

Does the use of recombinant TSH in preparation for I-131 scintigraphy scan affect hearing function?

Mehtap Doğan^a, Kasım Durmuş^{a,*}, Zekiye Hasbek^b, Emine Elif Altuntaş^a

^a Department of Otolaryngology, Faculty of Medicine Cumhuriyet University 58140, Sivas, Turkey

^b Cumhuriyet Univ. School of Medicine, Dept. of Nuclear Medicine, Campus, 58140, Sivas, Turkey

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Abstract

Objective: The objective of this study was to examine the effect of hypothyroidism on hearing function in patients surgically treated for differentiated thyroid cancer and subsequently experienced hypothyroidism during preparation for follow up I-131 scintigraphy scan by either recombinant human thyroid stimulating hormone (rhTSH) treatment or thyroid hormone withdrawal (THW).

Methods: A total of 55 patients undergoing I-131 scintigraphy scan following surgeries for differentiated thyroid cancer were included in the study, including 25 patients prepared by administration of recombinant TSH (rhTSH Group) and 30 patients by thyroid hormone withdrawal (THW Group).

Results: Air conduction thresholds at 1, 2 and 4 kHz for both ears were higher during hypothyroid period than during euthyroid period for patients in the THW group ($p < 0.05$) but not for patients in the rhTSH group.

Conclusion: Sensorineural hearing loss was detected, especially at low frequencies, in patients with DTC after surgical treatment whose hormone replacement therapy was withdrawn but not in those receiving rhTSH. It is therefore preferred to use rhTSH when preparing for I-131 scintigraphy scan in patients at risk for hearing loss.

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Keywords: Hearing loss; Recombinant TSH; Thyroid hormone withdrawal; Radioiodine

1. Introduction

Differentiated thyroid cancer (DTC) is the most common endocrine malignancy and its prevalence is increasing worldwide (McNally et al., 2012; Nixon, 2015). The mainstay of therapy for DTC is surgery and the initial surgical approach is total or nearly total thyroidectomy with or without lymph node dissection (Nixon, 2015; Chen et al., 2008). Thyroid hormone

replacement therapy is initiated in all patients after total thyroidectomy and used throughout their lives.

In patients with DTC, postoperative ablation therapy with high-dose I-131 (radioactive iodine, RAI) is administered to both ablate residual thyroid tissue and treat unrecognized micrometastases. Whole body scintigraphy is conducted on the 8th–9th days following high-dose I-131 treatment, and low-dose I-131 whole body scintigraphy is repeated at the follow-up in the 8th–12th months after high-dose I-131 treatment. I-131 scintigraphy has a higher sensitivity than morphologically based imaging modalities in detecting residual and metastatic DTC (Buck et al., 2008; Al Balooshi and Vinjamuri, 2015).

Certain patient preparation is needed in order to increase I-131 uptake by tumor tissue both before high-dose ablation therapy and

* Corresponding author. Fax: +90 346 2191155.

E-mail addresses: drm_dogan@hotmail.com (M. Doğan), kasimdurmus58@gmail.com (K. Durmuş), ealtunta@yahoo.com (E.E. Altuntaş).

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before low-dose I-131 scintigraphic scanning during follow-up. For optimal sensitivity, I-131 imaging requires stimulation of thyroid tissue by elevated TSH levels. This can be achieved either with thyroid hormone withdrawal (THW) for 4 weeks to achieve a TSH level ≥ 30 uIU/mL, or with stimulation by recombinant human TSH (rhTSH) (American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer Cooper et al., 2009; Verbarg et al., 2011). Foods, drinks and drugs that may interfere with iodine uptake by thyroid cells are also routinely limited. In patients undergoing thyroid hormone withdrawal, symptoms such as depression, dysmnnesia, concentration difficulty, fatigue, dry hair and skin, facial and eye swelling, cold intolerance, weight gain, constipation, and increased signs of menstrual cycle may be observed during hypothyroid period (Dietlein et al., 2005). Recombinant TSH is well tolerated due to its short half-life. Hypothyroidism symptoms can be avoided or progress more mildly in these patients, although side effects like minimal nausea, headache, and fatigue may occur (Klubo-Gwiedzinska et al., 2012).

According to American Thyroid Association Management Guidelines, in patients with low and intermediate risk DTC without extensive lymph node involvement (i.e. T1-T3, N0/Nx/N1a, M0), in whom radioiodine remnant ablation or adjuvant therapy is planned, preparation with rhTSH stimulation is an acceptable alternative to thyroid hormone withdrawal for achieving remnant ablation, based on evidence of superior short-term quality of life, non-inferiority of remnant ablation efficacy, and multiple consistent observations suggesting no significant difference in long-term outcomes (Haugen et al., 2016).

The relationship between hypothyroidism and hearing loss has been known for many years. In various studies investigating the relationship between hypothyroidism and hearing loss in DTC patients in the literature, it is observed that acute hypothyroidism may cause an increase in hearing thresholds and subclinical cochlear damage (Psaltakos et al., 2013; Hasbek et al., 2014). We could not find any study investigating the effect of rhTSH usage on hearing in the literature. Therefore, the aim of the present study was to examine the effect of hypothyroidism on hearing function in patients who experienced hypothyroidism while receiving rhTSH, as well as thyroid hormone withdrawal, in preparation for I-131 scintigraphy scan, using pure tone audiometry, otoacoustic emissions and tympanometry.

2. Materials and methods

Study subjects were patients who had undergone total/nearly total thyroidectomy between January and December 2014 for differentiated thyroid carcinoma followed by ablation therapy with high-dose I-131, and were referred to the Nuclear Medicine Department in the 8th–12th months with the request for routine whole body low-dose I-131 scintigraphy scan. A total of 55 patients were recruited, including 25 patients who experienced hypothyroidism following administration of recombinant TSH (rhTSH Group) and 30 patients who developed hypothyroidism following thyroid hormone therapy withdrawal for 4 weeks (THW Group). Audiological tests

were conducted during both hypothyroid and euthyroid periods in both groups of patients and results were compared.

TSH stimulation before oral administration of I-131 for patients in the THW Group was achieved by discontinuing thyroxine (LT4) intake for 4 weeks, or by IM injection of rhTSH (0.9 mg/day for 2 days) for patients in the rhTSH group. Patients on rhTSH did not discontinue thyroxine therapy. The authors did not have a primary role in selecting the patients into these two groups, but patient treatment strategies were determined by specialists in the Endocrine and Metabolism Department, while scintigraphy scan was prepared by the same physician (ZH) from the Nuclear Medicine Department. Therefore, there were no healthy control subjects in the study and only patients' euthyroid and hypothyroid data were compared in both rhTSH and THW groups.

Serum thyroglobulin (Tg), anti-thyroglobulin antibody (anti-TgAb), free T3 (fT3), free T4 (fT4) and thyroid stimulating hormone (TSH) levels were recorded before whole body scintigraphy scan in all patients. The reference range of fT4, fT3, and TSH was 0.7–1.48 ng/dL, 1.71–3.71 pg/mL and 0.35–4.94 mIU/mL, respectively.

Hearing tests included pure tone audiometry, otoacoustic emissions and tympanometry performed by the same tester at the ENT clinic who was unaware of the thyroid hormone state of the patient during both hypothyroid and euthyroid periods. Detailed anamnesis information, thyroid function test results, otoscopic examination notes, audiograms and otoacoustic emission findings were recorded in the patient follow-up forms.

Air and bone conduction thresholds at 0.25, 0.5, 1, 2, 4, 6, 8, 12 and 16 kHz were measured using a clinical audiometer (INTERACOUSTICS AC 40 Clinical Audiometer, Assen, Denmark) which was calibrated according to ISO standards. Masking was provided to the opposite ear. Transient evoked otoacoustic emissions (TEOAE) testing and analysis were performed using a commercially available device (Maico, ERO Scan Analyzer, GmbH Salzufer, 13/14, 10587, Berlin GE), which was calibrated before being used, and disposable probe tips inserted into the ear canal. Clicks (0.7–4 kHz, 83 ± 3 dB/SPL) were used as stimuli and responses at less than 6 dB above noise floor signified no otoacoustic emissions. Based on whether TEOAEs were determined to be present, the ear was marked as “PASS” or “REFER”. Testing was repeated in ears marked as “REFER” for verification. Results were recorded in individual frequency bands (bandwidth = 1.5–4 kHz) at 1.5, 2, 2.5, 3, 3.5 and 4 kHz.

Exclusion criteria were as follows: history of ear surgery, ear or head trauma, acute or chronic otitis media, syphilis, other malignancy, upper respiratory tract infection, intake of ototoxic drugs or employment in a noisy environment, diseases potentially associated with hearing loss such as hypertension, liver failure, and renal failure, receiving radiotherapy or chemotherapy treatment in the last month, vascular diseases, congenital cochlear malformation, neurologic disease (causing a loss of hearing), and TSH level of <30 mIU/mL before whole body scintigraphy scan. Moreover, patients who did not agree to participate in hearing tests, had ear infection

symptoms during the euthyroid period, failed to keep on follow-up of hearing and hormone levels, and were unwilling to continue the study were also excluded from the study.

This study was conducted in accordance with the principles of the Declaration of Helsinki and approved by the Cumhuriyet University Research Ethics Committee. Verbal and written consents were obtained from the patients.

2.1. Statistical analysis

All the statistical analyses were performed using Statistical Package for Social Sciences 22.0 program (SPSS inc., Chicago, IL, USA). Because parametric test assumptions could not be carried out to assess the obtained data, “Kolmogorov Smirnov Test”, “Friedman Test”, “Mann Whitney U Test”, “Wilcoxon Signed- Rank Test” and “Fisher's Exact Chi-Square Test” were used. Level of significance was set at 0.05.

3. Results

The mean age was 45.08 ± 10.95 (29–64) years for patients in the rhTSH group and 44.70 ± 9.24 (21–63) years for patients in the THW group, respectively. Twenty one of the 25 patients (84%) in the rhTSH Group and 26 of the 30 patients (86.7%) in the THW Group were female. The two groups were similar in terms of distribution of gender and age ($p > 0.005$).

The fT3, fT4 and TSH levels were 2.28 ± 0.76 ng/dL, 1.45 ± 0.76 pg/dL and 125.66 ± 33.50 mIU/mL for patients in the rhTSH Group and 1.20 ± 0.40 ng/dL, 0.45 ± 0.28 pg/dL and 110.64 ± 44.03 mIU/mL for patients in the THW Group, respectively, during hypothyroid period, again showing no significant difference ($p > 0.05$).

When compared during euthyroid period, there was no statistically insignificant difference in air conduction audiometric thresholds between patients in the rhTSH group and those in the THW group ($p > 0.05$) (Table 1). For the rhTSH group, hearing thresholds showed no significant difference between euthyroid and hypothyroid periods ($p > 0.05$). However, the average pure tone hearing thresholds of both ears taken during hypothyroid period were higher as compared to those obtained during euthyroid period for patients in the THW group ($p < 0.05$). Also, during hypothyroid period, the average pure tone hearing threshold of the THW group was higher than that of the rhTSH group in both ears ($p < 0.05$).

Table 1
Average air conduction pure tone hearing thresholds (dB HL) in the rh-TSH (n = 25) and THW (n = 30) Groups.

Thyroid state and study group	Right ear (X ± SD)	p Value	Left ear (X ± SD)	p Value
HT* rhTSH	20.04 ± 10.48	0.015	19.24 ± 7.54	0.008
THW	24.30 ± 8.31		26.37 ± 14.04	
ET** rhTSH	19.80 ± 11.67	0.637	19.60 ± 8.82	0.383
THW	18.90 ± 6.88		22.03 ± 14.25	

$p < 0.05$ is accepted as the significant level and the significant differences between the groups are shown in bold.

*HT = hypothyroid.

**ET = euthyroid.

Specifically, hearing thresholds at 1, 2 and 4 kHz in the THW Group during hypothyroid period were higher than those in the rhTSH Group, as well as than during euthyroid period, for both ears ($p < 0.05$) (Table 2). While thresholds at 0.25, 0.5, 6, 8, 12 and 16 kHz during hypothyroid period were also elevated in the THW group compared to the rhTSH group and to euthyroid period, the difference was statistically insignificant ($p > 0.05$) (Table 3).

All patients in both groups passed otoacoustic emission evaluations.

4. Discussion

The present study was aimed to investigate the effects of withdrawal of thyroid hormone replacement therapy and the use of rhTSH on hearing in patients following surgical treatment for DTC. The results show that while no hearing change was observed in patients receiving rhTSH even during hypothyroid period, there was mild sensorineural hearing loss at low frequencies for patients whose thyroid hormone therapy was interrupted for 4 weeks, despite that there was no difference in hearing between patients from both groups during euthyroid period.

Several studies have addressed auditory pathology associated with thyroid function disorders. The relationship between goiter and hearing loss was defined in a case published by Bircher in 1883 (Bircher, 1883) for the first time. The second case related to this issue was a 53 year-old female patient with hypothyroidism published by Kemp in 1907 (Kemp, 1907).

Upon literature review, only a limited number of studies on cochleovestibular effects in patients with acquired or non-congenital hypothyroidism has been found. The first study

Table 2
Average air conduction hearing thresholds (dB HL) in the rhTSH (n = 25) and TRW (n = 30) groups at specific frequencies during hypothyroid period.

Side	frequency (Hz)	rhTSH Group (X ± SD)	THW Group (X ± SD)	p Value
Right	1000	17.00 ± 14.29	22.50 ± 7.96	0.001
	2000	15.40 ± 12.07	23.17 ± 9.33	0.000
	4000	19.80 ± 15.64	25.67 ± 10.56	0.008
Left	1000	15.00 ± 6.45	23.67 ± 14.68	0.002
	2000	14.20 ± 7.31	24.00 ± 14.88	0.001
	4000	19.40 ± 13.79	28.33 ± 14.76	0.005

$p < 0.05$ was accepted as the significant level and the significant differences between the groups were shown in bold.

Table 3
Average air conduction hearing thresholds (dB HL) in the THW Group at specific frequencies during hypothyroid and euthyroid periods.

Side	frequency (Hz)	Hypothyroid (X ± SD)	Euthyroid (X ± SD)	p Value
Right	1000	22.50 ± 7.96	14.83 ± 7.25	0.000
	2000	23.17 ± 9.33	13.83 ± 7.15	0.000
	4000	25.67 ± 10.56	18.33 ± 11.24	0.004
Left	1000	23.67 ± 14.68	17.17 ± 15.35	0.002
	2000	24.00 ± 14.88	16.67 ± 15.72	0.001

$p < 0.05$ value was accepted as the significant level.

on this subject by Bhatia et al. indicated moderate hearing loss on pure tone audiometry in 43% of 72 patients with hypothyroidism (Bhatia et al., 1977). In the study by Jahnke et al. (1979), hearings of 56 patients with latent or clinical hypothyroidism and 18 patients with acute hypothyroidism were assessed and hearing loss was determined in 45% of the patients with chronic hypothyroidism. It was found that two of the patients with hearing loss had conductive hearing loss, 7 had mixed hearing loss, 18 had sensorineural hearing loss, and 13 had hair cell damage. One of the results of the study also revealed that 90% of hearing loss determined for these patients was of moderate to severe degrees. Probably the most interesting point in the study by Jahnke et al. (1979), was that a slight recovery occurred in 50% of the patients with hearing loss owing to thyroid hormone replacement therapy. In the study conducted by Malik et al. (2002), hearing loss related to decreases in T3 and T4 concentrations or to increase in TSH concentration was reported in 45 patients with hypothyroidism, aged between 10 and 57 years. It was also revealed in this study that hearing loss could recover through replacement therapy with T4. In the present study, increase in hearing thresholds was demonstrated in patients who were progressively taken to a hypothyroid state by withdrawing the hormone replacement therapy, as compared to during a euthyroid state, while hearing thresholds in patients with acute hypothyroidism following administration of rhTSH did not change findings supporting the results of Jahnke et al. (Jahnke et al., 1979).

In our clinic, there are two previous studies evaluating the correlation between hypothyroidism and hearing loss. The first one (Hasbek et al. (2014)) examined the effect of acute hypothyroidism on cochlear function in 75 patients who underwent total or nearly total thyroidectomy due to thyroid carcinoma, by pure tone audiometry, tympanometry and transient evoked otoacoustic emissions. The study identified mild sensorineural hearing loss in 12% of the patients on pure tone audiometry but no significant difference in otoacoustic emission response rate. The second study (Karakuş et al. (2015)) compared hearing levels during hypothyroid and euthyroid periods in 31 patients with hypothyroidism and mild sensorineural hearing loss was found during hypothyroid period. A significant recovery in hearing levels was identified during euthyroid period following treatment, indicating that hearing loss caused by hypothyroidism may be reversed by hormone replacement therapy. Our present study was aimed to examine whether or not the use of rhTSH would have an impact on hearing. We could not find any study evaluating hearing in patients with acute hypothyroidism after using rhTSH. Among the publications available to the authors, only the study by Psaltakos et al. (2013), drew attention to the correlation between acute hypothyroidism and hearing loss. In this study on 52 patients who had undergone total thyroidectomy due to thyroid carcinoma, effects of acute hypothyroidism on cochlear function were examined via pure tone audiometry, tympanometry and transient evoked otoacoustic emissions, and it was determined that there was a significant increase in postoperative hearing thresholds in all of the cases,

as well as a significant decrease in otoacoustic emission response rates, with no significant change in tympanometry results, as compared to healthy individuals. From their results, they pointed out that acute hypothyroidism could cause an increase in hearing thresholds as well as subclinical cochlear damage. In the present study, however, a significant difference was not observed in terms of OAE measurements when both within-group and between-groups comparisons were made. We are of the opinion that this difference between the present study and the study of Psaltakos et al. (2013), may be from the different methods used in collecting otoacoustic emissions and the mild nature of hearing thresholds increase seen in this study.

When postoperative air conduction audiometric thresholds in hypothyroid period were compared in the study by Psaltakos et al. (2013), the difference at 1000–6000 Hz was found to be statistically significant, similar to findings in this study, showing statistically significant differences at 1000, 2000 and 4000 Hz in patients with hypothyroidism from thyroid hormone withdrawal, although not in patients whose hypothyroidism followed administration of recombinant TSH. This finding suggests that, even though temporary, thyroid hormone replacement therapy withdrawal can cause an increase in audiometric thresholds, and that, therefore, the use of rhTSH should probably be considered in preparation for I-131 scintigraphy scan in patients with a risk factor for hearing dysfunction.

The correlation between hypothyroidism and hearing loss, which is one of the main goals of the present study, has been shown in studies in the literature, but we were unable to identify any study indicating the effect of use of rhTSH on hearing. Results of the present study show that, because hypothyroidism developed over a very short period of time after administration of rhTSH, hearing was not affected despite the change in T3, T4 and TSH levels; whereas, hearing thresholds showed an increase in those patients whose hypothyroidism developed progressively or chronically as a result of THW.

5. Conclusion

With the use of rhTSH, TSH levels are elevated only for a few days, with minimal effects at tissue level while thyrocytes uptake of iodine is increased. This is the underlying reason for no impairment in hearing functions in patients using rhTSH for preparation for I-131 scans in our study. In contrast, hearing levels in DTC patients whose hormone replacement therapy is withdrawn should be followed up closely with audiometric evaluation.

Based on our results, we recommend the use of rhTSH to increase thyrocytes uptake of radioiodine following surgical treatment for DTC, especially in patients with hearing loss or tendency of hearing loss.

The strongest side of the present study is that it is the first study on this issue. However, we are of the opinion that it would be a proper approach to support our results with studies evaluating hearing in more details through electrophysiological methods using larger case serials.

Ethics committee approval

Ethics committee approval for this study was received from the ethics committee of University of Cumhuriyet, Sivas, Turkey (Decision Number: 2014-03/22; Date: 18.03.2014).

Informed consent

Written and verbal informed consents were obtained from the patients who participated in this study.

Peer-review

Externally peer-reviewed.

Author contributions

Concept – MD, E. E. A.; Design – ZH, E. E. A.; Supervision – E. E. A.; Resources – K. D.; Materials – M.D., Z. H., K. D.; Data Collection and/or Processing – M.D., Z. H.; Analysis and/or Interpretation – M.D., E. E. A. K. D.; Literature Search – K. D., E. E. A., M.D.; Writing Manuscript – K. D., M.D., E. E. A.; Critical Review – Z. H., E. E. A.; Other – K. D.

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Conflict of interest

The authors declared no conflict of interest.

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