European Journal of Therapeutics
DOI: 10.5152/eurjther.2020.20066
Original Research

Do Patients with Differentiated Thyroid Cancer Face the Risk of Hyponatremia at the Expense of Preparation for Radioactive Iodine Treatment?

Elif Özdemir[1], Şefika Burçak Polat[2], Nahide Belgit Talay[3]

[1]Department of Nuclear Medicine, Ankara Yıldırım Beyazıt University, School of Medicine, Ankara, Turkey

[2]Department of Endocrinology and Metabolism, Ankara Yıldırım Beyazıt University, School of Medicine, Ankara, Turkey

[3]Clinic of Nuclear Medicine, Ankara Bilkent City Hospital, Ankara, Turkey

ABSTRACT

Objective: Differentiated thyroid cancer (DTC) is the most common endocrine cancer. The main therapeutic strategies are surgery and radioactive iodine (RAI) treatment in selected intermediate- and high-risk patients. Hyponatremia is the most frequent form of electrolyte imbalance and few studies have assessed the frequency and clinical impact of hyponatremia in patients with thyroid cancer. In this study, we aimed to determine the prevalence and severity of hypo¬natremia among hypothyroid patients in the peri-ablation period. The secondary objective was to assess the correlation between Sodium (Na) level and hypothyroidism severity, age, and RAI dosage.

Methods: A total of 51 patients with DTC who were referred to our Nuclear Medicine Department for RAI ablation/treatment were enrolled. Serum Na, thyroid-stimulating hormone (TSH), and free triiodothyronine and thyroxine levels were measured three times during the study (under LT4 suppression, when the patient was hypothyroid before and after receiving RAI). Baseline, pre-, and post-RAI mean serum Na and other hormonal parameters were compared. The number of patients with hyponatremia and possible related symptoms were noted. Correlation of serum Na levels with age, RAI dosage, and hypothyroidism severity was determined.

Results: The number of patients with hyponatremia did not differ significantly in the baseline, pre-, and post-RAI periods. None of the patients experienced moderate-to-severe hyponatremia. There was no significant correlation between serum Na levels and age, serum TSH, or the hormone levels.

Conclusion: In conclusion, preparation for RAI treatment with LT4 withdrawal and or a low-iodine diet is not a common etiological factor for the development of hyponatremia in patients with DTC.

Keywords: Hyponatremia, radioactive iodine, thyroid neoplasms

INTRODUCTION

Differentiated thyroid cancer (DTC) is the most common endocrine cancer and its incidence is increasing worldwide (1). Mortality rates are low, and it has an excellent prognosis in the absence of high-risk factors such as distant metastasis (2). The cornerstones of therapy are surgery and radioactive iodine (RAI) in selected intermediate and high-risk patients (3). RAI can be given for ablative, adjuvant, or treatment purposes. It decreases regional recurrences and disease specific mortality (4). RAI treatment has acute and chronic complications such as sialadenitis, transient testicular or ovarian dysfunction, and secondary malignancies (2).

Before RAI treatment, high levels of TSH is essential to increase the uptake of iodine and for effective ablation of the remnant tissue. High TSH can be achieved either with withdrawal of levothyroxine for 4–6 weeks after total or near total thyroidectomy or with the highly purified, recombinant form of TSH (rhTSH).

Hyponatremia is the most frequent electrolyte imbalance in routine clinical practice. To date, few studies have assessed the frequency and clinical impact of electrolyte imbalance on patients with thyroid cancer (5). It can be caused by lowered water clearance and inappropriately high concentration of anti-diuretic hormone (ADH) due to iatrogenic hypothyroidism, which is required for the maximum uptake of RAI within the remnant tissue and for effective ablation (6). In the setting of hypothyroidism, a decreased glomerular filtration rate is shown to directly lower the free water excretion by decreasing the delivery of water to the diluting segment of the renal tubules, which may contribute

How to cite: Özdemir E, Polat ŞB, Talay NB. Do patients with differentiated thyroid cancer face the risk of hyponatremia at the expense of preparation for radioactive iodine treatment? Eur J Ther 2020; 26(3): 233-7.

ORCID iDs of the authors: E.Ö. 0000-0002-9142-8752; Ş.B.P. 0000-0002-7729-5586; N.B.T. 0000-0001-8483-2776.

Corresponding Author: Elif Özdemir **E-mail:** ecingi@yahoo.com

Received: 07.07.2020 • **Accepted:** 28.07.2020

to the further dilution and worsen the hyponatremia (6). Another possible explanation for hyponatremia is the low-iodine diet (LID) that is started two to four weeks prior to RAI treatment to eliminate dietary iodine interference and facilitate the uptake of RAI (7). Such a LID protocol usually ends up with low dietary salt intake, and rarely severe hyponatremia cases.

In this study, we aimed to determine the prevalence and severity of hyponatremia in hypothyroid patients during the peri-ablation period. In order to show the effect of hypothyroidism on the occurrence of hyponatremia, we compared the sodium levels measured on and off LT4 treatment. We also compared the pre and post-RAI hyponatremia prevalence to see if RAI treatment itself had a separate effect on the serum sodium levels. Secondary purposes were to describe the demographic profile of hypothyroid DTC patients, to determine the correlation of TSH, age, fT3 and T4 levels and RAI dosage with serum sodium levels in the pre- and post-RAI period.

METHODS

We prospectively enrolled 51 patients who were admitted to our tertiary center's endocrinology outpatient clinics and diagnosed with DTC after total thyroidectomy with or without lymph nodes dissection and referred to the Nuclear Medicine Department for RAI ablation between September 2019 and February 2020. Before starting the study, we obtained the local ethical board approval in accordance with principles of the Declaration of Helsinki. RAI ablation decision was made by a multidisciplinary team including endocrinologists, surgeons, nuclear medicine, and pathology specialists. Informed consent was obtained for each patient before the treatment. To minimize the confounding factors that could cause hyponatremia, patients with comorbid conditions such as congestive heart failure, using diuretics including thiazides, chronic or acute kidney failure or cirrhosis were excluded. Demographic and clinical data of the patients such as age, gender, presence of hypertension or diabetes, the dosage of the RAI received, tumor subtype, duration of LID, and indication for RAI were recorded.

The standard protocol for RAI treatment in our institution is L-thyroxine withdrawal for 21 days and LID for 14 days before the treatment. Serum Na, TSH, free T3 and T4 levels were measured (Siemens, Atellica®) three times during the study; at the time when the patient was seen in the multidisciplinary council while using L-thyroxine (8–12 weeks after the operation) (baseline), the day before RAI ablation, and five to seven days after RAI at the time of post treatment whole body scanning. Mean sodium concentrations and the prevalence of mild hyponatremia (130–134 mEq/L), moderate hyponatremia (120–129 mEq/L), and severe hyponatremia (<120 mEq/L) were determined. The normal reference range for serum sodium concentrations is 135–145 mEq/L. Clinical symptoms of hyponatremia that may be associated with hyponatremia were questioned if hyponatremia was detected.

Main Points:

- Postoperative RAI treatment is widely recommended in DTC for remnant ablation and treatment of residual or metastatic disease. Before RAI treatment, LID and high levels of TSH are essential to increase the uptake of iodine.
- Hyponatremia is the most frequent electrolyte imbalance and hyponatremia could be present in patients with hypothyroidism; however, its frequency and severity has not been well documented in the pre-ablation and post-RAI period.
- Our results present that; preparation for RAI treatment with LT4 withdrawal and or LID is not a common etiological factor for the development of hyponatremia in patients with DTC and clinicians should not be greatly concerned about rare, life-threatening hyponatremia during preparation for RAI treatment

Statistical Analysis

The Statistical Package for the Social Sciences, version 25 (IBM SPSS Corp.; Armonk, NY, USA) was used for the statistical analysis. Descriptive analysis was performed in order to identify the baseline characteristics of the hypothyroid patients. Mean, standard deviation, and range were used to describe continuous variables (serum sodium levels), while Median was used to describe non-parametric variables (age and TSH concentration). Baseline Na (under LT4 treatment), pre-RAI and post-RAI Na, TSH, and free T3 and T4 levels were compared with the Non-parametric Friedman test. Sex was described using number and percentage. Correlations were analyzed using Spearman test. A P value of less than 0.05 was statistically significant.

RESULTS

A total of 51 patients with DTC who underwent total/near total thyroidectomy and were determined to receive RAI treatment (ablative/adjuvant or therapeutic) were enrolled. Of these, 38 (74.5%) were females and 13 (25.5%) were male. The mean age was 47.9±12.5 years (min–max; 20–77). As a comorbid condition, four patients had asthma, seven had diabetes, and eleven had hypertension. Median RAI dosage was 50 mCi (min–max; 30–200 mCi). Forty-seven patients had papillary thyroid carcinoma (4 with columnar cell, 2 with tall cell 1 with hobnail, and 40 with classical variant), whereas four had follicular carcinoma (one was minimally invasive and three had vascular invasion). The indications for RAI were large tumor size, presence of lymph node or distant metastasis, extrathyroidal extension, presence of poor prognostic variant or inappropriately high thyroglobulin (Tg) level after the surgery (1). Demographic and clinical characteristics of patients are presented in Table 1.

Median TSH concentration under L-thyroxine treatment before withdrawal was 1.3 (min–max; 0.01–15) (mU/L). Median free T3 and T4 levels at the baseline under LT4 treatment were 3.0 ng/L (0.2–5.4) and 1.14 ng/dL (0.4–1.7), respectively. Mean baseline serum Na level was 140.2±0.7 mEq/mL. The minimum Na level was 135 mEq/L and none of the patients had hyponatremia (Table 2).

Median TSH concentration measured the day before RAI treatment was 103 (mU/L) (min–max; 0.5–150). Median free T3 and T4 levels were 1.3 ng/L (0.2–3.5) and 0.5 (0.09–0.98), respectively. Pre-RAI mean Na was 139±2.4 and only one patient had hyponatremia (134 mEq/L) (Table 2).

Table 1. Demographic and Clinical Characteristics of the Patients with DTC

Mean age (years)	47.9±12.5
Sex (female/male) (no/%)	38 (74.5)/13 (25.5)
Median RAI dosage (mCi)(min-max)	50 (30-200)
Pathologic subtype (no) (papillary/follicular)	Papillary: 47
	Classical variant: 40
	Columnar cell:4
	Tall cell: 2
	Hobnail: 1
	Follicular Cancer:4
	Minimally invasive :1
	Extensive vascular invasion:3
Comorbid condition	Asthma:4
	DM:7
	HT:11
Duration of low-iodine diet (days)	14 days
Indications for RAI treatment (no)	Extrathyroidal extension :3
	Distant metastasis:2
	Poor prognostic variant:7
	Vascular invasion:3
	Lymph node metastasis:9
	Inappropriately high postoperative Tg:9
	Large Tumor size:8
	Anti Tg positivity:2
	Patient's choice: 2
	Multifocality:6

Table 2. Comparison of baseline, pre and post-RAI laboratory parameters

	Baseline (under LT4)	**Pre-RAI**	**Post-RAI**	**p**
TSH (mU/L) (median; min-max)	1.3 (0.01-15)	103(0.5-150)	87(4-150)	<0.001
f T4 (ng/dL) (median; min-max)	1.14 (0.4-1.7	0.5 (0.09-0.98)	0.29(0.021.13)	<0.001
f T3 (ng/L) (median; min-max)	3.0 (0.2-5.4)	1,3 (0.2-3.5)	1.38 (0.2-3)	<0.001
Na (mean) mEq/L	140.2±0.7	139±2.4	140±2.5	0.28

Median TSH concentration measured 5–7 days after RAI was 87 (mU/L) (min–max; 4–150). Median free T3 and T4 levels were 1.38 (0.2–3) and 0.29 ng/dl (0.02–1.13), respectively. Mean Na was 140±2.5 and minimum Na was 131 mEq/L (Table 2). Two patients had mild hyponatremia (134 and 131 mEq/L)

Baseline TSH under LT4 treatment was significantly lower than the pre- and post-RAI TSH levels as expected (p<0.001). There was no significant difference between the pre-RAI and post-RAI TSH levels. Free T3 level was significantly lower in pre-and post-RAI measurements compared to the baseline (under LT4) (p<0.001). Baseline Free T4 was significantly higher than pre-and post-RAI fT4 (p<0.001). There was also no significant difference between the pre- and post-RAI groups regarding ft4, with higher levels in the post-RAI measurements (p=0.01). There was no statistically significant difference between baseline, pre-RAI, and post-RAI Na levels (p=0.28). The number of patients with hyponatremia did not differ significantly in baseline, pre- and post-RAI periods. None of the patients experienced moderate-to-severe hyponatremia or related symptom.

In Spearman test, there was no significant correlation between serum Na and age, Serum TSH and free hormone levels (Table 3).

Table 3. Correlation of serum Na with age, f T3, T4 andRAI dosage

	Pre-RAI Sodium		Post-RAI Sodium	
	Correlation Coefficient	**p**	**Correlation Coeeficient**	**p**
TSH	0.084	0.57	0.48	0.74
f T4	−0.15	0.92	0.109	0.44
f T3	0.40	0.68	−0.68	0.63
Age	−0.91	0.54	−0.93	0.52
RAI dose	–	–	0.22	0.12

DISCUSSION

Thyroid cancer constitutes the 3.0% of all new cancer cases in the U.S.A and based on the national cancer database, there were 52,070 newly diagnosed cases with 2170 deaths from the disease in 2019 (8). Papillary and follicular carcinoma make up 95% of all DTC cases. RAI after total/near total thyroidectomy are well established treatments in DTC. RAI treatment is now being reserved for high and selected intermediate risk patients since there should be a balance between therapeutic efficacy and unwanted side effects (9).

In patients who undergo RAI treatment, the uptake depends on the adequate stimulation with TSH that can be obtained either by LT4 withdrawal (THW) or administration rhTSH (10). LT4 withdrawal is associated with side effects such as fatigue, constipation, emotional disturbance, decreased intellectual functions, and worsening of heart failure symptoms. Hyponatremia is one of possible complications of RAI (11). Hyponatremia developing due to hypothyroidism may occur as a result of several mechanisms involving renal, cardiovascular and hypothalamo-adrenal systems (12). Hypothyroidism also has effects on almost all components of the renin-angiotensin-aldosterone system, including renin generation, production of angiotensinogen in the liver, secretion and inactivation of aldosterone in the adrenal glands (5).

In our study, the aim was to determine the frequency of hyponatremia during the peri-ablation period in the absence of other confounding etiological factors. We also aimed to determine the association between hypothyroidism severity, RAI dosage, and age with the serum Na levels. In our study, severe or moderate hyponatremia or associated symptoms were not detected. There was mild hyponatremia in pre- and post-ablation measurements in two cases, but the frequency was not different from that of the baseline measurements taken under LT4 suppression. The rate of hyponatremia in our study group was lower than that of other cancers, which may be attributed to the patients' characteristics such as young age, short hospital stay, and less comorbid conditions (13). There are several case reports of severe and symptomatic hyponatremia in the literature after thyroid hormone withdrawal that mostly occurred in elderly patients using diuretics (14). Our results are compatible with the two previous studies such that none of the patients prepared for RAI with both THW and LID had Na levels of <130 mEq/L (8, 15). To determine the effect of RAI itself on the development of hyponatremia, we compared Na levels for the day before and 5–7 days after RAI treatment. The frequency of hyponatremia was similar in pre- and post-RAI measurements in our study. However in a previous report, hyponatremia after RAI and isolation was more common at a prevalence of 26.7% compared with that at 7% pre-RAI treatment (16). The possible explanations for that difference were nausea and vomiting after RAI treatment and patient anxiety that potentiated the ADH secretion. In our study, we did not detect any correlation between serum Na level and hypothyroidism severity, which was consistent with that reported by two previous studies (17, 18).

LID was administered to the patients 2 weeks before RAI treatment at our center. Such an LID is usually accompanied with low salt intake, and reports of severe symptomatic hyponatremia developed due to LID are scarce. In those reports, it was suggested that a prolonged LID, low salt intake, and the use of thiazide diuretics in elderly patients are risk factors for the development of severe hyponatremia (19). We advise our patients to take non-iodinated salt in the diet, which may have reduced the incidence of hyponatremia. Moreover, exclusion of patients using medications that may worsen hyponatremia might have contributed to the low incidence of Na imbalance.

This study had some limitations, including the limited number of patients. Another limitation is that patient-related factors such as the amount of hydration performed post-RAI treatment and adherence to low salt intake and LID pre-RAI therapy that may affect results of this study were not evaluated.

CONCLUSION

Preparation for RAI treatment with LT4 withdrawal and or LID is not a common etiological factor for the development of hyponatremia in patients with DTC. Hyponatremia was neither prevalent nor severe or symptomatic during preparation for RAI treatment when it occurred. Clinicians should not be greatly concerned about rare, life-threatening hyponatremia during preparation for RAI treatment and should not exaggerate the possibility of the development of severe hyponatremia.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Ankara City Hospital (E1- 20-428).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - E.Ö., S.B.P., N.B.T.; Design - E.Ö., S.B.P., N.B.T. ; Resource - E.Ö.-N.B.T.; Data Collection - N.B.T.; Analysis and Interpretation - E.Ö., S.B.P.; Literature Search - E.Ö., N.B.T., S.B.P.; Writing Manuscript - E.Ö., S.B.P., N.B.T.; Critical Review - E.Ö., S.B.P.

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

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

REFERENCES

1. Kitahara CM, Sosa JA. The changing incidence of thyroid cancer. Nat Rev Endocrinol 2016; 12: 646-53. [Crossref]
2. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, 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. [Crossref]
3. Orosco RK, Hussain T, Noel JE, Chang DC, Dosiou C, Mittra E, et al. Radioactive iodine in differentiated thyroid cancer: a national database perspective. Endocr Relat Cancer 2019; 26: 795-802. [Crossref]
4. Twining CL, Lupo MA, Tuttle RM. Implementing Key Changes in the American Thyroid Association 2015 Thyroid Nodules/Differentiated Thyroid Cancer Guidelines Across Practice Types. Endocr Pract 2018; 24: 833-40. [Crossref]
5. Niri T, Horie I, Ando T, Kawahara H, Ueda M, Eto M, et al. Renal Function and Plasma Renin Activity as Potential Factors Causing Hyperkalemia in Patients with Thyroid Carcinoma Undergoing Thyroid Hormone Withdrawal for Radioactive Iodine Therapy. Endocr Pract 2020; 26: 197-206. [Crossref]
6. Vannucci L, Parenti G, Simontacchi G, Rastrelli G, Giuliani C, Ognibene A, et al. Hypothyroidism and hyponatremia: data from a series of patients with iatrogenic acute hypothyroidism undergoing radioactive iodine therapy after total thyroidectomy for thyroid cancer. J Endocrinol Invest 2017; 40: 49-54. [Crossref]
7. Nozu T, Yoshida Y, Ohira M, Okumura T. Severe hyponatremia in association with I(131) therapy in a patient with metastatic thyroid cancer. Intern Med 2011; 50: 2169-74. [Crossref]
8. Kim J, Cho SG, Kang SR, Kwon SY, Cho DH, Cho JS, et al. Preparation for radioactive iodine therapy is not a risk factor for the development of hyponatremia in thyroid cancer patients. Medicine (Baltimore) 2017; 96: e6004. [Crossref]
9. Tuttle RM, Ahuja S, Avram AM, Bernet VJ, Bourguet P, Daniels GH, et al. Controversies, Consensus, and Collaboration in the Use of (131) I Therapy in Differentiated Thyroid Cancer: A Joint Statement from the American Thyroid Association, the European Association of Nuclear Medicine, the Society of Nuclear Medicine and Molecular Imaging, and the European Thyroid Association. Thyroid 2019; 29: 461-70. [Crossref]
10. Tang CYL, Thang SP, Zaheer S, Kwan CK, Ng DC. Recombinant human thyrotropin versus thyroid hormone withdrawal in an Asian population. Endocrine 2020; 69: 126-32. [Crossref]
11. Silva MC, Furlanetto TW. Another possible contributor to hyponatremia after radioactive iodine. Thyroid 2014; 24: 923. [Crossref]
12. Ota K, Kimura T, Sakurada T, Shoji M, Inoue M, Sato K, et al. Effects of an acute water load on plasma ANP and AVP, and renal water handling in hypothyroidism: comparison of before and after L-thyroxine treatment. Endocr J 1994; 41: 99-105. [Crossref]
13. Doshi SM, Shah P, Lei X, Lahoti A, Salahudeen AK. Hyponatremia in hospitalized cancer patients and its impact on clinical outcomes. Am J Kidney Dis 2012; 59: 222-8. [Crossref]
14. Shakir MK, Krook LS, Schraml FV, Hays JH, Clyde PW. Symptomatic hyponatremia in association with a low-iodine diet and levothyroxine withdrawal prior to I131 in patients with metastatic thyroid carcinoma. Thyroid 2008; 18: 787-92. [Crossref]
15. Baajafer FS, Hammami MM, Mohamed GE. Prevalence and severity of hyponatremia and hypercreatininemia in short-term uncomplicated hypothyroidism. J Endocrinol Invest 1999; 22: 35-9. [Crossref]
16. Dayrit JC, Cunanan EC, Kho SA. Prevalence of Hyponatremia in Hypothyroid Patients during Radioactive 131I Ablation for Differentiated Thyroid Cancer: Single Institution Experience. Endocrinol Metab (Seoul) 2016; 31: 410-5. [Crossref]
17. Hammami MM, Almogbel F, Hammami S, Faifi J, Alqahtani A, Hashem W. Acute severe hypothyroidism is not associated with hyponatremia even with increased water intake: a prospective study in thyroid cancer patients. BMC Endocr Disord 2013; 13: 27. [Crossref]
18. Tyack PL, Calambokidis J, Friedlaender A, Goldbogen J, Southall B. Formal Comment on Schorr GS, Falcone EA, Moretti DJ, Andrews RD. First Long-Term Behavioral Records from Cuvier's Beaked Whales (Ziphius cavirostris) Reveal Record-Breaking Dives. PLoS ONE 2014; 9: e92633. [Crossref]
19. Al Nozha OM, Vautour L, How J. Life-threatening hyponatremia following a low-iodine diet: a case report and review of all reported cases. Endocr Pract 2011; 17: e113-7. [Crossref]