-Whitney U-test was performed to compare parametric distributed continuous variables. Relationships between variables were assessed with Pearson's and Spearman's correlation coefficients. A p value of less than 0.05 was considered statistically significant. Linear regression analysis was used to determine the independent predictors of the scores from STAI, BDI and SF-36 survey forms.

Results

The demographic and biochemical characteristics of the study population are shown in Table 1. The control group was well matched regarding age and sex distribution. The serum levels of Ca and PTH were significantly higher in patients with asymptomatic PHPT than in controls [(10.92 \pm 0.66 mg/dL vs. 9.49 \pm 0.66 mg/dL, p=0.016, and 133 (34-736) pg/mL vs. 52.95 pg/mL (25-75.50), p<0.001], respectively). The levels of serum vitamin D were lower in patients when compared with controls [(12.85 (4.0-62.50) ng/mL vs 20.30 (5.90-55.00) ng/mL, p=0.041)].

Results of the HRQOL surveys are shown in Table 2. BDI scores were higher in patients than in controls (12.49 \pm 10.34 vs. 7.46 \pm 5.33, p=0.011). Patients with APHPT showed lower scores in the HRQOL inventory including SF-36 mental health (60.55 \pm 20.75 vs. 69.62 \pm 14.31, p=0.034), SF-36 physical functioning (55.83 \pm 27.30 vs. 75.67 \pm 24.18,

p=0.002), SF-36 social functioning (66.32 \pm 27.69 vs. 82.08 \pm 14.89, p=0.003), SF-36 emotional role functioning (42.55 \pm 37.85 vs. 69.30 \pm 35.43, p=0.003). The patients showed higher scores for state anxiety (STAI-1) (39.95 \pm 11.52 vs. 34.70 \pm 8.01, p=0.026) than the controls.

When the correlations between the biochemical properties of the patients and survey results were evaluated in a model, which serum Ca, PTH, vitamin D and age included, we showed a positive correlation between the serum Ca level and STAI-1 (r=0.391; p=0.018); and PTH and STAI-1 (r=0.341; p=0.042). No correlation was observed between serum Ca, PTH, and vitamin D levels and the other parameters of health surveys of QoL.

Discussion

The results of our study showed that patients with asymptomatic PHPT have more depressive and anxiety symptoms than control subjects. BDI scores were significantly higher in our patient group when compared with the controls. However, mean BDI scores in both groups were not suggestive of depression in the Turkish population. STAI-1 scores, which refer state anxiety, were significantly higher in the patients group than in controls and showed positive correlation with serum Ca and PTH levels. Although the GHQ scores were not different between the groups, our results showed that patients with asymptomatic PHPT had some restrictions in physical, social and emotional functioning and mental health. Our results suggest that patients with asymptomatic PHPT may have some discomfort in different aspects of daily life causing impairment in QoL. Clinical importance of this situation is not clear.

Neuropsychiatric changes and HRQOL in patients with asymptomatic PHPT were the issues in some studies. Burney et al. (9) showed that scores in all domains of the SF-36 were lower in patients with low serum Ca levels (<10.9 mg/dL) as well as in patients with higher serum Ca levels. In a study by Sheldon et al. (11) patients with asymptomatic PHPT showed impairment in three domains of SF-36. Rao et al. (26) showed no difference in SF-36 scores between the healthy population and patients with asymptomatic PHPT, however, two domains of SF-36 improved after parathyroidectomy. Bollerslev et al. (4) showed that patients with asymptomatic PHPT had decreased SF-36 scores, had more psychological symptoms; but patients who were randomized for parathyroidectomy did not show improvement in QoL and psychological symptoms. Ambrogini et al. (2) reported that the difference was minimal between patients with asymptomatic PHPT and healthy controls, but successful parathyroidectomy followed by an improvement in QoL scores. Veras et al. (27) reported that depression was more frequently diagnosed in patients with asymptomatic PHPT than in normal population. Four domains of SF-36 scores were lower in patients with asymptomatic PHPT who had a longer diagnosis time than in newly diagnosed patients. Our results also showed that QoL was impaired in patients with asymptomatic PHPT, who have mildly elevated serum Ca levels and who would be followed up without parathyroidectomy for a long time. Clinical importance of this situation is not clear. Whether it is a progressive condition or patients with asymptomatic PHPT benefit from parathyroidectomy regarding improvement in the QoL is not clear either. There is no sufficient evidence to suggest parathyroidectomy to these patients in terms of reduced QoL (3).

Table 1. Demographic and biochemical characteristics of the study population

	Patients n=37	Controls n=37	p
Age (years)	53.89 \pm 7.27	55.91 \pm 6.85	0.221
Sex (F/M)	30/7	31/6	1.000
Ca (mg/dL)	10.92 \pm 0.66	9.49 \pm 0.66	0.016
P (mg/dL)	2.75 (1.62-4.0)	3.46 (2.90-4.70)	<0.001
PTH (pg/mL)	133 (34-736)	52.95 (25-75.50)	<0.001
25(OH) vitamin D (ng/mL)	12.85 (4.0-62.50)	20.30 (5.90-55.00)	0.041
F: Female, M: Male, Ca: Calcium, P: Phosphorus, PTH: Parathyroid hormone			

Obvious neuropsychological impairment is considered as classical features of symptomatic PHPT. The prevalence of major depression was reported as 10% and 31% when the patients were evaluated with validated depression surveys (28,29). Espiritu et al. (29) also showed that patients with PHPT, including both symptomatic and asymptomatic patients, were more depressive, and higher serum Ca levels of 11 mg/dL or greater were associated with higher depression scores. Walker et al. (30) evaluated patients with mildly elevated serum Ca levels; their study result suggested that patients with PHPT had more symptoms of depression and anxiety, even though mean performance levels on tests were not in the range of clinical depression or anxiety. Roman et al. (17) also stated that depression and state anxiety scores were higher in patients with PHPT including both symptomatic and asymptomatic patients. Benge et al. (31) reported higher depression and anxiety scores in patients with mildly elevated serum Ca levels. On the other hand, a number of studies showed no significant difference in depression and anxiety scores between patients with PHPT and controls (6,32). Our study results suggest that asymptomatic patients with mildly elevated serum Ca levels have higher depression and anxiety scores, when compared with sex- and age-matched controls. Although mean performance levels on tests were not in the range of clinical depression or anxiety in both groups; patients with asymptomatic PHPT might feel uncomfortable due to having a chronic disease. The results of studies investigating whether psychiatric symptoms improve after parathyroidectomy are inconsistent. While there were no healthy control groups in some studies (14,15,33); patients who had thyroid or orthopedic surgeries were used as control groups to exclude the placebo effect of the surgery in the other studies (6,12,17,29). Our study showed that patients with asymptomatic PHPT, who could be followed without parathyroidectomy for a long period, had vague psychiatric symptoms. The clinical importance of this situation is not clear. The question whether these subtle neuropsychological symptoms would progress during observation period has paramount importance that we can then answer the main question is it worth to take the risk of the adverse effects and complications of the parathyroidectomy.

Ambrogini et al. (2) stated that patients with asymptomatic PHPT who were followed up without parathyroidectomy did not show evidence of progression in QoL. However, this result should be confirmed by further studies. Whether improvement of these neuropsychological symptoms is cost-effective should also be evaluated. Wilhelm et al. (28) reported that parathyroidectomy reduced the symptoms of major depression, improved QoL and reduced antidepressant medication resulted in drastic reduction in expenses related to neuropsychiatric medications in patients with symptomatic PHPT. Whether this is also valid for the asymptomatic patient group has not been evaluated and is still an open issue. However, data are still insufficient to predict the improvement in neuropsychological symptoms and QoL after parathyroidectomy, thus, neurological or psychological dysfunction was not considered as parathyroidectomy indication (3).

Pathogenetic mechanism of neurological dysfunction in PHPT is elusive. Functional imaging studies showed that reduced regional cerebral blood flow significantly improved following parathyroidectomy (34,35). Biochemical analysis of the cerebrospinal fluid (CSF) in patients with PHPT revealed that increased levels of Ca and PTH in the CSF decreased CSF levels of the monoamine metabolites 5-hydroxyindoleacetic acid and homovanillic acid, and damaged blood brain barrier. The decreasing levels of Ca in CSF of the patients with PHPT after parathyroidectomy were correlated with the alleviation of psychiatric symptoms (36). These findings conflict with other clinical observation studies. Normalization of serum Ca after parathyroidectomy did not always lead to neuropsychological symptoms in clinical studies (4). The levels of serum Ca did not predict the severity of neuropsychological symptoms, HRQOL, or the potential improvement in the neuropsychological symptoms following parathyroidectomy in a study by Burney et al. (9).

Conclusion

Our study demonstrated that patients with asymptomatic PHPT have more depressive and anxiety symptoms and reduced HRQOL. Our findings showed a correlation between the trait anxiety and serum levels of Ca and PTH. The major advantages of our study were as

Table 2. Results of the Beck Depression Inventory, Short Form 36, Spielberger State-Trait Anxiety Inventory and General Health Questionnaire forms

	Patients n=37	Controls n=37	p
BDI	12.49±10.34	7.46±5.33	0.011
SF-36 bodily pain	60.61±23.40	69.10±21.56	0.165
SF-36 general health perception	54.22±15.56	49.18±13.64	0.145
SF-36 mental health	60.55±20.75	69.62±14.31	0.034
SF-36 vitality	58.37±22.80	67.16±21.45	0.092
SF-36 physical role functioning	47.22±44.23	66.12±40.50	0.080
SF-36 physical functioning	55.83±27.30	75.67±24.18	0.002
SF-36 social functioning	66.32±27.69	82.08±14.89	0.003
SF-36 emotional role functioning	42.55±37.85	69.30±35.43	0.003
General Health Questionnaire	11.78±7.81	9.49±4.03	0.119
STAI-1 (state anxiety)	39.95±11.52	34.70±8.01	0.026
STAI -2 (trait anxiety)	44.70±8.41	42.84±7.72	0.324

BDI: Beck Depression Inventory, SF-36: Short Form 36; STAI: The Spielberger State-Trait Anxiety Inventory

follows; we had a very homogenous patient group whose serum Ca levels were in the very narrow ranges; and we compared the results with age-, sex- and co-morbidities-matched controls. We evaluated our patients and controls with standardized psychiatric interviews, not with self-rating scales. The limited number of the patients is the disadvantage of our study. There are number of studies discussing the advantages of parathyroidectomy regarding neuropsychiatric findings and QoL. Another issue that should be investigated in larger and prospective studies is that whether these subtle neuropsychiatric findings and HRQOL scores deteriorate during the follow-up of patients. In our opinion, the answers to these two questions might change the parathyroidectomy indications for patients with asymptomatic PHPT.

Ethics

Ethics Committee Approval: The study was approved by the Ethics Committee of the Medical Faculty at Gazi University (approval date and number: 23.03.2011/44, by the chairman Prof. Dr. Canan Ulubay), Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally and Internally peer-reviewed.

Authorship Contributions

Concept: Banu Aktaş Yılmaz, Füsün Baloş Törüner, Burhaneddin Kaya, Design: Banu Aktaş Yılmaz, Füsün Baloş Törüner, Burhaneddin Kaya, Data Collection or Processing: Banu Aktaş Yılmaz, Ceyla Konca Değertekin, Özlem Turhan İyidir, Analysis or Interpretation: Banu Aktaş Yılmaz, Ceyla Konca Değertekin, Özlem Turhan İyidir, Burhaneddin Kaya, Nuri Çakır, Literature Search: Banu Aktaş Yılmaz, Ceyla Konca Değertekin, Writing: Banu Aktaş Yılmaz, Füsün Baloş Törüner.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Silverberg SJ, Shane E, Jacobs TP, Siris E, Bilezikian JP. A 10-year prospective study of primary hyperparathyroidism with or without parathyroid surgery. *N Engl J Med.* 1999;341:1249-1255.
2. Ambrogini E, Cetani F, Cianferotti L, Vignali E, Banti C, Viccica G, Oppo A, Miccoli P, Berti P, Bilezikian JP, Pinchera A, Marcocci C. Surgery or surveillance for mild asymptomatic primary hyperparathyroidism: a prospective, randomized clinical trial. *J Clin Endocrinol Metab.* 2007;92:3114-3121.
3. Bilezikian JP, Brandi ML, Eastell R, Silverberg SJ, Udelsman R, Marcocci C, Potts JT Jr.. Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the Fourth International Workshop. *J Clin Endocrinol Metab.* 2014;99:3561-3569.
4. Bollerslev J, Jansson S, Mollerup CL, Nordenström J, Lundgren E, Tørring O, Varhaug JE, Baranowski M, Aanderud S, Franco C, Freyschuss B, Isaksen GA, Ueland T, Rosen T. Medical observation, compared with parathyroidectomy, for asymptomatic primary hyperparathyroidism: a prospective, randomized trial. *J Clin Endocrinol Metab.* 2007;92:1687-1692.
5. Lundgren E, Ljunghall S, Akerstrom G, Hetta J, Mallmin H, Rastad J. Case-control study on symptoms and signs of "asymptomatic" primary hyperparathyroidism. *Surgery.* 1998;124:980-985.
6. Dotzenrath CM, Kaetsch AK, Pflingsten H, Cupisti K, Weyerbrock N, Vossough A, Verde PE, Ohmann C. Neuropsychiatric and cognitive changes after surgery for primary hyperparathyroidism. *World J Surg.* 2006;30:680-685.
7. Hasse C, Sitter H, Bachmann S, Zielke A, Koller M, Nies C, Lorenz W, Rothmund M. How asymptomatic is asymptomatic primary hyperparathyroidism? *Exp Clin Endocrinol Diabetes.* 2000;108:265-274.
8. Prager G, Kalaschek A, Kaczirek K, Passler C, Scheuba C, Sonneck G, Niederle B. Parathyroidectomy improves concentration and retentiveness in patients with primary hyperparathyroidism. *Surgery.* 2002;132:930-935.
9. Burney RE, Jones KR, Christy B, Thompson NW. Health status improvement after surgical correction of primary hyperparathyroidism in patients with high and low preoperative calcium levels. *Surgery.* 1999;125:608-614.
10. Pasieka JL, Parsons LL. Prospective surgical outcome study of relief of symptoms following surgery in patients with primary hyperparathyroidism. *World J Surg.* 1998;22:513-518.
11. Sheldon DG, Lee FT, Neil NJ, Ryan JA Jr. Surgical treatment of hyperparathyroidism improves health-related quality of life. *Arch Surg.* 2002;137:1022-1026.
12. Kahal H, Aye M, Rigby AS, Sathyapalan T, England RJ, Atkin SL. The effect of parathyroidectomy on neuropsychological symptoms and biochemical parameters in patients with asymptomatic primary hyperparathyroidism. *Clin Endocrinol (Oxf).* 2012;76:196-200.
13. Blanchard C, Mathonnet M, Sebag F, Caillard C, Hamy A, Volteau C, Heymann MF, Wyart V, Drui D, Roy M, Cariou B, Archambeaud F, Rodien P, Henry JF, Zarnegar R, Hardouin JB, Mirallié E. Surgery for 'asymptomatic' mild primary hyperparathyroidism improves some clinical symptoms postoperatively. *Eur J Endocrinol.* 2013;169:665-672.
14. Caillard C, Sebag F, Mathonnet M, Gibelin H, Brunaud L, Loudot C, Kraimps JL, Hamy A, Bresler L, Charbonnel B, Leborgne J, Henry JF, Nguyen JM, Mirallié E. Prospective evaluation of quality of life (SF-36v2) and nonspecific symptoms before and after cure of primary hyperparathyroidism (1-year follow-up). *Surgery.* 2007;141:153-159.
15. Talpos GB, Bone HG, 3rd, Kleerekoper M, Phillips ER, Alam M, Honasoge M, Divine GW, Rao DS. Randomized trial of parathyroidectomy in mild asymptomatic primary hyperparathyroidism: patient description and effects on the SF-36 health survey. *Surgery.* 2000;128:1013-1020.
16. Pasieka JL, Parsons L, Jones J. The long-term benefit of parathyroidectomy in primary hyperparathyroidism: a 10-year prospective surgical outcome study. *Surgery.* 2009;146:1006-1013.
17. Roman SA, Sosa JA, Mayes L, Desmond E, Boudourakis L, Lin R, Snyder PJ, Holt E, Udelsman R. Parathyroidectomy improves neurocognitive deficits in patients with primary hyperparathyroidism. *Surgery.* 2005;138:1121-1128.
18. Aktaş Yılmaz B, Akyel A, Kan E, Erçin U, Tavil Y, Bilgihan A, Çakır N, Arslan M, Balos Toruner F. Cardiac structure and functions in patients with asymptomatic primary hyperparathyroidism. *J Endocrinol Invest.* 2013;36:848-852.
19. Koçyiğit H, Aydemir O, Fişek G, Ölmez N, Memiş A. Kısa form-36 (KF-36)'nın Türkçe Versiyonunun Güvenilirliği ve Geçerliliği. *İlaç ve Tedavi Dergisi.* 1999;12:102-106.
20. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. *Arch Gen Psychiatry.* 1961;4:561-571.
21. Hisli N. Beck Depresyon Envanterinin Üniversite Öğrencileri İçin Geçerliliği, Güvenilirliği. 1989;7:3-13.
22. Spielberger CD. State-Trait Anxiety Inventory for adults. Manual, Test, Scoring key. Redwood City, CA: Mind Garden Inc; 1999.
23. Le Compte A ON. A study related to adaptation and standardization of State-Trait Anxiety Inventory into Turkish. *Proceeding of 9th. National Congress of Psychiatry and Neurologic Sciences;* 1975:457-462.
24. Golderberg D. WP. A user's guide to the General Health Questionnaire. Windsor, UK: NFER-Nelson; 1988.
25. Kılıç C. Genel Sağlık Anketi: Güvenilirlik ve Geçerlilik Çalışması. *Türk Psikiyatri Dergisi.* 1996;7:3-9.
26. Rao DS, Phillips ER, Divine GW, Talpos GB. Randomized controlled clinical trial of surgery versus no surgery in patients with mild asymptomatic primary hyperparathyroidism. *J Clin Endocrinol Metab.* 2004;89:5415-5422.
27. Veras A, Maia J, Mesquita P, Eufrazino C, Bandeira F. Lower quality of life in longstanding mild primary hyperparathyroidism. *Arq Bras Endocrinol Metabol.* 2013;57:139-143.
28. Wilhelm SM, Lee J, Prinz RA. Major depression due to primary hyperparathyroidism: a frequent and correctable disorder. *Am Surg.* 2004;70:175-179.
29. Espiritu RP, Kearns AE, Vickers KS, Grant C, Ryu E, Wermers RA. Depression in primary hyperparathyroidism: prevalence and benefit of surgery. *J Clin Endocrinol Metab.* 2011;96:1737-1745.

30. Walker MD, McMahon DJ, Inabnet WB, Lazar RM, Brown I, Vardy S, Cosman F, Silverberg SJ. Neuropsychological features in primary hyperparathyroidism: a prospective study. *J Clin Endocrinol Metab.* 2009;94:1951-1958.
31. Bengtson JF, Perrier ND, Massman PJ, Meyers CA, Kayl AE, Wefel JS. Cognitive and affective sequelae of primary hyperparathyroidism and early response to parathyroidectomy. *J Int Neuropsychol Soc.* 2009;15:1002-1011.
32. Chiang CY, Andrewes DG, Anderson D, Devere M, Schweitzer I, Zajac JD. A controlled, prospective study of neuropsychological outcomes post parathyroidectomy in primary hyperparathyroid patients. *Clin Endocrinol (Oxf).* 2005;62:99-104.
33. Quiros RM, Alef MJ, Wilhelm SM, Djuricin G, Loviscek K, Prinz RA. Health-related quality of life in hyperparathyroidism measurably improves after parathyroidectomy. *Surgery.* 2003;134:675-681.
34. Cermik TF, Kaya M, Ugur-Altun B, Bedel D, Berkarda S, Yigitbasi ON. Regional cerebral blood flow abnormalities in patients with primary hyperparathyroidism. *Neuroradiology.* 2007;49:379-385.
35. Mjaland O, Normann E, Halvorsen E, Rynning S, Egeland T. Regional cerebral blood flow in patients with primary hyperparathyroidism before and after successful parathyroidectomy. *Br J Surg.* 2003;90:732-737.
36. Joborn C, Hetta J, Niklasson F, Rastad J, Wide L, Agren H, Akerström G, Ljunghall S. Cerebrospinal fluid calcium, parathyroid hormone, and monoamine and purine metabolites and the blood-brain barrier function in primary hyperparathyroidism. *Psychoneuroendocrinology.* 1991;16:311-322.