

Aspects of Psychological Stress in Success of Parathyroid Allotransplantation

Şule Terzioğlu-Uşak¹ , Birsen Elibol¹ , Çiğdem Dilek Şahbaz² , Erhan Aysan³ 

¹Department of Medical Biology, Faculty of Medicine, Bezmialem Vakif University, Istanbul, Türkiye

²Department of Psychiatry, Liv Hospital Ulus, Istanbul, Türkiye

³Department of General Surgery, Yeditepe University Faculty of Medicine, Istanbul, Türkiye

ORCID ID: Ş.T.U. 0000-0002-4594-2697; B.E. 0000-0002-9462-0862; Ç.D.Ş. 0000-0001-7572-882X; E.A. 0000-0002-9563-3761

Cite this article as: Terzioğlu-Uşak S, Elibol B, Şahbaz CD, Aysan E. Aspects of psychological stress in success of parathyroid allotransplantation. *Experimed* 2022; 12(1): 29-32.

ABSTRACT

Parathyroid auto/allotransplant (PA) may be a valuable alternative in the treatment of permanent hypoparathyroidism which is defined by insufficient levels of parathyroid hormone (PTH). Here, we aimed to investigate a possible association between the PTH levels of the patients who had undergone PA and their psychological stress conditions. The three patients with hypoparathyroidism were reported before and after PA for three-month-follow-up period. The examinations of patients were assessed by biochemical parameters [intact PTH (iPTH), Ca, and P]. The anxiety and stress levels of patients were assessed by self-report measures: State-Trait Anxiety Inventory (STAI-S/T) and Perceived Stress Scale (PSS). Although iPTH levels of all patients had a tendency to increase after PA, one of the patients with a low level of anxiety and stress only reached the normal range of PTH levels. The recovery of the serum iPTH levels at month 1 post-PA was negatively correlated with PSS scores of patients ($r = -0.999$, $p = 0.028$). The outcomes of this report showed for the first time that insufficient PTH release, even after PA, might be related to the stress level of patients. By taking all results into consideration, PTH could be speculated as a stress biomarker.

Keywords: Parathyroid allotransplantation, parathyroid hormone, psychological stress, STAI, PSS

INTRODUCTION

Hypoparathyroidism is an uncommon endocrine disorder related to hypocalcemia, hyperphosphatemia, and low levels of parathyroid hormone (PTH) in the blood (1). The extended or complicated thyroidectomy operations often result in permanent hypoparathyroidism (2). Untreated hypoparathyroidism results in some complications such as nephropathy, cataract, muscle dysfunction, myositis, fasciitis, basal ganglia and/or cerebellar calcifications, and teeth malformations (3). Treatment with calcium and vitamin D replacement is recommended for deficient patients, yet this therapy may be inadequate (4).

Parathyroid allo/autotransplant is a valuable alternative strategy in treating hypoparathyroidism (5-8). Living patients or cadavers have been selected as donors in para-

thyroid transplantation. For many years, Aysan and his colleagues have been using new techniques to describe parathyroid allotransplantation (PA). According to one of their methods, after the mechanical disruption, the small pieces of parathyroid glands obtained from donors with parathyroid hyperplasia are grafted onto the patients with hypoparathyroidism (6). Another technique which is used by Goncu et al. (9) is a laparoscopic transplantation of cultivated parathyroid cell suspension into omentum rather than transplantation of tissue fragments.

During 12-month follow-up, success in the allograft function has been observed in most patients (8). However, increasing PTH levels after transplantation have suddenly declined in some of the patients. When the patients with altered PTH levels were questioned about their daily routines to investigate their psychosomatic problems, it was

Corresponding Author: Şule Terzioğlu-Uşak **E-mail:** sule.terzioglu@gmail.com

Submitted: 17.12.2021 **Revision Requested:** 06.02.2022 **Last Revision Received:** 16.02.2022

Accepted: 01.03.2022 **Published Online:** 21.03.2022



Content of this journal is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.

revealed that they had stressful/fatiguing events during those days. These conjectural findings turned our attention to discover the possible interaction between levels of PTH and psychological stress. The limited available information related to the levels of PTH and stress showed that patients with primary hyperparathyroidism were frequently associated with psychosis as well as with other psychiatric symptoms like dementia, anxiety, depression, lethargy or apathy, stupor, or coma (10). The current literature has also described secondary hypoparathyroidism accompanying mental disorders commonly with a picture of delirium, anxiety, or depression (11, 12). In a study, Tigranian and his colleagues found a remarkable increase in the PTH level, as well as an increase in blood pressure, in students before an examination (13). However, confirmatory evidence on the association between psychological stress and PTH remains insufficient to draw definitive conclusions at present. Therefore, we reported here, for the first time, the possible association between the PTH levels of three patients who had undergone PA and their psychological stress conditions.

CASE REPORT

This study describes three patients with chronic symptomatic hypocalcaemia and hypoparathyroidism who were admitted to our outpatient clinic. They all had a similar history that hypoparathyroidism emerged in the postoperative early stage after total thyroidectomy. The local human ethics commission of Bezmialem Vakif University approved the study, and informed consents were taken from the patients. Then, they were scheduled for PA. Following successful surgical interventions, all three patients were able to leave the hospital without any problems.

The three patients were assessed with the State-Trait Anxiety Inventory (STAI-S/T) (14) and Perceived Stress Scale (PSS) (15) tests. In a single session, patients completed both of the scales without assistance. There was no time limit, and all queries about the items were addressed. The STAI-S assesses a person's current level of anxiety, whereas the STAI-T assesses a person's long-term anxiety level and overall feeling. The STAI had a Cronbach's alpha reliability coefficient, ranging from 0.83 to 0.87 for STAI-S and from 0.26 to 0.68 for STAI-T. The STAI-S and STAI-T have scores ranging between 20 and 80. A higher test result suggests a higher level of anxiety. The three patients performed the Turkish version of both STAI-S and STAI-T (16) before PA and after PA for three-month follow-up period.

The PSS (a 14-item version) is the most validated psychological instrument for assessing stress perception. The perceived stress is a measure of stress based on stressful situations, and the ability to cope with them at an individual level over the previous month. The seven negative items in PSS are designated to examine a lack of control and unpleasant affective reactions, whereas another seven positive elements test the ability to cope with the current stressors. The ratings ranged from 0 to 56, with higher scores suggesting higher stress levels and the lower scores suggesting lower stress levels (17). The total

score from the scale suggests the individual's level of stress, indicating a low level between 11 and 26, a middle level between 27 and 41, and a high stress level between 42 and 56 (18). We demonstrated the occurrence of post-operation stress-related symptoms by assessing with the PSS at month 1 post-PA.

Statistical Package for Social Sciences (SPSS) 19.0 for Windows software was used for statistical analysis. Pearson's correlation test was performed to examine the relationship among the recovery of serum iPTH level and STAI-S, STAI-T, PSS scores at month 1 post-PA. $p \leq 0.05$ was considered for significant differences.

The serum PTH levels and the psychological conditions of three patients before and after PA were presented in Table 1. The iPTH levels of all patients were increased following PA. However, the levels of iPTH did not reach to the normal physiologic levels in the patients 1 and 3 (normal range for iPTH: 15 - 68.3 pg/mL). In contrast to the patients 1 and 3, the iPTH level of patient 2 reached to the normal range after PA. It was 10.7 pg/mL before PA, then increased to 16.4 pg/mL at month 1 after PA, 18.1 pg/mL at month 2 after PA, and 17 pg/mL at month 3 after PA. In addition, we did not notice any change for three-month follow-up period after PA in both calcium (normal range for Ca: 8.4 - 10.2 ng/mL) and phosphorus (normal range for P: 2.3 - 4.7 ng/mL) levels of patients were compared to the levels of those before PA.

Lastly, the STAI-S/T and PSS scores of patient 2 (STAI-S/STAI-T/PSS: 28/44/17) were lower than those of other two patients (STAI-S/STAI-T/PSS: 37/46/31 for patient 1; STAI-S/STAI-T/PSS: 51/57/43 for patient 3) at month 1 post-PA (Table 1). In addition, according to the results of Pearson's correlation test, the recovery of serum iPTH level at month 1 post-PA was negatively correlated with the PSS scores of patients ($r = -0.999$, $p = 0.028$) (Table 2).

DISCUSSION

The role of the adrenergic system in the regulation of PTH secretion has not been clarified yet. However, it was observed that the secretion of PTH may be related to the presence of beta-adrenergic receptors and the sympathetic nerve endings on the parathyroid cells as a psychological stress response (19). The study began with observations in an outpatient clinic to determine which psychological risk factors were linked to alterations in PTH levels of patients who had undergone PA. We assumed that psychological factors and PTH levels had a causal relationship.

The effects of psychological stress on low graft function or rejection in organ transplantation are poorly understood, and this issue is valid for parathyroid gland transplantation, too. Most research on depression and/or anxiety looked at it pre- or early post-transplantation, and how it might affect post-transplant mortality risk. A growing body of evidence suggests that stress influences immune system that could lead to reduced lymphocyte function, especially in T-cell response to mitogens

Table 1. The results of three- month- follow-up for recipients.

		pre-PA	month 1 post-PA	month 2 post-PA	month 3 post-PA
Patient 1	iPTH (pg/mL)	10.3	13.1	13.9	13
	Ca (mg/dL)	8.5	7.5	7.3	7.3
	P (mg/dL)	5.7	5	5.6	5.3
	STAI-S	37	37	42	41
	STAI-T	46	46	51	49
	PSS		31		
Patient 2	iPTH (pg/mL)	10.7	16.4	18.1	17
	Ca (mg/dL)	8.4	7.4	7.8	7.2
	P (mg/dL)	4.1	4.1	5	4.8
	STAI-S	42	28	39	44
	STAI-T	36	44	48	43
	PSS		17		
Patient 3	iPTH (pg/mL)	10.4	10.3	11.7	12.6
	Ca (mg/dL)	7.3	7.7	6.7	7.3
	P (mg/dL)	4.7	4.5	5.6	5.7
	STAI-S	58	51	58	48
	STAI-T	61	57	54	57
	PSS		43		

iPTH: Intact parathyroid hormone; Ca: Calcium; P: Phosphorus; STAI: State and Trait Anxiety Scale; PSS: Perceived Scale Test; PA: Parathyroid allotransplantation.

Table 2. Statistical evaluation by Pearson`s correlation among the recovery of serum iPTH level (pg/mL) at month 1 post-PA and STAI-S, STAI-T, PSS scores.

Time	month 1 post-PA	
iPTH (pg/mL) correlations with	r	p
STAI-S	-0.992	0.079
STAI-T	-0.929	0.242
PSS	-0.999*	0.028

iPTH: Intact parathyroid hormone; PSS: Perceived Scale Test; PA: Parathyroid allotransplantation.*p< 0.05.

(20). In addition, depression appears to lead to higher C-reactive protein and pro-inflammatory cytokines levels (21), each of these factors raises the chance of death in the general population and in people with severe organ disease (22). Therefore, those aforementioned conditions might also adversely affect

the adherence, and thereby undermine effective immunosuppression after organ transplantation. In an early study on 11 patients with acute rejection of a corneal graft which had occurred just after emotional stress, it was clearly evidenced that there was a relationship between psychological stress and graft rejection (23). Furthermore, depression was linked to a two-fold increased risk of graft failure, dialysis, and mortality with a working graft among kidney transplant patients (24).

In our study, all surgical interventions were successful due to the following factors: First, the patients were discharged from the hospital without any complications. In addition, they all had a tendency to increase their PTH levels after PA, too. Interestingly, the PTH level of patient 2 started to reach the normal range at month 1 post-PA and continued during the follow-up period. This patient had the lowest STAI-S and PSS scores implying low anxiety and stress level at the month 1 post-PA. Furthermore, we found that the recovery of iPTH levels of patients were negatively correlated with their perceived stress, rather than their anxiety levels at the month 1 post-PA. The findings of this study were in line with our previous animal study in which we discovered a negative connection between levels of iPTH

and corticosterone in acute restraint stress (25). In summary, all these observations suggested that there is a cross-connection between stress and PTH release.

CONCLUSION

This study concluded that PTH could be speculated as a stress biomarker. Thus, clinicians and psychiatrists should be alerted by the outcomes of this study to the possibility of stress as a risk factor for irregularity/alterations in the PTH levels among recipients after parathyroid transplantation.

Ethics Committee Approval: The local human ethics commission of Bezmialem Vakif University approved the study (15.09.2015-12926), and informed consents were taken from the patients.

Peer-review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study - Ş.T.U., E.A.; Data Acquisition - Ş.T.U., E.A.; Data Analysis/Interpretation - Ş.T.U., B.E.; Ç.D.Ş.; Drafting Manuscript - Ş.T.U., B.E.; Critical Revision of Manuscript - B.E., Ç.D.Ş.; Final Approval and Accountability - Ş.T.U., B.E.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: This work was supported by the Bezmialem Vakif University Research Council (grant number: BAP-9.2015/24).

REFERENCES

- Aggarwal S, Kailash S, Sagar R, Tripathi M, Sreenivas V, Sharma R, et al. Neuropsychological dysfunction in idiopathic hypoparathyroidism and its relationship with intracranial calcification and serum total calcium. *Eur J Endocrinol* 2013; 168(6): 895-903. [\[CrossRef\]](#)
- Testini M, Gurrado A, Lissidini G, Nacchiero M. Hypoparathyroidism after total thyroidectomy. *Minerva Chir* 2007; 62(5): 409-15.
- Khan MI, Waguespack SG, Hu MI. Medical management of post-surgical hypoparathyroidism. *Endoc Pract* 2011; 17(Suppl 1): 18-25. [\[CrossRef\]](#)
- Safioleas M, Stamatakos M, Rompoti N, Mouzopoulos G, Iannescu R, Salichou V, et al. Complications of thyroid surgery. *Chirurgia (Bucur)* 2006; 101: 571-81.
- Nawrot I, Wozniwicz B, Tolloczko T, Sawicki A, Górski A, Chudziński W, et al. Allotransplantation of cultured parathyroid progenitor cells without immunosuppression: Clinical results. *Transplantation* 2007; 83: 734-40. [\[CrossRef\]](#)
- Aysan E, Altug B, Ercan C, Kesgin Toka C, Idiz UO, Muslumanoglu M. Parathyroid allotransplant with a new technique: A prospective clinical trial. *Exp Clin Transplant* 2016; 14(4): 431-5.
- Barczynski M, Golkowski F, Nawrot I. Parathyroid transplantation in thyroid surgery. *Gland Surg* 2017; 6: 530-6. [\[CrossRef\]](#)
- Yucesan E, Goncu B, Basoglu H, Ozten Kandas N, Ersoy YE, Akbas F, et al. Fresh tissue parathyroid allotransplantation with short-term immunosuppression: 1-year follow-up. *Clin Transplant* 2017; 31(11). [\[CrossRef\]](#)
- Goncu B, Yucesan E, Ozdemir B, Basoglu H, Kandas NO, Akbas F, et al. A new transport solution for parathyroid allotransplantation: Effects on cell viability and calcium-sensing receptors. *Biopreserv Biobank* 2018; 16(4): 278-84. [\[CrossRef\]](#)
- Geffken GR, Ward HE, Staab JP, Carmichael SL, Evans DL. Psychiatric morbidity in endocrine disorders. *Psychiatr Clin North Am* 1998; 21(2): 473-89. [\[CrossRef\]](#)
- Ang AW, Ko SM, Tan CH. Calcium, magnesium, and psychotic symptoms in a girl with idiopathic hypoparathyroidism. *Psychosom Med* 1995; 57(3): 299-302. [\[CrossRef\]](#)
- Rosa RG, Barros AJ, de Lima AR, Lorenzi W, Da Rosa RR, Zambonato KD, et al. Mood disorder as a manifestation of primary hypoparathyroidism: a case report. *J Medical Case Rep* 2014; 8: 326. [\[CrossRef\]](#)
- Tigranian RA, Orloff LL, Kalita NF, Davydova NA, Pavlova EA. Changes of blood levels of several hormones, catecholamines, prostaglandins, electrolytes and cAMP in man during emotional stress. *Endocrinol Exp* 1980; 14(2): 101-12.
- Spielberger CD. Manual for the state-trait anxiety inventory form y, self evaluation questionnaire. Palo Alto, CA: Consulting Psychologists Press, 1983. [\[CrossRef\]](#)
- Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. *J Health Soc Behav* 1983; 24: 385-96. [\[CrossRef\]](#)
- Le Compte WA, Oner N. Development of the Turkish edition of the State-trait anxiety inventory. *Cross-Cultural Anxiety* 1976; 1: 51-67.
- Mane Abhaya B, Krishnakuma, MK, Niranjana PC, Hiremath SG. Differences in perceived stress and its correlates among students in professional courses. *J Clin Diagn Res* 2011; 5(6): 1228-33.
- Baltaş Z, Atakuman Y, Duman Y. Standardization of the perceived stress scale: Perceived stress in Turkish middle managers. *Stress and Anxiety Research Society*. 1998: In 19th International Conference, Istanbul.
- Joborn H, Hjemdahl P, Wide L, Akerström G, Ljunghall S. Reduction of serum parathyroid hormone levels during sympathetic stimulation in man. *J Endocrinol Invest* 1987; 10(2): 153-6. [\[CrossRef\]](#)
- Bartrop RW, Lazarus L, Luckhurst E, Kiloh LG. Depressed lymphocyte function after bereavement. *Lancet* 1987; i: 834-6. [\[CrossRef\]](#)
- Elovainio M, Aalto AM, Kivimäki M, Pirkola S, Sundvall J, Lönnqvist J, Reunanen A. Depression and C-reactive protein: Population-based health 2000 study. *Psychosom Med* 2009; 71: 423-30. [\[CrossRef\]](#)
- Tilg H, Wilmer A, Vogel W, Herold M, Nolchen B, Judmaier G, et al. Serum levels of cytokines in chronic liver disease. *Gastroenterology* 1992; 103: 264-74. [\[CrossRef\]](#)
- Kok-van Alphen CC, Völker-Dieben HJ. Emotional stress and rejection, cause and effect. *Doc Ophthalmol* 1983; 56(1-2): 171-5. [\[CrossRef\]](#)
- Dobbels F, Skeans MA, Snyder JJ, Tuomari AV, Maclean JR, Kasiske BL. Depressive disorder in renal transplantation: An analysis of medicare claims. *Am J Kidney Dis* 2008; 51: 819. [\[CrossRef\]](#)
- Terzioğlu-Uşak S, Elibol B, Dalli T, Guler C, Aysan E. Effect of restraint stress on parathyroid hormone secretion in wistar rats. *Int J Endocrinol Metabol* 2018; 16(4): e66979.