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The Causes of Thyrotoxicosis, Clinical Features, and Treatment Strategies in a Former Iodine Deficient Area

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ABSTRACT

Thyrotoxicosis is a hypermetabolic condition caused by excess thyroid hormones in the circulation with/without increased production from the thyroid gland. In this prospective study, we aimed to investigate the causes of thyrotoxicosis, clinical features, and treatment strategies in a former iodine-deficient area. Thyroid function tests, antithyroid and antithyroid receptor antibodies, and routine thyroid ultrasonography was obtained, and a thyroid scintigraphy/radioactive iodine uptake test was performed on need. A statistically significant difference was found between toxic multinodular goiter (TMNG) and Graves' disease (GD) groups when mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) values were analyzed. TSH levels were significantly lower in GD patients compared to those in TMNG and TNG patients, but free triiodothyronine (FT3) and free thyroxine (FT4) values were higher. A high level of TSH receptor antibody (TRAb) was observed in patients with normal antithyroid peroxidase (Anti-TPO). TRAb levels were found to be high. Anti-TPO and anti-thyroglobulin (Anti-Tg) levels were observed to be positively correlated with sT3 and sT4 levels. TMNG is the leading cause of thyrotoxicosis; despite sufficient iodide intake in our former iodine-deficient region, TMNG is characteristically seen in older patients with much lower thyroid hormone levels than GD. According to the study results, the diagnosis of patients with thyrotoxicosis, their clinical presentation, the treatment they will receive, early detection of postoperative complications were predicted.

Keywords: Thyrotoxicosis, Toxic multinodular goiter, Graves' disease, TSH.

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Introduction

"Thyrotoxicosis" describes the classical clinical symptoms caused by excessive circulating thyroid hormones [1]. Although the term "hyperthyroidism" is frequently used instead of "thyrotoxicosis," this term refers to instances when the thyroid gland's excessive synthesis of thyroid hormones results in "thyrotoxicosis"[2]. Thyrotoxicosis is a significant health issue that affects women more commonly than males. Thyrotoxicosis is observed more frequently in the elderly, Caucasians, and regions with iodine deficiency [3]. The most common reason for non-iatrogenic thyrotoxicosis in regions without iodine deficiency is Graves' disease (GD), which constitutes 80% of the cases, as nodular thyroid disease and thyroiditis [4]. However, the prevalence of these etiologies varies depending on the degree of iodine consumption (in iodine-deficit areas, nodular thyroid disorders make up around 50% of cases), the population's age (toxic-nodular goiter affects the elderly more commonly), and the region [4,5]. The prevalence of thyrotoxicosis is about 2%, and GD causes 70 to 90% of the cases [6]. Graves' disease is an autoimmune disorder that causes hyperthyroidism, diffuse goiter, ophthalmopathy, and dermopathy. In regions with adequate iodine intake, this is the most frequent cause of thyrotoxicosis. In women, it occurs 7 to 10 times more frequently than men [2]. The overgrowth and overfunctioning of thyroid cells are caused by stimulating antibodies against the TSH receptor on the thyroid cell membrane in GD [7].

The second most frequent cause of thyrotoxicosis is toxic multinodular goiter (TMNG). Functional nodules, which had gained autonomy among the multiple nodules of thyroid glands, cause the typical TMNG symptoms. It is inversely correlated with iodine intake, and TMNG is more prevalent in iodine-deficient areas. It is stated that the pathogenesis may be associated with the receptor activation caused by somatic mutation that has occurred in the thyroid-stimulating hormone receptor (TSHR) gene and with cyclic adenosine monophosphate (cAMP) upregulation [8].

Toxic nodular goiter (toxic adenoma, TNG) develops as a result of a single hyperfunctioning adenoma in the thyroid gland, which produces too many thyroid hormones. Similar to TMNG, it is more prevalent in areas with an iodine deficiency. TNG generally develops slowly and occurs when the nodule, which has been present for years, gains autonomy. It displays the increased Thyroxine (T4) and Triiodothyronine (T3) levels along with the suppressed Thyroid stimulating hormone (TSH) [9].

A surplus of thyroid hormone has an impact on numerous organ systems. Fatigue, anxiety, palpitations,

sweating, heat intolerance, anxiety, sleep disorders, and weight loss are examples of clinical symptoms [9]. These clinical signs and symptoms are generally not very specific and might change based on the patient's age, sex, comorbidities, and the duration and cause of the disease [10]. The variety of non-specific symptoms and signs makes diagnosing or evaluating the disease state difficult based on traditionally obtained information on the symptoms and findings. Clinical examination is the first step in the diagnostic evaluation of thyrotoxicosis, and then the proper biochemical tests, nuclear medicine data, and ultrasound are used to make the diagnosis [1].

This prospective study aims to determine the causes of thyrotoxicosis, clinical features, and treatment strategies in a former iodine-deficient area, which will be very important for clinical practice.

Material and Methods

Study Design and Patient Selection

In this study, a total number of 195 patients with thyrotoxicosis who had been admitted to Karadeniz University Endocrinology outpatient clinics were evaluated. The patient's demographic characteristics, symptoms, and signs were questioned. Thyroid function tests, antithyroid and antithyroid receptor antibodies, and routine thyroid ultrasonography were obtained, and thyroid scintigraphy or radioactive iodine uptake test was performed on need. Treatment choice, medical care, and post-treatment problems were also assessed.

Patients over 18 years old who received a de novo thyrotoxicosis diagnosis were included in the study. In comparison, patients under 18 years old, pregnant patients, and patients who had received treatment for thyrotoxicosis previously were excluded. The characteristics of the patients with thyrotoxicosis who were followed up in this study were recorded, including age, sex, clinical symptoms, physical examination findings, diagnosis techniques (laboratory values, imaging methods), treatment options, treatment side effects, and treatment outcomes.

The study was performed according to the principles of the Declaration of Helsinki as revised in 1983 and approval was obtained by the Ethics Committee of Karadeniz University Medical Faculty. The permission has been granted by Karadeniz University Medical Faculty of Ethics Committee via the resolution dated 18.11.2014 and no. 2014/81. All participants in the study obtained informed consent before entering the study.

Biochemical Analysis

TSH, free triiodothyronine (FT3), free thyroxine (FT4), anti-thyroglobulin (Anti-Tg), and anti-thyroid peroxidase (Anti-TPO) analyses were performed by using Beckman Coulter DX1-800 (Minnesota, USA) device. Biochemistry analyses Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), albumin, glucose, sodium, potassium, calcium, phosphorus, cholesterol, Low-density lipoprotein-cholesterol (LDL-C), triglyceride) were measured by the Beckman Coulter AU-5800 (Shizuoka, Japan) autoanalyzer. The whole blood count was performed by using Beckman Coulter LH-780. TSH receptor antibody (TRAb) analysis has been determined via an immunoassay kit at Anka laboratory. TRAb levels were performed following kit protocol.

Ultrasound Evaluation of Thyroid Gland

Thyroid gland ultrasound assessment was performed using ToshibaAplio 500 Series No: 00134z04 Version of the software: AB V5.00*R204.

Scintigraphic Evaluation

Scintigraphic evaluation of the patients was performed via Scintigraphy Siemens E. Cam Signature Serie Series No:9231.

Statistical Analysis

All data were analyzed using IBM SPSS Statistics for Windows (version 20.0; Chicago, IL). The distribution of variables was assessed using Kolmogorov-Smirnov test. Data were expressed as the normal distribution's mean ± standard deviation (SD). One-way ANOVA test was carried out for normal distribution followed by the Bonferroni post-hoc test and the Kruskal-Wallis test for non-normal distribution followed by the Mann Whitney U post-hoc test among groups. Correlation coefficients and statistical significance were evaluated using Spearman's correlation test. $p < 0.05$ were considered as statistically significant.

Results

The demographic properties and clinical diagnoses of all patients with thyrotoxicosis are given in Table 1. The patients with thyrotoxicosis were identified to have TMNG:100 (51%), GD:73 (37%), TNG:14 (7%), subacute granulomatous thyroiditis:4 (2%), Hashimoto's disease with Hashitoxicosis:2 (1%), subacute lymphocytic thyroiditis:2 (1%). GD was primarily observed in younger cases, whereas TNG and TMNG were observed mainly in the elderly. The mean age of the GD group was 36.9±13.5, while this was 64.08±14.5 in the patients with TMNG (p=0.0001).

Table 1. Demographic characteristics and clinical diagnosis of thyrotoxicosis patients

		N	%
Age	Male	74	37.9
	Female	121	62.1
Symtoms/Signs	Palpitation	78	%40
	Weight Loss	67	%34.4
	Sweating	49	%25.1
	Shaking Hands	40	%20.5
	Irritability	38	%19.5
	Insomnia	14	%7.2
	Hair loss	14	%7.2
	Diarrhea Complaint	6	% 3.1
	Palpable Goiter	32	%16.4
	Exophthalmos	23	%11.8
	HT	18	%9.2
	Tachycardia	22	%11.3
Accompanying Diesases	Hypertension	23	%11.7
	Diabetes Mellitus	14	%7
	Osteoporosis	10	%5

N: Number

The most common accompanying medical conditions of patients were hypertension (11.7%), diabetes mellitus (7%), and osteoporosis (5%). When the patient symptoms were questioned, the most common complaints were palpitation (40%), weight loss (34.4%), sweating (25.1%), hand tremors (20.5%), irritability (19.5%), insomnia (7.2%), alopecia (7.2%) and diarrhea (3.1%). The patients' physical examination results revealed palpable goiter (16.4%), hypertension (9.2%), tachycardia (11.3%), and exophthalmos (11.8).

A comparison of biochemical values between patient groups with TMNG, TNG, and GD is shown in Table 2.

Table 2: Comparison of biochemical values of patients with TMNG, TNG and GD

	Thyrotoxicosis (N=195)	TMNG (N=100)	TNG (N=14)	GD (N=73)	p
TSH (µIU/mL)	0.062±0.09	0.077±0.081	0.090±0.080	0.032±0.033[a,b]	0.0001*
FT4 (ng/dL)	2.21±1.41	1.55±0.726	1.72±1.27	3.18±1.60 [a, b]	0.0001*
FT3 (pg/mL)	7.11±6.05	4.16±1.54	4.94±2.03	11.4±7.61 [a, b]	0.0001*
Anti Tg (IU/ml)	91.1±278	11.9±5.95	79.4±50.5	199±48.7 [a, b]	0.0001*
Anti TPO (IU/ml)	101±214	10.9±4.61	36.7±29.9	257±38.2 [a, b]	0.0001*
TRAb (U/l)	49.32±70.5	8.55±8.26	6.54±4.94	61.1±75.9 [a, b]	0.0001*
Haemoglobin(Hb) (mg/dL)	13.3±1.70	13.3±1.50	13.9±1.63	13.3±1.87	0.406
MCV (fL)	84.68±7.60	86.9±5.79	83.9±15.7	82.5±6.57 [a]	0.0001
MCH (pg)	28.2±2.53	28.8±2.17	28.9±2.30	27.5±2.69 [a]	0.002
MPV (fL)	8.85±1.3	8.92±1.35	8.74±1.66	8.81±1.29	0.794
Glucose (mg/dL)	104.3±33	109±37.2	106±46.0	98.4±23.2	0.132
Sodium (mEq/L)	138±2.4	139±2.55	139±2.17	138±2.17	0.466
Potassium (mEq/L)	4.41±0.44	4.41±0.435	4.51±0.428	4.31±0.327	0.095
Calcium (mg/dL)	9.5±0.51	9.49±0.501	9.50±0.406	9.57±0.414	0.519
Phosphorus (mg/dL)	3.6±0.83	3.52±0.838	3.26±0.366	3.79±0.813 [b]	0.022
Albumin (mg/dL)	4.1±0.4	4.02±0.468	4.13±0.360	4.19±0.352 [a]	0.028
ALT (U/L)	21.7±13.4	18.0±10.6	19.0±11.3	27.4±15.5 [a]	0.0001
AST (U/L)	22.9±7.5	21.8±6.08	21±6.08	24.8±8.90 [a]	0.018
LDL-C(mg/dL)	149±82.5	131±43.1	135±51.2	113±38.5 [a]	0.013
TG(mg/dL)	47.0±10.3	148±81.8	185±143	141±67.1	0.200

P values according to One way ANOVA test, post hoc Bonferroni test.
*P values according to Kruskal-Wallis test, post hoc Mann Whitney U test.
a; Significantly different from TMNG.
b; Significantly different from TNG.
Data were expressed as mean ± SD.

ALT and AST values of the patients with thyrotoxicosis were 21.7±13.4 and 22.9±7.5 U/L, respectively. It was determined that hemoglobin (Hb) levels anemia (Hb<12 mg/dL) was found in 36 patients (18.5%), and the mean Hb value was found to be 13.3±1.70 mg/dL. The values for mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH) and mean platelet volume (MPV) were 84.68±7.60 fL, 28.2±2.53 pg, and 8.85±1.3 fL, respectively. Lipid levels were high in 87 patients (44.6%). The sodium, potassium, calcium, and phosphorus values were found to be 138±2.4 mEq/L, 4.41±0.44 mEq/L, 9.5±0.51 mg/dL, and 3.6±0.83 mg/dL, respectively. When the glucose values were examined, the glucose values of 140 patients were within the normal range, while 40 patients had impaired fasting glucose and 15 had diabetes. The mean glucose level was found to be 104.3±33 mg/dL. While 180 patients' albumin levels were normal, 15 were low; the mean albumin value was 4.1±0.4 mg/dL. The mean TSH level was 0.062±0.09 IU/mL, the FT3 level was 7.11±6.05 pg/mL, and the FT4 level was 2.21±1.41 ng/dL. The mean TRAb was found to be 49.32±70.5 U/L. TRAb values were measured to be above average (>14 U/L) in 55 patients and above 100 U/L in 35 patients.

Comparing the MCV and MCH values in patients with TMNG, TNG, and GD, a statistically significant difference was observed between the TMNG and GD groups, both lower in the GD group (p=0.0001, p=0.002, respectively). ALT and AST levels were higher in patients with GD compared with the TMNG patients group, although in the normal range (p=0.0001, p=0.018, respectively). LDL levels were lower in GD patients, statistically significant between GD and TMNG groups (p=0.013). The group of patients with TMNG had lower albumin values than the GD group (p=0.028). When the average TSH, FT3, and FT4 values of patients with TMNG, TNG, and GD were compared, a statistically significant difference was observed for all, with FT3 and FT4 being significantly higher and TSH being significantly lower in the GD group compared with TMNG and TNG groups. There was no significant difference regarding other biochemical parameters.

The relationship of TSH, FT3, and FT4 with Anti-TPO and Anti-Tg levels are shown in Table 3.

Anti-TPO levels were compared with TSH, TRab, sT3, and sT4 levels, and there happened to be a statistically significant correlation of Anti-TPO with FT3 and FT4 levels (p=0.0001). While 40% of patients with normal Anti-TPO values had high levels of TRAb, 74.5% of patients with high Anti-TPO values had high levels of TRAb. There is also a statistically significant correlation of Anti-Tg with FT3 and FT4 levels (p=0.0001). Anti-Tg levels were positively correlated with TRab. A negative, weak correlation was found between TRAb and TSH (rho:-0.283 p=0.007). A positive correlation was observed between FT3-TRAb (rho:0.418, p=0.0001) and between FT4-TRAb (rho:0.332, p=0.001).

Table 3. TSH, sT3, sT4 relationship between Anti-TPO and Anti-Tg levels in patients with thyrotoxicosis

		Anti TPO (-) N=125 rho	P- value	Anti TPO (+) N=70 rho	P- value
	TSH	-0.187	0.013	-0.128	0.075
N=95	FT3	0.472	0.0001	0.466	0.0001
	FT4	0.415	0.0001	0.391	0.0001
		Anti TPO (-)		Anti TPO (+)	
		N=35		N=55	
N=90	TRAb	0.400	0.0001	0.331	0.001
		Anti Tg (-)		Anti Tg (+)	p value
		N=145		N=50	
	TSH	0.012	0.869	0.008	0.907
N=95	FT3	0.325	0.0001	0.331	0.0001
	FT4	0.245	0.001	0.256	0.0001
		Anti Tg (-)		Anti Tg (+)	
		N=54		N=36	
N=90	TRAb	0.257	0.014	0.188	0.078

p and rho values according to Spearman tests. N:number

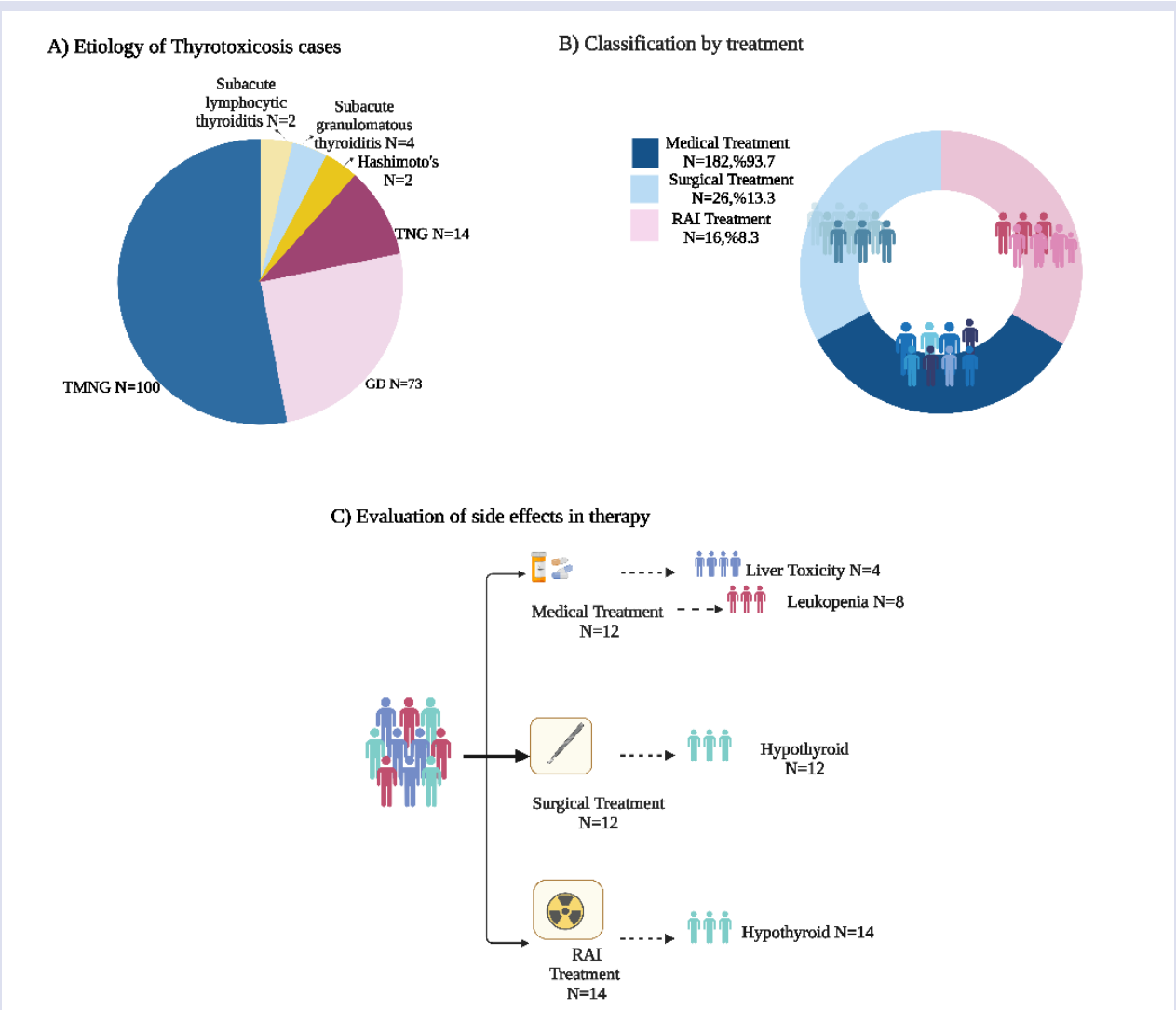

Figure 1. A) Etiology of Thyrotoxicosis cases, B) Classification by treatment, C) Evaluation of side effects in treatment

The etiology of thyrotoxicosis cases, the classification according to treatment and the side effects that occurred in the patients receiving treatment are shown in Figure 1. A total number of 182 patients received medical therapy (93.7%), 16 (8.3%) received surgical treatment, and 26 patients received radioactive iodine (RAI) therapy (13.3). Propylthiouracil (PTU) in 54 patients and methimazole (MMI) in 128 patients were used as a medical treatment agent. Leukopenia (6 patients) and elevation of liver function tests (3 patients) were observed in 9 cases

(16.7%) who received PTU. In contrast, one case experienced elevated liver enzymes, and two patients developed leukopenia in the MMI group (2%). In total, 12 (75%) of the 16 patients who had undergone surgical treatment developed hypothyroidism during the post-op period, while only 14 (53.8%) of the 26 patients who had undergone RAI treatment experienced hypothyroidism

Discussion

Thyrotoxicosis is a significant health issue that is more prevalent in women than men [11]. It is frequently observed in the elderly, Caucasians, and regions with iodine deficiency [3]. GD most frequently causes thyrotoxicosis; in areas with adequate iodine intake, GD causes 80% of thyrotoxicosis, while TNG-dependent hyperthyroidism occurs at a rate of 50% in areas with an iodine deficit [4]. The diagnosis of thyrotoxicosis is obtained through a careful clinical examination and the appropriate laboratory and imaging techniques [6]. The treatment options for hyperthyroidism include surgery, antithyroid medication, and radioactive iodine; however, the clinical profile of the patient and readily available therapy options determine a treatment strategy [12].

In this prospective study, we analyzed the causes of thyrotoxicosis, clinical features, and treatment strategies in a former iodine-deficient area. A total number of 195 patients with thyrotoxicosis were examined. Surprisingly, TMNG was still the leading cause, affecting 51% of patients, while GD was only apparent in 37%; TNG was the third common cause, affecting 7% of the patients. As expected, female patients took the lead with 62% while male patients were only 38% with an overall mean age of 52.3 ±.19.1. Considering the age distribution, GD claimed the top spot in the younger patients group, while TMNG was the leading cause in the older.

The finding of a higher prevalence of TMNG compared to GD amongst thyrotoxicosis cases should have resulted from endemic iodine deficiency in the Eastern Black Sea Region. It was much earlier established by a study by Kologlu et al. in 1966 in the Black Sea region when iodine levels in food and water were low [13]. The overall prevalence of goiter had been calculated as 30.5% by palpation in a national survey conducted by Urgancıoglu and Hatemi in 1987, being most prominent in the Black Sea region [14]. In a comparative study by Erdogan et al., they measured sonographic thyroid volumes (STV) and urinary iodine concentrations (UIC) in 1226 school-age children (SAC) (9–11 years old) from Ankara, located in central Anatolia and three highly endemic goiter areas of the Black Sea region on of them being Trabzon. A considerable number of school-age children (SAC) were found to have STV exceeding the recommended upper normal limits for their age and gender obtained from iodine-replete European children (26.7, 40.3, 44.8 and 51.7% of children from Ankara, Kastamonu, Bayburt, and Trabzon respectively). UIC indicated moderate to severe ID in these areas with median concentrations of 25.5, 30.5, 16.0, and 14 µg/L, respectively. This study showed severe to moderate ID as the primary etiological factor for the goiter endemic observed in Ankara and the Black Sea region of Turkey, with goiter prevalence and iodine deficiency being most prominent in the Trabzon region [15].

According to research released by the WHO in 2007, the average person should excrete between 100-199 g/L of iodine through their urine. Furthermore, in endemic goiter etiology, selenium deficiency, other goitrogenic factors affecting iodine bioavailability, dietary habits, and soil structure should be considered in endemic goiter etiology [16].

Legislation for mandatory iodization of household salt in Turkey was passed in July 1999. The overall scenery before the legislation was again established by another study by Erdogan et al., which ascertained the prevalence of goiter and iodine nutrition in school-age children (SAC) living in known endemic areas of Turkey. Sonographic thyroid volumes (STV) and urinary iodine concentrations (UIC) of 5.948 SAC from 20 cities were measured between 1997 and 1999. STV of 31.8% of the SAC examined stayed above the upper-normal limits for the same age and gender recommended by the World Health Organization (WHO). Goiter prevalence ranged between 5 and 56%, and median UIC ranged between 14 and 78 microg/l, indicating severe to moderate ID in 14 and mild ID in 6 surveyed cities. Both of the cities were found to have insufficient median UIC levels. That study showed that endemic goiter was an essential public health problem and iodine nutrition was inadequate nationwide [17].

Subsequent studies by Erdogan et al. revealed a significant reduction in iodine deficiency in Turkey. In 2007, moderate to severe ID was still prevalent in 27.8% of the population, a marked improvement from the 1997 and 2002 surveys of the same group (58% and 38.9%, respectively). The follow-up monitoring study showed that ID had been eliminated in 20 of 30 cities surveyed, with a median UIC of 130 µg/l. This progress, while significant, also highlighted the ongoing challenge of addressing iodine deficiency in rural areas and specific geographical regions [18].

In a subsequent study by Koçak et al. in the Trabzon region, it was found that the mean urine iodine excretion was 122.79 µg/L, males had a urine iodine level of 124.52 g/L, while females had 121.20 g/L, being quite similar by the study of Erdogan et al. The range of urinary iodine excretion was still below 100 µg/L in 37% of participants. The median UIE value in subjects with goiter was 122.78 lg/L and 122.80 lg/L in those without being not statistically significant. Iodized salt was used by 98.5 % of participants, while only 0.24 % of all subjects in the study used iodine-free salt, and 1.24 % used other salts. Koçak et al. stated that the province of Trabzon's urine iodine excretion largely complies with WHO standards [19].

However, a novel study performed in Turkey demonstrated a different dilemma for older subjects. In a senior group with a mean age of 70.9 years, the mean urinary iodine concentration was 98 µg/L. Goiter was found in 18.2% of women, 6.7% of men, and 43.8% of men

had nodules. Overt hyperthyroidism was present in 0.8%, T3 thyrotoxicosis in 0.3%, and subclinical hyperthyroidism in 2.2%. Toxic multinodular goiter and toxic adenoma caused 80% of hyperthyroidism cases. After the iodization of table salt, iodine levels have not yet reached favorable levels in older people. Iodization of salt seems insufficient to achieve these levels in older people for whom alternative iodine supplementation should be considered [20].

As previously stated, the pathogenesis of thyrotoxicosis is proposed to be associated with the receptor activation caused by a somatic mutation that has occurred in the thyroid-stimulating hormone receptor (TSHR) gene and with cyclic adenosine monophosphate (cAMP) upregulation [8]. In the study by Gozu et al. performed in Turkey in TNG and TMNG patients, TSHR mutations were identified in 70.2% of 74 toxic thyroid nodules (TTN). A Gs alpha mutation was identified in one TTN, and three new TSHR mutations were detected (A627V, I640K, I486N). However, there was no significant difference between frequencies of TSHR mutations in iodine deficient/sufficient regions. The frequency of non-random X-chromosome inactivation was similar in iodine-sufficient or -deficient regions and TSHR mutation-positive or negative hot nodules [21]. These findings suggest that TTNs in iodine deficient/sufficient areas predominantly arise from aberrant growth of a single cell, and they suggested that neither the prevalence of TSHR mutations nor that of monoclonal TTNs is related to iodine supply.

The most common symptoms in patients with thyrotoxicosis are palpitation, weight loss, sweating, irritability, heat intolerance, hand tremors, menstrual irregularity, and diarrhea. The patients mainly complained about palpitation at a rate of 40% and weight loss at 34.4%. A similar study by Esen et al. performed in Turkish children found that the most common presenting features were tachycardia and palpitations, weight loss, and excessive sweating, which were quite similar to our adult population [22]. In our study, goiter, thyroid nodules, hypertension, tachycardia, and exophthalmos are the most typical signs we observed in patients with thyrotoxicosis. Exophthalmos occurs at a rate of 11.8%; GD findings are observed to be less common because TMNG is the more common cause in the Black Sea region. According to the literature, an average of 20-50% of ophthalmopathy in GD was reported as 40% in the study by Burch et al. [23], and Bartley GB et al. found it 62% [24].

Graves' disease is diagnosed using TSH, sT3, sT4, Anti-Tg, anti-TPO, and TRAb. According to the literature, the TRAb test, in particular, is recommended in differential diagnosis. A study stated that the TRAb test has a 98% specificity and 99% sensitivity for diagnosing GD [25]. Another study found that the TRAb test had a 99.6% specificity and a 98.8% sensitivity [26]. According to two studies, the TRAb positivity rate in GD is 88.2% [27] and 80% [28]. In a study performed in the UK, the specificity of the TRAb test was once more emphasized, and in patients with GD, a correlation between the degree of thyrotoxicosis and the TRAb value was found [29]. Regarding thyroid antibodies' role in diagnosing GD, it is remarkable that anti-TPO has been found positive at 74% [30] and anti-Tg positivity at 53% in another study [27]. According to our research, the TRAb, anti-TPO, and anti-Tg positive percentages in GD were 75.3%, 71.2%, and 49.3%, respectively.

In this study, we also assessed the liver function tests in the patients diagnosed with thyrotoxicosis. Of the 195 patients whose ALT-AST values were tested, we found that the ALT value was above average in 11 (5.6%) of them, while the AST value was higher than usual in 13 (6.7%). The rate of abnormal liver function tests reported in the literature is 15 to 76% for different series [31, 32].

Anemia was identified in 36 (18.5%) of 195 patients. The literature states that erythrocyte mass has increased in hyperthyroid individuals; however, due to various metabolic factors, the erythrocyte lifecycle has been reduced, resulting in a fall in Hb and hematocrit values [33]. Omar S et al. reported that 40.9% of the patients had anemia, a strong association between erythrocyte count and hemoglobin level, and anemia was treated to improve the condition [34]. On the other hand, Hambsch K et al. showed that 38% of the patients had normochromic normocytic anemia [35].

When 195 patients diagnosed with thyrotoxicosis were examined, it was determined that 182 (93.7%) of them had received anti-thyroid medical treatment, 16 (8.3%) had undergone surgery, and 26 (13.3%) received RAI treatment. In the studies performed, it was stated that the medical treatment should be the first-line treatment, with methimazole being the first option [36,37]. The incidence of hypothyroidism after surgical therapy is higher than the rate of hypothyroidism after RAI. We assessed the incidence of hypothyroidism after surgery and after RAI. Following surgical therapy, hypothyroidism incidence was found to be 75%, while post-RAI hypothyroidism incidence was reported to be 53.8%. Therefore, it was determined that hypothyroidism developed in most of the patients who received surgical treatment and in some of the patients who received RAI treatment. According to the literature, research performed in Turkey found that 16.9% of patients developed hypothyroidism after a year of receiving RAI [38], and another study found that around 50% of patients developed hypothyroidism within ten years [39]. This rate is 67.9% after a year in another study [40]. This discrepancy is assumed to be caused by the treatment dose given, the length of the post-treatment follow-up period for RAI, and the operation technique.

Conclusion

Based on the study's findings, a fundamental prediction was ensured regarding the diagnosis of thyrotoxicosis patients, the clinical picture they would present, the therapy they will receive, the early

identification of post-operative problems, and the changing biochemical parameters.

Conflicts of interest

There are no conflicts of interest in this work.

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