Original Article

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1196968
J Health Sci Med 2023; 6(1): 66-72

The effect of thyroid hormone withdrawal performed to evaluate the success of I-131 ablation on quality of life and psychological symptoms in female patients with low-risk differentiated thyroid cancer

Osman Kupik[1], Bayram Şen[2], Medeni Arpa[2], Uğur Avcı[3], Hasan Gündoğdu[4], Süleyman Kalcan[5], Hasan Güçer[6], Şafak Akın[7], Murat Tuncel[8]

[1]Department of Nuclear Medicine, Faculty of Medicine, Muğla University, Muğla, Turkey
[2]Department of Biochemistry, Faculty of Medicine, Recep Tayyip Erdoğan University, Rize, Turkey
[3]Division of Endocrinology and Metabolism, Department of Internal Medicine, Faculty of Medicine, Recep Tayyip Erdoğan University, Rize, Turkey
[4]Department of Radiology, Faculty of Medicine, Recep Tayyip Erdoğan University, Rize, Turkey
[5]Department of General Surgery, Faculty of Medicine, Recep Tayyip Erdoğan University, Rize, Turkey
[6]Department of Medical Pathology, Faculty of Medicine, Recep Tayyip Erdoğan University, Rize, Turkey
[7]Department of Endocrinology, Gülhane Training and Research Hospital, University of Health Sciences, Ankara, Turkey
[8]Department of Nuclear Medicine, Faculty of Medicine, Hacettepe University, Ankara, Turkey

Cite this article as: Kupik O, Şen B, Arpa M, et al. The effect of thyroid hormone withdrawal performed to evaluate the success of i-131 ablation on quality of life and psychological symptoms in female patients with low-risk differentiated thyroid cancer. J Health Sci Med 2023; 6(1): 66-72.

ABSTRACT

Aim: There is a need to evaluate the treatment response in patients who have undergone radioiodine treatment (RIT) for differentiated thyroid cancer. Diagnostic tests that are used for this purpose include radioiodine whole-body scan (WBS) and serum thyroglobulin (Tg) measurement, which are most accurate during thyroid-stimulating hormone (TSH) stimulation. However, temporary discontinuation of thyroid hormone therapy to increase TSH (withdrawal) may be associated with the morbidity of hypothyroidism. The study aimed to show the effects of thyroid hormone withdrawal (THW) on quality of life and psychological symptoms in female patients with low-risk, well-differentiated papillary thyroid cancer.

Material and Method: We applied the short form-36 (SF-36) and Symptom Checklist-90-R (SCL-90-R) questionnaires to the patients in the euthyroid state who have referred a median of 9 months (6-13 months) after RIT to perform a dWBS and to evaluate stimulated Tg. We applied the same questionnaire again when thyroid-stimulating hormone (TSH) was > 30 μIU/mL 4 weeks after THW (hypothyroid state).

Results: 52 patients were evaluated (median age 48 years, range 23-65 years). There was a statistically significant worsening in anxiety, psychosis, additional items, and general symptoms of the SCL-90-R questionnaire. With the SF-36 questionnaire, we observed statistically significant worsening in physical functioning, role limitation due to physical health, energy/fatigue, emotional well-being, social functioning, and general health change.

Conclusion: THW worsened the patients' psychological symptoms and quality of life. To reduce the side effects of hypothyroidism, treatment response assessment with TSH stimulation should be used only in a selected group of patients.

Keywords: Thyroid cancer, hypothyroidism, life quality, psychological symptom

This manuscript has been published as pre-print with a DOI of 10.21203/rs.3.rs-684400/v. It was presented at the 2022 Turkish national nuclear medicine congress as an oral presentation.

INTRODUCTION

The survival rate of patients with thyroid cancer is >90%, although it varies among disease subgroups. The standard treatment for DTC is total thyroidectomy, with cervical lymph node dissection if necessary, followed by radioiodine treatment (RIT) (1,2). Administration of iodine 131 (I-131) after total thyroidectomy has three main goals: (1) to destroy possibly benign residual thyroid tissue, which increases the specificity of serum thyroglobulin (Tg) measurement during follow-up; (2) to eliminate suspected but unidentified residual disease or known persistent or recurrent disease that may decrease disease-free survival (DFS) and overall survival (O.S.); and (3) to perform a highly

Corresponding Author: Osman Kupik, osmankupik@gmail.com
Received: 01.11.2022 **Accepted:** 24.11.2022

sensitive post-treatment whole-body scan (WBS) (3). In patients undergoing ablation, diagnostic whole-body scans (dWBS) with stimulated Tg test are performed 6-12 months after treatment to evaluate treatment success (4). Although the sensitivity of a dWBS in demonstrating residual normal thyroid tissue is high, its success in demonstrating metastatic disease is limited. For this reason, this method has steadily decreased, especially in low-risk patients. In some centers, stimulated Tg levels can be used alone for evaluation of the treatment response (5-8). However, both tests require TSH stimulation for optimal sensitivity (9). TSH stimulation can be performed by thyroid hormone withdrawal (THW) or administration of recombinant human thyrotropin (thyrotropin alfa) (10). THW is a cheap, readily available method of TSH stimulation. However, it is associated with clinical hypothyroidism, which has many side effects, including drowsiness, constipation, weakness, myalgia, emotional dysfunction, and physical discomfort (11,12). While improving survival is essential in cancer patient management, quality of life (QoL) preservation should also be one of the ultimate goals. However, temporary hypothyroidism reduces QoL (13,14). The 36-item Short-Form Health Survey (SF-36) is a validated questionnaire on general health and well-being. It has also been used in studies on thyroid diseases. The Symptom Checklist 90–Revised (SCL-90-R) is a questionnaire evaluating psychological symptoms and has been used in studies on hypothyroidism (15-17).

Our study aimed to determine the effects of THW, during the dWBS, on QoL and psychological symptoms by questionnaires in female patients with low-risk, well-differentiated thyroid cancer.

MATERIAL AND METHOD

The study was carried out with the permission of Recep Tayyip Erdoğan University Faculty of Medicine Non-interventional Clinical Researches Ethics Committee (Date: 28.11.2019, Decision No: 2019-191). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patient Selection

We included 52 female patients who underwent RIT between March 2017 and November 2017 (median age 48 years, range 23-65 years). (40465587-102.01-274). All patients provided written informed consent.

Inclusion Criteria

We included female patients aged 18-65 who underwent RIT for differentiated thyroid cancer. After RIT, regular TSH, free thyroxine (fT4), Tg, and thyroglobulin antibody (TgAb) levels were followed up until the dWBS.

Exclusion Criteria

We excluded patients with diabetes mellitus, chronic kidney disease, chronic liver disease, chronic rheumatic disease, chronic musculoskeletal disease, and patients with non-thyroid cancer. We also excluded patients who were using active psychiatric drugs at that time. After RIT, some patients did not have regular TSH and fT4 level follow-up; hence, there were patients with overt hypothyroidism and hyperthyroidism, and we excluded them.

Treatment Protocol

Surgical treatment: 44% of our patients (n=23) were operated on in our center. 56% of them (n=29) were operated on in other centers and referred to our center for RIT. Total thyroidectomy (T.T.) was performed in 18 patients (34.6%), and total thyroidectomy plus central neck dissection (CND) was performed in 5 patients (9.6%). Near-total thyroidectomy (nTT) was performed in 15 patients (28.8%), and subtotal thyroidectomy (sTT) was performed in 14 patients (26.9%). The surgeon who performed the operations in our center (S.K.) is experienced in thyroid surgery (12 years of experience with endocrine surgery). The total number of patients in our center was 23 (18 patients TT, five patients TT + CND). Biopsy-proven lymph node metastases (n= 1) or suspicious findings were found preoperatively on neck ultrasound (n= 4) and were evaluated with CND. None of the patients underwent lateral neck dissection.

I-131 administration decision: Pathology results; TSH, Tg, and Tg-Ab levels; pre-ablation technetium-99m scintigraphy; and ultrasonography results of the patients were evaluated by the pathologists, endocrinologists, surgeons, radiologists, and nuclear medicine specialists, and a consensus decided the treatment. I-131 administration was initiated 2-4 months after surgery. Patients received 1.85 or 3.7 GBq of I-131 approximately four weeks after THW 2-to three weeks of a low iodine diet. At the time of I-131 administration, serum TSH levels were > 30 μIU/mL in all patients.

Research Protocol

A nuclear medicine specialist (O.K.) and two thyroid endocrinologists (Ş.A. and U.A.) reviewed each patient's staging and initial risk stratification based on the clinical, surgical, and pathological information and the post-ablation scintigraphy findings.

Risk Stratification

We classified the tumors using TNM staging according to the American Joint Committee on Cancer (AJCC) 8th edition criteria. The risk classification of the patients and the RIT response were made according to the 2015 American Thyroid Association (ATA) criteria (10).

Clinical Outcome and Questionnaire Administration

After the I-131 administration, the patients were followed up in the endocrinology clinic. The patients were referred to the nuclear medicine clinic for the dWBS and evaluation of stimulated Tg at a median of 9 months (6-13 months) after RIT. We evaluated the TSH and fT4 levels of the patients. We informed the patients without overt hyperthyroidism and hypothyroidism about the questionnaire and administrated the SF-36 and SCL-90-R under the guidance of an expert (O.K.) (questionnaire 1: euthyroid state). We terminated the patients' LT4 use. After four weeks, the patients were given an appointment to receive 185 MBq in an oral I-131 capsule. Patients were recommended to consume a low-iodine diet for two weeks. After four weeks, we measured TSH, Tg, TgAb, and fT4 levels. The same specialist (O.K.) applied the SF-36 and SCL-90-R questionnaires again to the patients with serum TSH > 30 μIU/mL (questionnaire 2: hypothyroid state). Ultrasonography was performed on the patients by O.K. and H.G. We evaluated the absence of residue in the thyroid bed and the absence of pathological lymph nodes in the central/lateral neck compartment as a negative result. We then administered 185 MBq via an oral I-131 capsule to the patients. Two days after I-131 administration, a planar WBS was performed in anterior and posterior projections using a dual-head camera equipped with high-energy, parallel-hole collimators. The WBS was evaluated by the same specialist (O.K.), blinded to the patients' Tg, TgAb levels, clinical findings, and post-ablation WBS images. Radioiodine uptake in the thyroid bed, midline superior thyroglossal duct cyst/pyramidal lodge, and the central and lateral neck compartment were evaluated as a residual disease. RIT response assessments were made according to the 2015 American Thyroid Association (ATA) criteria (10).

Measurement of QoL and Psychological Symptoms

We applied the SF-36 to evaluate the patients' QoL. We also applied the SCL90-R psychological symptom screening test and calculated the total score of these tests for each patient.

The SF-36 scale was developed by Ware et al. (18). The validity and reliability study of the SF-36 in the Turkish population was performed by Koçyiğit et al. (19). We used this version of the scale in our study. The SF-36 consists of 36 items and provides eight symptoms: physical functioning, role limitation due to physical health, energy/fatigue, emotional well-being, social functioning, pain, general health, and health changes. The total score is obtained by adding the points for each sub-scale, with a total score of 100. A decrease in the numerical score indicates deterioration in health.

The SCL-90-R psychological symptom screening test is a self-assessment instrument. The psychopathological symptoms are scored from 0 to 4 for 90 items, and the sub-scale scores – somatization, anxiety, depression, obsession, intersensitivity, anger, paranoid, psychoticism, phobia, general symptom index, and additional items (symptoms related to sleep disorders, appetite disorders and guilt) – are calculated (20). The validity and reliability study of the SLC-90-R in the Turkish population was performed by Dağ et al. (21). We used this version in our study.

Statistical Analysis

Statistical analyses were performed using SPSS Statistics version 23.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics of categorical variables are reported as frequency and percentages within the group (n, %). Continuous variables were subjected to normality analysis to determine their distributions. Changes between questionnaires 1 and 2 were evaluated with the paired-samples t-test or the Wilcoxon signed-rank test. The mean±standard deviation (S.D.) and t values of the normally distributed variables or the median (min-max) and Z values of the non-normally distributed variables are presented. The limit of significance was accepted as $p < 0.05$.

RESULTS

General Findings

Metastatic lymph nodes were detected in 5 patients who underwent CND (17 metastatic lymph nodes with a mean size of 8.4 mm [range 4-11 mm]). The mean time between surgery and RIT was 60.85±17.34 days. All patients had papillary thyroid carcinoma. Only one patient (2%) had stage 2 disease according to the TNM classification; all other patients had stage 1 disease. According to the ATA risk classification, forty-eight patients (92%) were in the low-risk group. Four patients (8%) were in the intermediate group. For treatment, 1850 MBq was administered to 7 patients, and 3700 MBq I-131 was administered to 45 patients. The main characteristics of the study population are shown in **Table 1**. Ablation success based on the dWBS only was 96.2%, on Tg only was 98%, and on TgAb only was 88.5%.

Table 1. The characteristics of the study population.	
Parameter	**N (%)**
Histology	
Classical variant	33 (63.5)
Mixt+classical variant	3 (5.8)
Folicular variant	13 (25)
Tall cell variant	2 (3.8)
Oncositic variant	1 (1.9)
Multifocality	39 (75)
Tumor at surgery margin	6 (11.5)
Microcarcinoma	21 (40.4)
Vascular invasion	2 (3.8)
TNM stage 1	51 (98)
T1	37 (71.2)
T1a	20 (38.5)
T1b	17 (32.7)
T2	13 (25)
T3a	2 (3.8)
N0	46 (88.4)
N0a	10 (19.2)
N0b	36 (69.2)
N1a	5 (9.6)
Nx	1 (1.9)
M0	52 (100)
I-131 dose	
1850 MBq	7 (13.5)
3700 MBq	45 (86.5)
Treatment response	
Excellent	45 (86.5)
Indeterminate	7 (13.5)

SCL-90-R Analysis

Between questionnaire 1 and questionnaire 2, there was significant worsening in anxiety (Z=-2.052, p=0.040), psychoticism (Z=-2.187, p=0.029), additional items (Z=-2.306, p=0.021) and the general symptom index (Z=-2.086, p=0.037). None of the other symptoms showed a significant change (depression, t=-1.390, p=0.171; somatisation, Z=-1.453, p=0.146; obsession, Z=-0.700, p=0.484; intersensitivity, Z=-1.194, p=0.232; paranoia, Z=-0.261, p=0.794; anger, Z=-1.115, p=0.265; phobia, Z=-0.834, p=0.404) (**Figure 1**).

SF-36 Analysis

Between questionnaire 1 and questionnaire 2, there was significant worsening in physical functioning (t=2.588, p=0.013), role limitation due to physical health (Z=-2.677, p=0.007), energy/fatigue (Z=-2.502, p=0.012), emotional well-being (Z=-3.618, p < 0.0001), social function (Z=-3.179, p=0.001), general health (Z=-2.397, p=0.017) and health change (Z=-1.996, p=0.046). There was worsening of the pain symptom, but it was not statistically significant (t=1.234, p=0.223) (**Figure 2**). A summary of the questionnaire data is given in **Table 2**.

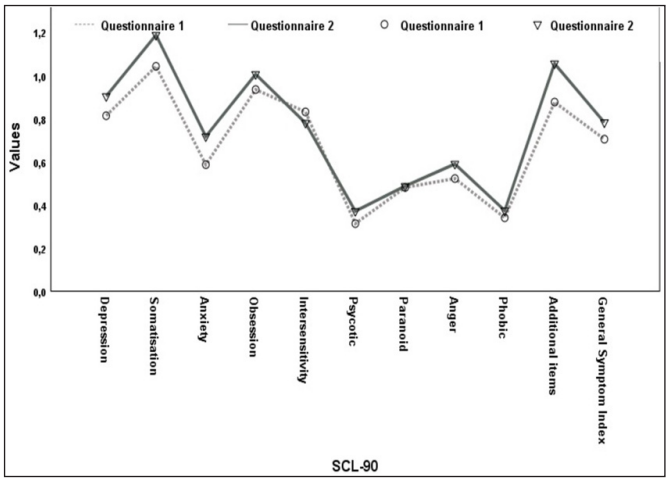

Figure 1. Graph showing the differences in The Symptom Checklist-90-Revised symptoms between questionnaires one and 2.

Table 2. The summary of SF-36 and SCL-90-R questionnaires.				
SCL-90 mean±SD/median (min-max)				
Sypmthoms	**Questionnaire 1**	**Questionnaire 2**	**p**	**t/Z**
Depression	0.814±0.580	0.903±0.605	0.171	-1.390
Somatisation	1.0 (0.25-2.75)	0.958 (0.083-3.0)	0.146	-1.453
Anxiety	0.450 (0.0-2.1)	0.600 (0.0-2.0)	0.04	-2.052
Obsession	0.850 (0.1-3)	0.900 (0.0-2.8)	0.484	-0.700
intersensitivity	0.666 (0.00-3.11)	0.666 (0.00-3.22)	0.232	-1.194
Psycotic	0.200 (0.00-2.00)	0.250 (0.00-1.7)	0.029	-2.187
Paranoid	0.333 (0.00-2.17)	0.333 (0.00-1.83)	0.794	-0.261
Anger	0.416 (0.00-1.67)	0.500 (0.00-1.83)	0.265	-1.115
Phobic	0.285 (0-1.28)	0.285 (0-1.42)	0.404	-0.834
Additional items	0.857 (0-2.57)	1.0 (0.0-2.571)	0.021	-2.306
General Sympthom index	0.583 (0.06-2.02)	0.767 (0.78-1.82)	0.037	-2.086
SF-36 mean±SD/median (min-max)				
Sypmthoms	**Questionnaire 1**	**Questionnaire 2**	**p**	**t/Z**
Energy fatique	60 (0-100)	50 (5-100)	0.012	-2.502
Physical function	80 (10-100)	70 (5-100)	0.013	2.588
Phsical health (role limit)	83.350 (0-100)	50 (0-100)	0.007	-2.677
Emotional well-being	68 (12-100)	60 (24-92)	0.0001	-3.618
Social function	81.97±17.045	71.57±22.649	0.001	-3.179
Health change	62.50 (25-100)	50 (0-100)	0.046	-1.996
Pain	72.75±25.52	68.43±22.66	0.223	1.234
General health	60 (0-90)	55 (0-95)	0.017	-2.397

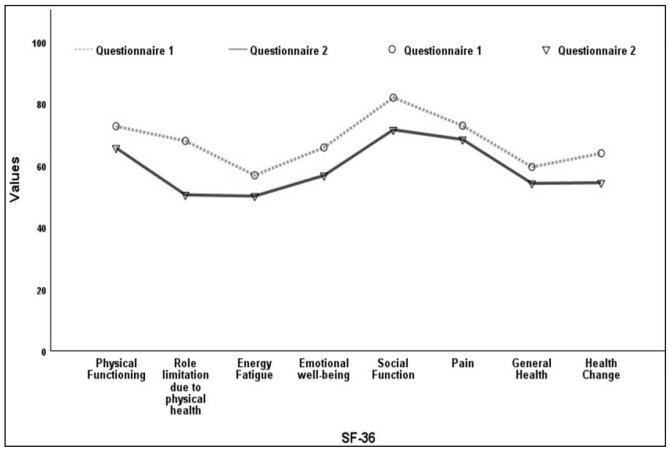

Figure 1. Graph showing the differences in Short form-36 symptoms between questionnaire one and questionnaire 2

DISCUSSION

There is a need to evaluate the treatment response in patients undergoing RIT for differentiated thyroid cancer. Treatment response evaluation is usually done by evaluating the dWBS or stimulated Tg. However, hypothyroidism that we created with THW causes some patient complaints and negatively affects QoL. Using questionnaires, we found that hypothyroidism adversely affected QoL (based on the SF-36) and worsened psychological symptoms (based on the SCL-90-R). With the SF-36, we found significant worsening in physical functioning, role limitation due to physical health, energy/fatigue, emotional well-being, social function, general health, and health change symptoms at the time of the dWBS. There was a worsening of the pain symptom, but it was not statistically significant. With the SCL-90-R, we detected significant worsening in anxiety, psychoticism, additional items, and general symptom index symptoms at the time of the dWBS. Although other symptoms worsened, the results were not statistically significant.

Banihashem et al. (22) investigated the psychological status and QoL of 150 patients who had undergone thyroidectomy for differentiated thyroid cancer. They evaluated the patients at four different times: 1 month before RIT, at the time of RIT, and one week and six months after RIT. Differently from our study, they used the Hospital Anxiety and Depression Scale (HADS) to measure the psychological state of the patients. The SF-36 was applied to determine QoL. According to the SF-36 survey, they determined that the most significant deterioration in QoL was during RIT. They stated that the reason for this was hypothyroidism caused by LT4 withdrawal. Botella-Carretero et al. (23) investigated psychometric functionality and QoL in patients with DTC. Fifty female patients with differentiated thyroid carcinoma were compared with 18 healthy females in the same age group. At the time of the dWBS, when in the hypothyroid state, a comparison was made with healthy female patients in the control group, and impairment was found in QoL and cognitive performance. Tagay et al. (24) applied QoL assessments to 136 patients with thyroid cancer while in a hypothyroid state in preparation for radioiodine administration. The available results were compared with German population reference values. All values of the SF-36 were lower than the reference values of the population. In another study evaluating 61 patients with thyroid cancer who underwent LT4 withdrawal, quality of life was evaluated with a self-rating questionnaire and Hamilton depression scale. The scores were worse than the control group. Hamilton depression scale was found to be worse in women (14). Another study included 228 patients with DTC, the quality of life was evaluated separately with the SF-36 scale while using LT4, in the withdrawal period, and while applying tyrogen. It was determined that the quality of life was significantly worse in the withdrawal period (12). One of the differences from our study is that we have compared the QoL and psychological symptoms scores in the hypothyroid period with the QoL and psychological symptoms scores of the same patients in the euthyroid period four weeks before, not with the reference values of the population. We tried to evaluate the effects of deep hypothyroidism, which we developed in a short time, on QoL and psychological symptoms free from all factors. When comparing a patient's QoL with community reference values, it should be taken into account that there may be differences in QoL within the society due to social, cultural, economic, and regional reasons.

Thyrotropin alfa has been used for a long time to prepare thyroid cancer patients before radioiodine administration to reduce the adverse effects of LT4 THW on QoL, reduce the radiation dose to the body, and perhaps reduce the cost of the treatment by shortening the hospital stay (11,12,25-27). In two prospective studies (25,28) evaluating the ablation success of low-dose and high-dose I-131 administration in patients with low-risk differentiated thyroid cancer, QoL deteriorated in the group of patients who had undergone THW. The authors reported no deterioration in QoL in the group administered thyrotropin alfa, or the deterioration was much less compared with the LT4 withdrawal group, and this effect was independent of the applied radiation dose. The authors stated that thyrotropin alfa is superior to LT4 withdrawal in radiation exposure and side effects. Because our study aimed to evaluate whether the hypothyroidism we created adversely affected QoL, we did not administer thyrotropin alfa. In addition, thyrotropin alpha is imported into our country, access to it is not always possible, and

it is an expensive product, which is too high for our country and other developing countries. We can only administer thyrotropin alfa to select patients with comorbidities who cannot tolerate hypothyroidism. It has already been reported that in patients with a low-intermediate risk of well-differentiated thyroid cancer, basal thyroglobulin has an important prognostic value in predicting treatment response and prognosis, stimulating thyroglobulin may not be needed due to its cost and side effects (29-31).

One of the limitations of the study was that all surgeries were not performed in the same center, so a standard surgical procedure was not applied. Perhaps our most important limitation is why patients were not administered low-dose (1.1 GBq) I-131. However, in multicentre, randomized prospective studies (25,28), low-dose and high-dose I-131 administration did not differ in treatment success. Frankly, our treatment success is similar to theirs. However, we can explain the high dose I-131 administration; some of our patients had aggressive histological variants, tumors at the surgical margin, and lymph node metastases. In addition, since T.T. was not performed in all patients, the relatively high residuals in the pre-ablation evaluations were one of the reasons for our high dose administration. Multicentre, prospective, randomized studies were published in 2018 (32) and 2019 (33) on the association of low- and high-dose administration with recurrence in patients with low-risk differentiated thyroid cancer. The median follow-up was 6.5 and 5.4 years. As a result, it was stated that low-dose and high-dose administration did not have a statistically significant effect on recurrence, and low-dose administration caused fewer side effects. Our study group consisted of patients who received high-dose treatment in 2017. After these last two articles were published, low-dose administration in patients with low-risk thyroid cancer became more preferred in our center, as in many centers in our country. The number of our patients is not higher can be accepted as a limitation. Although some authors reported that the effects of hypothyroidism on quality of life were different in male and female patients (34), some authors stated that the gender factor was ineffective (35). We included only female patients in order to avoid suspicion of bias.

CONCLUSION

We have shown that THW adversely affects QoL and worsens psychological symptoms in female patients. In order to reduce the side effects of hypothyroidism treatment response assessment with TSH stimulation should be used only in a selected group of patients.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Recep Tayyip Erdoğan University Faculty of Medicine Non-interventional Clinical Researches Ethics Committee (Date: 28.11.2019, Decision No: 2019-191).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

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

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

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

Acknowledgment: Contributing to the preparation of the article, I commemorate my dear friend and colleague, Dr. Levent Akça, with mercy and respect.

REFERENCES

1. Mazzaferri EL. An overview of the management of papillary and follicular thyroid carcinoma. Thyroid 1999; 9: 421-7.
2. Tan LG, Nan L, Thumboo J, Sundram F, Tan LK. Health-related quality of life in thyroid cancer survivors. Laryngoscope 2007; 117: 507-10.
3. Lamartina L, Leboulleux S, Terroir M, Hartl D, Schlumberger M. An update on the management of low-risk differentiated thyroid cancer. Endocr Relat Cancer 2019; 26: R597-R610.
4. Reiners C, Dietlein M, Luster M. Radio-iodine therapy in differentiated thyroid cancer: indications and procedures. Best Pract Res Clin Endocrinol Metab 2008; 22: 989-1007.
5. Torlontano M, Crocetti U, D'Aloiso L, et al. Serum thyroglobulin and 131I whole body scan after recombinant human TSH stimulation in the follow-up of low-risk patients with differentiated thyroid cancer. Eur J Endocrinol 2003; 148: 19-24.
6. Berger F, Friedrich U, Knesewitsch P, Hahn K. Diagnostic 131 I whole-body scintigraphy 1 year after thyroablative therapy in patients with differentiated thyroid cancer: correlation of results to the individual risk profile and long-term follow-up. Eur J Nucl Med Mol Imaging 2011; 38: 451-8.
7. Torlontano, M, Attard, M, Crocetti, U, et al. Follow-up of low risk patients with papillary thyroid cancer: role of neck ultrasonography in detecting lymph node metastases. J Clin Endocrinol Metab 2004; 89: 3402-7.
8. Pacini F, Capezzone M, Elisei R, Ceccarelli C, Taddei D, Pinchera A. Diagnostic 131-iodine whole-body scan may be avoided in thyroid cancer patients who have undetectable stimulated serum Tg levels after initial treatment. J Clin Endocrinol Metab 2002; 87: 1499-501.
9. Mazzaferri EL, Robbins RJ, Spencer CA, et al. A consensus report of the role of serum thyroglobulin as a monitoring method for low-risk patients with papillary thyroid carcinoma. J Clin Endocrinol Metab 2003; 88: 1433-41.
10. Haugen BR, Alexander EK, Bible KC, et al. 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: 1-133.

11. Lee J, Yun MJ, Nam KH, Chung WY, Soh E-Y, Park CS. Quality of life and effectiveness comparisons of thyroxine withdrawal, triiodothyronine withdrawal, and recombinant thyroid-stimulating hormone administration for low-dose radioiodine remnant ablation of differentiated thyroid carcinoma. Thyroid 2010; 20: 173-9.
12. Schroeder PR, Haugen B, Pacini R, et al. A comparison of short-term changes in health-related quality of life in thyroid carcinoma patients undergoing diagnostic evaluation with recombinant human thyrotropin compared with thyroid hormone withdrawal. J Clin Endocrinol Metab 2006; 91: 878-84.
13. Dow KH, Ferrell BR, Anello C. Quality-of-life changes in patients with thyroid cancer after withdrawal of thyroid hormone therapy. Thyroid 1997; 7: 613-9.
14. Luster M, Felbinger R, Dietlein M, Reiners C. Thyroid hormone withdrawal in patients with differentiated thyroid carcinoma: a one hundred thirty-patient pilot survey on consequences of hypothyroidism and a pharmacoeconomic comparison to recombinant thyrotropin administration. Thyroid 2005; 15: 1147-55.
15. Wang T, Jiang M, Ren Y, et al. Health-related quality of life of community thyroid cancer survivors in Hangzhou, China. Thyroid 2018; 28: 1013-23.
16. Nygaard B, Jensen EW, Kvetny J, Jarløv A, Faber J. Effect of combination therapy with thyroxine (T4) and 3, 5, 3-triiodothyronine versus T4 monotherapy in patients with hypothyroidism, a double-blind, randomised cross-over study. Eur J Endocrinol 2009; 161: 895-902.
17. Samuels MH, Schuff KG, Carlson NE, Carello P, Janowsky JS. Health status, psychological symptoms, mood, and cognition in L-thyroxine-treated hypothyroid subjects. Thyroid 2007; 17: 249-58.
18. Ware JE Jr, Kosinski M, Bayliss MS, McHorney CA, Rogers WH, Raczek A. Comparison of methods for the scoring and statistical analysis of SF-36 health profile and summary measures: summary of results from the Medical Outcomes Study. Med Care 1995; 33: AS264-79.
19. Kocyigit H. Kisa Form-36 (KF-36)'nm versiyonunun guvenilirligi ve gecerliligi. Ilaç ve Tedavi Derg 1999; 12: 102-6.
20. Derogatis LR, Cleary PA. Confirmation of the dimensional structure of the SCL-90: A study in construct validation. J Clin Psychol 1977; 33: 981-9.
21. Dag I. Belirti tarama listesinin (SCL-90-R) üniversite ögrencileri için geçerligi ve güvenirligi. Türk Psikiyatri Derg 1991; 2: 5-12.
22. Banihashem S, Arabzadeh M, Jafarian Bahri RS, Qutbi M. Psychological Status and Quality of Life Associated with Radioactive Iodine Treatment of Patients with Differentiated Thyroid Cancer: Results of Hospital Anxiety and Depression Scale and Short-Form (36) Health Survey. Indian J Nucl Med 2020; 35: 216-21.
23. Botella-Carretero J, Gal J, Caballero C, Sancho J, Escobar-Morreale H. Quality of life and psychometric functionality in patients with differentiated thyroid carcinoma. Endocr Relat Cancer 2003; 10: 601-10.
24. Tagay, S, Herpertz, S, Langkafel, et al. Health-related quality of life, depression and anxiety in thyroid cancer patients. Qual Life Res 2006; 15: 695-703.
25. Mallick, U, Harmer, C, Yap, B, et al. Ablation with low-dose radioiodine and thyrotropin alfa in thyroid cancer. N Engl J Med 2012; 366: 1674-85.
26. Nygaard B, Bastholt L, Bennedbæk FN, Klausen TW, Bentzen J. A A placebo-controlled, blinded and randomised study on the effects of recombinant human thyrotropin on quality of life in the treatment of thyroid cancer. Eur Thyroid J 2013; 2: 195-202.
27. Husson O, Haak HR, Oranje WA, Mols F, Reemst PH, van de Poll-Franse LV. Health-related quality of life among thyroid cancer survivors: a systematic review. Clin Endocrinol 2011; 75: 544-54.
28. Schlumberger M, Catargi B, Borget I, et al. Strategies of radioiodine ablation in patients with low-risk thyroid cancer. N Engl J Med 2012; 366: 1663-73.
29. Rosario PW, Mourão GF, Calsolari MR. Definition of the response to initial therapy with radioiodine in patients with differentiated thyroid carcinoma: basal or stimulated thyroglobulin? Horm Metab Res 2019; 51: 634-8.
30. Shen F-C, Hsieh C-J, Huang I-C, Chang Y-H, Wang P-W. Dynamic risk estimates of outcome in Chinese patients with well-differentiated thyroid cancer after total thyroidectomy and radioactive iodine remnant ablation. Thyroid 2017; 27: 531-6
31. Rosario PW, Furtado MdS, Mourão GF, Calsolari MR. Patients with papillary thyroid carcinoma at intermediate risk of recurrence according to American Thyroid Association criteria can be reclassified as low risk when the postoperative thyroglobulin is low. Thyroid 2015; 25: 1243-8.
32. Schlumberger M, Leboulleux S, Catargi B, et al. Outcome after Ablation in patients with low-risk thyroid cancer (ESTIMABL1): 5-year follow-up results of a randomised, phase 3, equivalence trial. Lancet Diabetes Endocrinol 2018; 6: 618-26.
33. Dehbi H-M, Mallick U, Wadsley J, Newbold K, Harmer C, Hackshaw A. Recurrence after low-dose radioiodine ablation and recombinant human thyroid-stimulating hormone for differentiated thyroid cancer (HiLo): long-term results of an open-label, non-inferiority randomized controlled trial. Lancet Diabetes Endocrinol 2019; 7: 44-51.
34. Ellegård L, Krantz E, Trimpou P, Landin-Wilhelmsen K. Health-related quality of life in hypothyroidism—A population-based study, the WHO MONICA Project. Clin Endocrinol (Oxf) 2021; 95: 197-208.
35. Shivaprasad C, Rakesh B, Anish K, Annie P, Amit G, Dwarakanath C. Impairment of health-related quality of life among Indian patients with hypothyroidism. Indian J Endocrinol Metab 2018; 22: 335.