THYROID DISORDERS PREVALENCE IN A COHORT OF KIDNEY TRANSPLANT RECIPIENTS

S. Karakose¹, I. Cordan³, G. Gonulalan⁵, M. Karakose^{3,*}, P.O. Kurtgoz¹, I. Baloglu⁴, K. Turkmen⁴, I. Guney¹

University of Health Sciences - Konya Training and Research Hospital, ¹Dept. of Nephrology, ²Dept. of Nephrology, ³Necmettin Erbakan University - Dept. of Endocrinology and Metabolism, ⁴Dept. of Nephrology, Meram, ⁵KTO Karatay University - Endocrinology and Metabolic Disorders, Selçuklu, Konya, Turkey

Abstract

Context. As the life expectancy prolongs, malignancy has become an important issue in renal transplant recipients (RTRs). Thyroid cancer is the most common endocrine malignancy with ongoing increase in incidence all over the world.

Objective and design. This is a cross-sectional study that investigates the thyroid disorders and the prevalence of thyroid nodule and cancer in RTRs.

Subjects and methods. 204 RTRs were evaluated for the thyroid diseases with ultrasonography, serum thyroid stimulating hormone, free T4, free T3 levels, anti-thyroglobulin antibody and anti-thyroid peroxidase antibody levels; FNAB was carried if required.

Results. 191 patients (94.1%) had normal thyroid function. Subclinical hypothyroidism was diagnosed in 11 patients, subclinical hyperthyroidism in 1 patient and low T3 syndrome in 4 patients. The FNAB was performed in 17 (27.9%) from 61 patients with thyroid nodule. The cytological examination of biopsy materials revealed that 2 (11.8%) nodules were suspicious for malignancy, 13 (76.5%) were benign, and 2 (11.8%) with non diagnostic cytology. Thyroid cancer prevalence was 0.2% in Turkey but we detected that 0.98% of RTRs had thyroid cancer.

Conclusions. Screening the RTRs for thyroid disorders is necessary, so that early diagnosis and appropriate treatment of thyroid disease and cancer may improve the quality of life.

Keywords: renal transplant, thyroid dysfunction, thyroid cancer.

account for the 18 % of all deaths in RT recipients so that malignancy screening gains importance in this specific population (4).

In general population thyroid nodules are frequently encountered. As the nodule incidence increases with age, after 50 years of age the sonographic prevalence reaches 50%. The sonographic prevalence of thyroid nodules in our country was reported as 23.5% between 18-65 ages and 37.4% after 65 years of age. The thyroid nodule incidence increases with such factors such as aging, iodine deficiency, radiation exposure and female gender (5). Clinically it is significant to exclude the malignancy in a nodule because thyroid cancer was observed in 4% - 6.5 % of thyroid nodule cases (6, 7). The most encountered endocrine malignancy is thyroid cancer with ongoing increase in incidence all over the world (8). On the other hand, mortality of thyroid cancer is decreasing despite the increasing incidence owing to early diagnosis and effective treatment (9).

An important prognostic factor of mortality in RT recipients is post transplant malignancy (10). Malignancies associated with immunosuppressive drugs are generally blamed for this issue in RT recipients (11). The post transplant malignancy incidence changes with ethnic population and geographic location (12, 13). Herein we evaluated the thyroid disorders and prevalence of thyroid nodule and cancer in Turkish renal transplant recipients.

INTRODUCTION

The best treatment option for the end stage renal disease (ESRD) patients is renal transplantation (RT) (1). RT offers to ESRD patients a better life expectancy and quality of life compared to hemodialysis (2). As the life expectancy prolongs, malignancy has become an important issue in RT recipients (3). Malignancy

MATERIALS AND METHODS

Two hundred and four patients who underwent renal transplantation between January 1991-January 2020 were recruited in this cross-sectional study. Demographic and clinical data, laboratory results were recorded from patients' files. The study protocol was approved by the ethics committee of Meram Medical

*Correspondence to: Melia Karaköse MD, Diskapi Training and Research Hospital, Endocrinology and Metabolism, Selçuk Mah. Şehit Ömer Halisdemir Cad. No:17 Altınpark sitesi C2 blok No:14 Selçuklu Konya, Konya, 42080, Turkey, E-mail: meliakarakose@yahoo.com
Acta Endocrinologica (Buc), vol. XVI, no. 3, p. 324-328, 2020

RESULTS

Faculty of Necmettin Erbakan University (approval no:2020/2326) and the study was carried out in accordance with the Helsinki Declaration. Informed consents were gathered from patients prior to the study.

Chemiluminescent microparticle immunoassay (Abbott, Architect i2000, Abbott Laboratories Diagnosis Division, IL, USA) was used to measure the free T4 (fT4), free T3 (fT3) and thyroid stimulating hormone (TSH) levels. Anti-thyroid peroxidase antibody (anti-TPO Ab) and anti-thyroglobulin antibody (anti-TG Ab) levels were detected via chemiluminescent competitive immunoassay (Advia Centaur XP, Siemens, Tarrytown, USA). The reference ranges of TSH, fT3, fT4, anti-TPO and anti-TG were 0.27-4.2 mU/L, 2-4.4 ng/L, 0.93-1.7 ng/dL, 0-34 U/mL and 0-115 U/mL, respectively. If the results of anti-TG Ab and anti-TPO were above the upper limits they were considered as positive. An endocrinologist with radiological experience performed the ultrasonographic examinations of renal transplant recipients (RTRs) with an 11-MHz linear probe on a LOGIQ 3 (General Electric Healthcare, Waukesha, WI USA) device.

The ellipsoid formula was used to calculate the thyroid gland volume: volume (mL) = length (cm) x depth (cm) x width (cm) x $\pi/6$ (14). The threshold values of thyroid volume to accept as goiter were 25 mL for men and 18 mL for women (15). The properties of thyroid nodules were evaluated and recorded as recommended by the American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer (16). The same guideline recommendations were followed for fine-needle aspiration biopsy (FNAB) indications (17). Weight (kg) and Height (m) of patients were measured to calculate the body mass index (BMI) by the formula: weight (kg)/height square (m²).

Statistical analysis

The statistical analysis was performed via SPSS 22.0 (Statistical Package for Social Sciences) program. Categorical variables were analyzed either by Chi-square test or Fisher's exact test. The normality of the variables was determined with Kolmogorov-Smirnov test. The groups were compared with independent samples t-test and Mann-Whitney U test. Data were given as median-interquartile range or mean $\pm$ standard deviation, whichever is appropriate. Pearson's correlation coefficient was used to evaluate the continuous variables and for the evaluation of non-normally distributed variables. P values below 0.05 were accepted as statistically significant.

A total of 204 renal transplant recipients were included in the study. Of the 204 patients, 86 (42.2%) were female, 118 (57.8%) were male. The mean age of the patients was 46 ± 12 years.

Underlying diseases were hypertension in 63 (30.9%), glomerulonephritis in 34 (16.7%), diabetes mellitus in 27 (13.2%), polycystic kidney disease in 5 (2.5%), other causes in 28 (13.6%) and idiopathic in 47 (23.1%) cases. The 28.8% of cases were preemptive renal transplantation patients, 60% of patients were maintenance hemodialysis patients and 10.2 % were continuous peritoneal dialysis patients.

Median period of peritoneal dialysis or hemodialysis prior to renal transplantation was 16 months (range: 3–238 months). Post-transplantation follow-up period was 85 months (range: 8–348 months). Steroids, cyclosporine/tacrolimus, mycophenolate mofetil/azathioprine and sirolimus/everolimus were the drugs used for maintenance of immunosuppression.

One hundred and ninety one patients (94.1%) had normal thyroid function. Overt hypothyroidism was not encountered in any patient. Subclinical hypothyroidism in 11 patients, subclinical hyperthyroidism was diagnosed in 1 patient and low T3 syndrome in 4 patients. Mean thyroid volume was 9.8 ± 6.4 mL. Goiter was detected in 6.9 % of RTRs. Thyroid nodules were detected in 61 (29.9%) patients. Forty seven RTRs had a single nodule and 14 patients had multiple nodules. The prevalence of subjects who had either or both of the anti-TG Ab and anti-TPO Ab was 8.4% among the patients.

The FNAB was performed in 17 (27.9%) of 61 patients with thyroid nodule. The cytological examination of biopsy materials revealed that 2 (11.8%) nodules were suspicious for malignancy, 13 (76.5%) were benign, and 2 (11.8%) with non diagnostic cytology. The patients whose FNAB results were suspicious for malignancy underwent surgery. All of them were diagnosed with papillary thyroid carcinoma as a result of histopathological investigation of surgery materials. Distant metastasis was not detected. The RTRs with malignancy received adjuvant radioiodine treatment. The papillary thyroid cancer was diagnosed 180 months after RT in one of these patients and after 44 months in the other one. Both of the patients received steroid, mycophenolate mofetil and tacrolimus in treatment.

The tacrolimus serum level was reduced between 3-5 ng/ mL in both patients, mycophenolate mofetil was continued as 2X360 mg / day, but there

was no increase in creatinine levels and 24-hour proteinuria results in the follow-up of these patients. The serum TSH, fT3 and fT4 levels were not different among patients with or without nodules. There was no difference regarding the prevalence of positivity of either anti-Tg Ab or anti-TPO Ab in both groups of patients. Also nodule prevalences were not different according to the immunosuppressive regimens.

There was no difference in terms of hemodialysis/peritoneal dialysis time and post transplantation follow up duration in both groups. The characteristics of patients with and without nodules are given in Table 2.

DISCUSSION

It has been reported that RTRs had increased risk of malignancies compared to general population

due to long-term use of immunosuppressive drugs and hemodialysis treatment before transplantation (17-19). However, the data about thyroid cancer in RTRs are somewhat conflicting (20-24). These studies reported the thyroid cancer prevalence between 0 and 11.4% (21-25). Cengiz K. *et al.* reported only 10 (0.35%) papillary thyroid cancer cases from 2817 Turkish ESRD patients (25). Another study from Turkey reported the thyroid cancer prevalence as 0.8% in RTRs (26). Although the thyroid cancer prevalence was 0.2% in Turkey we detected the thyroid cancer prevalence as 0.98% in RTRs.

Pond F *et al.* detected 23 thyroid cancer cases among 10.689 RTRs and found the thyroid cancer prevalence as 0.22% (27). An interesting point in their study was that male patients had more thyroid cancer. In our study, one of the cases with thyroid cancer was a male and the other was a female. More recently, Gungor

Table 1. Clinical characteristics of the transplant patients

Age (years)	46 ± 12
Male/Female (n,%)	118 (57.8%) / 86 (42.2%)
BMI (kg/m ²)	26.4 ± 4.8
Underlying disease(n, %)	
Diabetes mellitus	27 (13.2%)
Hypertension	63 (30.9%)
Glomerulonephritis	34 (16.7%)
Polycystic kidney disease	5 (2.5%)
Other causes	28 (13.6%)
Idiopathic	47 (23.1%)
HD/PD time up to transplantation (months)	16 (range: 3–238)
Post-transplantation follow-up duration	85 (range: 8-348)
Creatinine (mg/dL)	1.4 ± 0.6
Immunosuppression (n,%)	
Tacrolimus/ cyclosporine+steroid+MMF	174 (85.3%)
Tacrolimus/cyclosporine+steroid+ azathioprine	12 (5.9%)
Everolimus/ sirolimus +steroid+ MMF	18 (8.8%)

BMI: body mass index, HD: hemodialysis, PD: peritoneal dialysis; MMF: mycophenolate mofetil.

Table 2. The characteristics of patients with and without thyroid nodule

	Without nodule (n=143)	With nodule (n=61)	P
Age (years)	45.5 ± 11.6	47.6 ± 14.1	0.3
Male/Female (n)	93 / 50	25 / 36	0.02
BMI (kg/m ²)	26.5 ± 4.6	26.3 ± 5.3	0.8
Post-transplantation follow-up duration (months)	70 (range: 2-348)	84 (range: 8-340)	0.6
HD/PD time up to transplantation (months)	13 (range: 3-238)	41 (range: 4-180)	0.3
Immunosuppression (n)			
Tacrolimus/ cyclosporine+steroid+MMF	124	50	0.6
Tacrolimus/cyclosporine+steroid+ azathioprine	7	5	0.6
Everolimus/ sirolimus +steroid+ MMF	12	6	0.4
TSH	1.6 ± 0.1	1.8 ± 0.9	0.3
fT4	1.3 ± 0.2	1.2 ± 0.2	0.1
fT3	3 ± 0.5	2.9 ± 0.6	0.3
Positive anti-TPO Ab (n)	2	2	0.5
Positive anti-Tg Ab	3	1	0.6

BMI: body mass index, HD: hemodialysis, PD: peritoneal dialysis, MMF: mycophenolate mofetil

et al. reported that thyroid nodule prevalence (40%) was higher in kidney transplant recipients compared with the normal population (26). However, the prevalence of thyroid nodule in our study was 29.9% and it was similar to thyroid nodule prevalence (33%) of Turkish population (28). Our results compatible with the studies that reported the presence of thyroid nodules were not related to age, post-transplantation follow-up period, duration of dialysis or serum TSH levels in RTRs (27, 29). Tauchmanova *et al.* in contrast to these results, reported that the occurrence of nodules increased with the duration of dialysis, but age and time after transplantation were similar between RTRs with and without nodules (30). We did not detect any relation between duration of dialysis and thyroid nodule presence. Also there was no difference in nodule prevalence according to the immunosuppressive regimens in our study.

The data about thyroid dysfunction in previous studies were limited and conflicting no specific functional disturbances were reported in most of them, but some reported an increased incidence of hypothyroidism after renal transplantation. In our study, thyroid dysfunction was encountered in 7.8% of RTRs. Subclinical hypothyroidism, low T3 syndrome and subclinical hyperthyroidism were detected in 11 patients, 4 and only 1 patient, respectively in our study. The scintigraphy of the patient with subclinical hyperthyroidism was found to be compatible with toxic multinodular goiter. As a result of immunosuppressive drugs thyroid diseases might worsen after renal transplantation (31).

The limitations of the study are the absence of ultrasonographic examination of the thyroid gland before transplantation and that the number of patients is not large.

In conclusion, thyroid disorders are common in RTRs. Presumably, as a result of immunosuppressive drugs, thyroid disorders may be encountered after renal transplantation. Screening the RTRs for thyroid disorders is necessary, so that early diagnosis and appropriate treatment of thyroid disease and cancer may improve the life quality of these patients. Also endocrinological investigation might be helpful to differentiate the thyroid dysfunctions which need treatment from those biochemical abnormalities that do not require a treatment.

Conflict of interest

The authors declare that they have no conflict of interest.

Ethical approval

All procedures performed in this study involving

human participants were in accordance with the ethical standards of the local ethic committee where the studies were conducted (approval number: 2020/2326), and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

References

1. Abecassis M, Bartlett ST, Collins AJ, Davis CL, Delmonico FL, Friedewald JJ, Hays R, Howard A, Jones E, Leichtman AB, Merion RM, Metzger RA, Pradel F, Schweitzer EJ, Velez RL, Gaston RS. Kidney transplantation as primary therapy for end-stage renal disease: a National Kidney Foundation/Kidney Disease Outcomes Quality Initiative (NKF/KDOQIM) Conference. Clin J Am Soc Nephrol. 2008;3(2):471-480.
2. Hassanzadeh J, Hashiani AA, Rajaeefard A, Salahi H, Khedmati E, Kakaei F, Nikeghbalian S, Malek-Hosseini A. Long-term survival of living donor renal transplants: a single center study. Indian Journal of Nephrology. 2010; 20(4):179-184.
3. Agraharkar ML, Cinclair RD, Kuo YF, Daller JA, Shahinian VB. Risk of malignancy with long-term immunosuppression in renal transplant recipients. Kidney Int. 2004; 66:383-389.
4. Farrugia D, Mahboob S, Cheshire J, Begaj I, Khosla S, Ray D, Sharif A. Malignancy-related mortality following kidney transplantation is common. Kidney Int. 2014; 85(6):1395-1403.
5. M.T. Rojeski, H. Gharib. Nodular thyroid disease: evaluation and management. The New England Journal of Medicine. 1985; 313:428-436.
6. Hegedus L. Clinical practice. The thyroid nodule. N Engl J Med. 2004; 351:1764-1771.
7. Lin JD, Chao TC, Huang BY, Chen ST, Chang HY, Hsueh C. Thyroid cancer in the thyroid nodules evaluated by ultrasonography and fine-needle aspiration cytology. Thyroid. 2005; 15: 708-717.
8. Cabanillas ME, McFadden DG, Durante C. Thyroid cancer. Lancet. 2016; 388: 2783-2795.
9. Mazzaferri EL. Thyroid cancer. In Becker KL (editor). Principles and Practice of Endocrinology and Metabolism, 3rd Ed. Philadelphia, PA, USA: Lippincott, Williams & Wilkins; pp. 2001; 382-402.
10. Marcen R. Immunosuppressive drugs in kidney transplantation: impact on patient survival, and incidence of cardiovascular disease, malignancy and infection. Drugs. 2009; 69(16):2227-2243.
11. Gallagher MP, Kelly PJ, Jardine M, Perkovic V, Cass A, Craig JC. Long-term Cancer risk of immunosuppressive regimens after kidney transplantation. J Am Soc Nephrol. 2010; 21(5):852-858.
12. Villeneuve PJ, Schaubel DE, Fenton SS, Shepherd FA, Jiang Y, Mao Y. Cancer incidence among Canadian kidney transplant recipients. Am J Transplant. 2007; 7(4):941-948.
13. Hoshida Y, Tsukuma H, Yasunaga Y, Xu N, Fujita MQ, T Satoh, Y Ichikawa, K Kurihara, M Imanishi, T Matsuno, K Aozasa. Cancer risk after renal transplantation in Japan. Int J Cancer. 1997; 71(4):517-520.
14. Brunn J, Block U, Ruf G, Bos I, Kunze WP, Scriba PC. Volumetric analysis of thyroid lobes by real-time ultrasound. Deutsch Med Wochenschr 1981; 106:1338-1340.
15. Gutekunst R, Becker W, Hehrmann R, Olbricht T, Pfannenstiel P. Ultrasonic diagnosis of the thyroid gland. Dtsch Med Wochenschr. 1988;113(27):1109-1112.
16. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, Pacini F, Randolph GW, Sawka AM, Schlumberger M, Schuff KG, Sherman SI, Sosa JA, Steward DL, Tuttle RM, Wartofsky L. 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American Thyroid Association Guidelines Task Force on thyroid nodules and differentiated thyroid cancer. Thyroid. 2016; 26(1):1-133.

17. Hibberd AD, Trevillian PR, Wlodarczyk JH, Kemp DG, Stein AM, Gillies AH, Heer MK, Sheil AG. Effect of immunosuppression for primary renal disease on the risk of cancer in subsequent renal transplantation: a population based retrospective cohort study. *Transplantation*. 2013; 95(1):122–127.
18. Wang Y, Lan G-B, Peng FH, Xie XB. Cancer risks in recipients of renal transplants: a meta-analysis of cohort studies. *Oncotarget*. 2018; 9(20):15375–15385.
19. Wong G, Turner RM, Chapman JR, Howell M, Lim WH, Webster AC, Craig JC. Time on dialysis and cancer risk after kidney transplantation. *Transplantation* 2013; 95(1):114–121.
20. Lebkowska U, Malyszko JS, Malyszko J, Dzieciol J, Walecki J, Mysliwiec M. Thyroid function and incidentaloma in kidney transplant patients. *Med Sci Monit*. 2003; 9(2):8–11.
21. Kyllönen L, Pukkala E, Eklund B. Cancer incidence in a kidney transplanted population. *Transplant Int*. 1994; 7(1):350–352.
22. Pond F, Serpell JW, Webster A. Thyroid cancer in the renal transplant population: Epidemiological study. *ANZ J Surg*. 2005; 75(3):106–109.
23. Nemes B, Zalatnai A, Podder H, Járny J, Sótonyi P Jr, Z Schaff, K Földes, F Perner. Papillary microcarcinoma of the thyroid gland in renal transplant patients. *Pathol Oncol Res*. 2000; 6(1):72–75.
24. Tauchmanova L, Carrano R, Musella T, F Orio, M Sabbatini, G Lombardi, G Fenzi, S Federico, A Colao. Thyroid function and morphology after a successful kidney transplantation. *J Endocrinol Invest*. 2006; 29(7):625–632.
25. Cengiz K. Increased incidence of neoplasia in chronic renal failure (20-year experience). *Int Urol Nephrol*. 2002; 33(1):121–126.
26. Gungor O, Celik A, Kebapcilar L, Karaoglu O, Ersan S, Atilla K, Canda T, Bayraktar F, Yesil S. Incidence of thyroid dysfunction and thyroid cancer in renal transplant recipients: a single center experience. *Ren Fail*. 2010; 32(2):167–171.
27. Pond F, Serpell JW, Webster A. Thyroid cancer in the renal transplant population: epidemiological study. *ANZ J Surg*. 2005; 75:106–109.
28. Ugurlu S, Caglar E, Yesim TE, Tanri kulu E, Can G, Kadioglu P. Evaluation of thyroid nodules in Turkish population. *Intern Med*. 2008; 47(4):205–209.
29. Lebkowska U, Malyszko JS, Malyszko J, Dzieciol J, Walecki J, Mysliwiec M. Thyroid function and incidentaloma in kidney transplant patients. *Med Sci Monit*. 2003; 9(2):8–11.
30. Tauchmanova L, Carrano R, Musella T, Orio F, Sabbatini M, Lombardi G, Fenzi G, Federico S, Colao A. Thyroid function and morphology after a successful kidney transplantation. *J Endocrinol Invest*. 2006; 29(7):625–632.
31. Veroux M, Giuffrida G, Gagliano M, Giaquinta A, Tallarita T, Sorbello M, Corona D, Zerbo D, Vizcarra D, Sciffignano V, Cannizzaro MA, Veroux P. Evaluation of thyroid disease in kidney transplantation candidates: management and follow-up. *Transplant Proc*. 2009; 41:1142–1144.