



## The etiological distribution and clinical and laboratory characteristics of pediatric patients presenting with goiter in the province of Adıyaman

*Adıyaman ilinde guatrla başvuran çocuk hastalarda etiyolojik dağılım ile klinik ve laboratuvar özellikler*

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### Abstract

**Aim:** The most common cause of goiter in developed countries is autoimmune diseases, while the most common cause in developing countries is iodine deficiency. We aimed to evaluate the clinical and laboratory results and etiological and demographic characteristics of cases presenting with goiter.

**Materials and Methods:** Seventy-five patients aged between 5 and 17 years presenting with goiter between October 2016 and January 2019 were included in the study.

**Results:** 90.7% (68) of children with goiter were female and 9.3% (7) male, the rate of goiter being 9.7-fold higher among girls. In terms of etiology, 43 patients (57.3%) were diagnosed with iodine deficiency, 25 (33.3%) with Hashimoto's thyroiditis (HT), five with Graves' disease (6.7%), and two (2.7%) with thyroid hormone resistance (THR). Mean ages were 13.7±2.1 years in the iodine deficient cases, 13.7±2.7 in the HT group, 14.3±1.4 in the Graves' disease patients, and 8.2±2.3 in the patients with THR. The highest mean urinary iodine level among iodine deficient patients was 45±27.1 (12.10-84.13) µg/L in Adıyaman center, while the lowest value was determined in Gerger district at 16.8±3.1 (14.27-20.25) µg/L, and 11 patients were diagnosed with mild iodine deficiency, 20 with moderate deficiency, and 12 with severe deficiency.

**Conclusion:** Iodine deficiency was the most common cause of goiter in children in the province of Adıyaman, followed by autoimmune thyroid gland diseases such as Graves' disease and HT. This study shows that iodine deficiency remains still as a problem in our province.

**Keywords:** Goiter in children, iodine deficiency, urinary iodine level.

### Öz

**Amaç:** Gelişmiş ülkelerde guatrın en sık sebebi otoimmün hastalıklar iken gelişmekte olan ülkelerde en yaygın neden iyot eksikliğidir. Guatr ile başvuran olguların klinik ve laboratuvar sonuçları ile etiyolojik ve demografik özelliklerini değerlendirmeyi amaçladık.

**Gereç ve Yöntem:** Çalışmaya Ekim 2016 ile Ocak 2019 tarihleri arasında guatr ile başvuran 5-17 yaş arasındaki 75 hasta dahil edildi.

**Bulgular:** Guatrlı çocukların % 90,7'si (68) kız, % 9,3'ü (7) erkek idi ve guatr oranı kızlarda 9,7 kat daha yüksek bulundu. Etiyoloji açısından 43 hastaya (% 57,3) iyot eksikliği, 25 hastaya (% 33,3) Hashimoto tiroiditi (HT), 5 hastaya Graves hastalığı (% 6,7) ve 2 hastaya (% 2,7) Tiroid hormon direnci (THD) tanısı konuldu. İyot eksikliği olan olgularda ortalama yaş 13,7 ± 2,1 yıl, HT grubunda 13,7 ± 2,7 yıl, Graves hastalarında 14,3 ± 1,4 yıl ve THD'li hastalarda 8,2 ± 2,3 yıl idi. İyot eksikliği olan hastalarda ortalama idrar iyot düzeyi en yüksek Adıyaman merkezde 45 ± 27,1 (12,10-84,13) µg/L olarak saptanırken, en düşük değer Gerger bölgesinde 16,8 ± 3,1 (14,27-20,25) µg/L idi.

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**Sonuç:** İyot eksikliği Adıyaman ilindeki çocuklarda guatrın en sık sebebi olup bunu Graves hastalığı ve HT gibi otoimmün tiroid bezi hastalıkları izliyordu. Bu çalışma iyot eksikliğinin ilimiz genelinde yaygın bir sorun olarak devam ettiğini göstermektedir.

**Anahtar Sözcükler:** Çocuklarda guatr, iyot eksikliği, idrar iyot düzeyi.

## Introduction

Thyroid disorders are endocrine problems frequently seen in children and adolescents, affecting 3.7% of children between the ages of 11 and 18 years (1). These generally present to hospital with thyroid gland enlargement (goiter), and hypothyroidism, euthyroidism, or hyperthyroidism may be present. The most common causes of pediatric goiter are iodine deficiency and autoimmune diseases (2). In terms of epidemiology, endemic goiter refers to thyroid hyperplasia concentrated in a specific geographic region. Any settlement region is said to be endemic for goiter when total goiter rate is more than 5% in school children (6–12 years) (3), and the most common cause of endemic goiter is iodine deficiency (4). The most suitable method for determining the prevalence and severity of iodine deficiency is urinary iodine measurement (5). Hashimoto's thyroiditis (HT) is the principal cause of goiter and hypothyroidism in regions without iodine deficiency (6). The pathology of this disease involves the formation of antithyroid antibodies that attack thyroid tissue and lead to progressive fibrosis (7). Graves' disease is the most common cause of hyperthyroidism in children and adolescents (8). Diffuse goiter is present in almost all patients. Symptoms of the disease include palpitation, tremor, tachycardia, weight loss, accelerated growth, decreased academic performance, and irritability.

Thyroid hormone resistance (THR) is a rare syndrome in which although thyroid hormone levels in circulation are high, thyroid stimulating hormone (TSH) levels are not suppressed as might be expected and may even be elevated. The clinical manifestation of the disease varies, but goiter is a common clinical finding, and there are generally no symptoms of thyroid hormone overproduction (9).

The purpose of this study was to evaluate the clinical and laboratory results and etiological and demographic characteristics of cases presenting to the Adıyaman Education and Research Hospital due to goiter.

## Materials and Methods

Seventy-five patients aged between five and 17 years and presenting to the Adıyaman Education

and Research Hospital, Pediatric Endocrinology Clinic due to goiter between October 2016 and January 2019 were included in this retrospective study. Patients' clinical characteristics and laboratory findings were retrieved from the electronic patient records. Patients with insufficient data or whose records were unavailable were excluded. Clinical symptoms and findings, demographic data such as sex, calendar age, consanguinity status, family history of goiter, weight, height, and body mass index (BMI), and laboratory tests retrieved from patient files were recorded. Our patients underwent routine physical examination and detailed goiter examination. Classification of goiter was made according to World Health Organization (WHO) criteria (10). Grade Ia, clearly palpable, but invisible with neck extension. Grade Ib, clearly palpable and visible with complete neck extension. Grade II, clearly visible when the head is in normal position. Grade III, thyroid seen from the distance. Our patients were divided into four groups according to etiology: iodine deficiency, HT, Graves' disease and THR. Their thyroid hormone status was defined as euthyroidism (T4 and TSH levels within normal ranges), hypothyroidism (low T4, high TSH), subclinical hypothyroidism (normal T4, high TSH) and hyperthyroidism (high T4- above the reference range).

The urine iodine concentration was measured by Sandhell Kolthoff reaction in randomly collected urine samples. Iodine deficiency were divided into three groups, spot urinary iodine levels of 50-99 µg/L as mild iodine deficiency, 20-49 µg/L as moderate and <20 µg/L as severe iodine deficiency.

Diagnostic criteria for HT were a) elevated TSH levels (above the upper limit of the laboratory's commercial kit reference range), the presence of serum thyroid peroxidase autoantibodies (anti-TPO) or thyroglobulin autoantibodies (anti-TG) at titers exceeding the upper limits of the reference ranges; b) a hypoechogenic thyroid pattern at ultrasonography (US) consistent with autoimmune thyroid disease. THR was defined as elevated free thyroxine (fT4), and/or free triiodothyronine (fT3) (above the upper limit of the laboratory's commercial kit reference range) and normal or elevated TSH levels (within or above

the upper limit of the laboratory's commercial kit reference range).

Graves' disease was defined as thyrotoxicosis with either elevated TSH receptor antibodies levels or clinical findings indicating of Graves' disease or diffuse radioisotope uptake at thyroid scans or persistent thyrotoxicosis of more than two years lasting without any other cause. The thyrotoxic phase of chronic lymphocytic thyroiditis (Hashitoxycosis) was defined as thyrotoxicosis together with the presence of one or more of the anti-TPO or anti-TG (based on commercial kit reference ranges) in patients with no other identified cause.

Body mass index (BMI) was calculated using the formula weight (kg) / height (m)<sup>2</sup>. Subjects with BMI values <5<sup>th</sup> percentile was defined as underweight, 5<sup>th</sup> to <85<sup>th</sup> percentile as normal weight, 85<sup>th</sup> to <95<sup>th</sup> percentile as overweight, and > 95<sup>th</sup> percentile as obese (11).

TSH, fT4, fT3, thyroid peroxidase antibodies, thyroglobulin antibodies and TSH receptor antibodies (TRAb) were studied using commercial kits. These tests were performed using electrochemiluminescence assay (ECLIA) on a Beckman Coulter DxI800 device and an appropriate kit (Beckman Coulter Access kit, USA). Values exceeding 4.18 IU/mL for anti-TG and 5.61 IU/mL for anti-TPO were regarded as positive.

The study protocol was approved by the Institutional Ethics Committee of the Adiyaman University Faculty of Medicine (decision number 1-9/03.01.2019). Written informed consent was obtained from participants.

Statistical analysis was performed using the SPSS version 24.0 software (SPSS Inc. Chicago, IL, USA). The chi-square test was used to compare categorical data. The Kolmogorov-Smirnov test was applied to determine whether

data were normally distributed. One-way analysis of variance (ANOVA) was used to compare more than two independent groups when data were normally distributed, and the Kruskal Wallis test for non-normally distributed data. Pearson's correlation test was used to determine correlation of existing parameters for normally distributed data, and Spearman's correlation test for non-normally distributed data. Categorical data were expressed as frequencies (percentages) and numerical data as mean ± standard deviation, p values <0.05 were regarded as statistically significant.

## Results

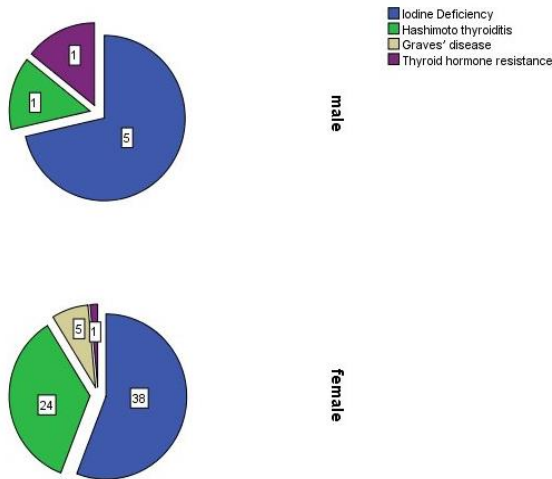
Sixty-eight (90.7%) of our patients were girls and seven (9.3%) were boys, and goiter was 9.7-fold more prevalent among girls. Forty-three patients (57.3%) were diagnosed with iodine deficiency, 25 (33.3%) with HT, five (6.7%) with Graves' disease, and two (2.7%) with THR (Figure-1). Thirty-eight (88%) of the iodine deficient patients were girls and five (12%) were boys, 24 (96%) of the HT patients were girls and one (4%) was a boy, all the patients with Graves' disease (five) were girls, and one (50%) of the two patients with THR was a girl and the other was a boy. Mean ages at time of diagnosis were 13.7±2.1 years in iodine deficient patients, 13.7±2.7 years in the HT group, 14.3±1.4 years in patients with Graves' disease, and 8.2±2.3 years in subjects with THR. Mean age was significantly lower in cases of THR compared to the other groups (p=0.011).

When thyroid hormone levels at presentation were examined in all patients with goiter, euthyroidism was determined in 46 patients (61.3%), hypothyroidism in 13 (17.3%), hyperthyroidism in nine (12%), and subclinical hypothyroidism in seven (9.3%) (Table-1).

**Table-1.** Comparison of patient thyroid status by diagnoses.

	Hypothyroidism	Euthyroid	Hyperthyroidism	Subclinical Hypothyroidism	Total
Iodine Deficiency	7	35	0	1	<b>43</b>
Hashimoto Thyroiditis	6	9	4	6	<b>25</b>
Graves' Disease	0	0	5	0	<b>5</b>
THR	0	2	0	0	<b>2</b>
<b>Total</b>	<b>13</b>	<b>46</b>	<b>9</b>	<b>7</b>	<b>75</b>

THR: Thyroid hormone resistance.



**Figure-1.** Distribution of goiter patients according to gender and etiology.

Isolated elevated TSH (compensated hypothyroidism) was determined in one child with iodine deficiency-related goiter, and iodine deficiency-related biochemical hypothyroidism in

eight (18%). The mean urinary iodine level in our iodine deficient patients was  $37.7 \pm 25.4$  (10.20-94.38)  $\mu\text{g/L}$ ; 11 patients were diagnosed with mild iodine deficiency, 20 with moderate deficiency and 12 with severe deficiency. The highest mean urinary level in our iodine deficient patients was  $45 \pm 27.1$  (12.10-84.13)  $\mu\text{g/L}$  in Adiyaman center, while the lowest level was determined in Gerger district at  $16.8 \pm 3.1$  (14.27-20.25)  $\mu\text{g/L}$  (Table-2). Weak inverse correlation was determined between spot urinary iodine levels and goiter grade in our iodine deficient patients (Table-3). Goiter grade increased as spot urinary iodine levels decreased, but this was not statistically significant ( $r = -0.262$ ,  $p = 0.090$ ). Analysis of correlation between thyroglobulin levels and spot urinary iodine in our iodine deficient patients revealed a moderate inverse correlation, with thyroglobulin levels increasing as spot urinary iodine levels decreased ( $r = -0.456$ ,  $p = 0.002$ ).

**Table-2.** Comparison of urinary iodine levels by places of residence of patients with iodine deficiency.

Places of residence	Urinary iodine Levels ( $\mu\text{g/L}$ )			Iodine Deficiency Level			Total
	Mean $\pm$ SD	Median	Min.-Max.	Mild	Moderate	Severe	
Adiyaman Center	45.01 $\pm$ 27.09	39.44	12.10-84.13	7	7	4	18
Kahta	37.30 $\pm$ 18,48	44.46	10.20-65.31	1	4	2	7
Besni	33.30 $\pm$ 34.41	21.38	12.88-94.38	1	2	2	5
Gölbashi	26.49 $\pm$ 0.51	26.49	26.13-26.86	0	2	0	2
Sincik	40.45 $\pm$ 29.66	24.80	16.82-78.62	2	2	2	6
Tut	18.19 $\pm$ 2.55	18.19	16.38-20.00	0	1	1	2
Gerger	16.83 $\pm$ 3.07	15.98	14.27-20.25	0	2	1	3
<b>Total</b>	<b>37.68<math>\pm</math>25.40</b>	<b>26.13</b>	<b>10.20-94.38</b>	<b>11</b>	<b>20</b>	<b>12</b>	<b>43</b>

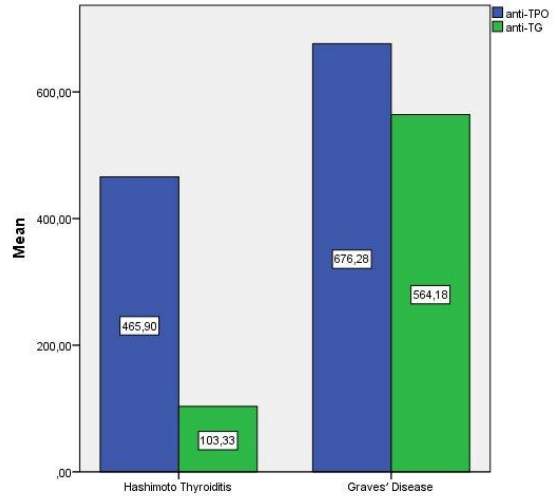
**Table-3.** Comparison of goiter stage and spot urinary iodine levels in patients with iodine deficiency.

	Count	Percent	Spot urinary iodine levels ( $\mu\text{g/L}$ )*
Stage Ia	10	%23.3	45.36 $\pm$ 28.25
Stage Ib	11	%25.6	37.38 $\pm$ 26,75
Stage II	15	%34.9	39.97 $\pm$ 26.76
Stage III	7	%16.3	22.27 $\pm$ 8.29
Total	43	%100	37.68 $\pm$ 25.40

\* Mean $\pm$ SD

Examination of thyroid functions at time of diagnosis in our patients with HT revealed hypothyroidism in 48% (12/25) (hypothyroidism + subclinical hypothyroidism), euthyroidism in 36% (9/25), and hyperthyroidism (Hashitoxycosis) in four (16%). In terms of thyroid autoantibodies, anti-TPO was positive in 20 patients (80%) and negative in five (20%), while anti-TG was positive in 18 patients (72%) and negative in five (20%), while anti-TG results were unavailable for two patients (8%). Combined anti-TPO and anti-TG positivity was determined in 16 patients. In terms of accompanying autoimmune diseases, type 1 diabetes mellitus (T1DM) was determined in one patient, and T1DM together with celiac disease in another. One or more accompanying autoimmune disease was thus determined in 8% (2/25) of our patients. Family history of goiter/thyroid disease was determined in 17 patients, while no family history was present in eight.

When mean thyroid antibody levels were compared by diagnoses, the mean anti-TPO levels and anti-TG in the group with Graves' disease were 676.28±359.26 IU/mL and 564,18±928,44 IU/mL, in the groups with HT were 467,13±427,42 IU/mL and 103,33±265,99 IU/mL, respectively (Figure-2). When our patients were compared in terms of thyroglobulin levels, the highest level was determined in subjects with iodine deficiency at 182.79±262.89 ng/ml, compared to 89.55±151.78 ng/ml in the HT group, and 72 ng/ml in the THR group, while the lowest level was determined in the Graves' disease group at 19.39±20.86 ng/ml (Table-4), although no statistically significant difference was determined among the groups (p= 0.440). Our two patients with THR were siblings, and the mean ages at presentation of these euthyroid patients were 9.8 and 6.5 years. When patients were compared in terms of BMI, 14 of the iodine deficient patients were underweight, 24 were normal, four were overweight, and one was obese. In the HT group, eight patients were underweight, 16 were normal, and one was overweight, while three of the patients with Graves' disease were underweight and two were normal, and both patients with THR were underweight. Improvement in goiter grades was observed at follow-up in 51.2% (22/43) of the iodine deficient goiter patients receiving hormone replacement therapy, and in 44% (11/25) of the HT cases.



**Figure-2.** Comparison of autoimmune thyroiditis patients according to autoantibody levels.

**Table-4.** Comparison of thyroglobulin levels by diagnoses.

	Mean±SD (ng/ml)	Min-Max (ng/ml)
Iodine Deficiency	182.79±262.89	0.51-1183
HT	89.55±151.78	0.11-527
Graves' Disease	19.39±20.86	0.75-41,93
THR	72	72
<b>Total</b>	<b>151.02±236.05</b>	<b>0.11-1183</b>

HT: Hashimoto thyroiditis; THR: Thyroid hormone resistance

## Discussion

The most common cause of goiter in developed countries is autoimmune diseases, while the most common cause in developing countries is iodine deficiency. Approximately 1.8 billion people live in iodine-deficient regions, and this causes problems such as hypothyroidism, impaired mental functions and growth delay being seen in addition to goiter. Iodine deficiency has been a problem in Turkey in general since the 1940s, and this is known to be more severe in some areas. In their study in 1968, Koloğlu et al. (12). reported low iodine levels in food and water in the Black Sea region. Hatemi et al. reported low iodine concentrations in 19% of drinking waters from various regions. They then scanned 73,750 subjects from different geographical regions using neck palpitation and determined a goiter prevalence in Turkey in 1987 of 30.5% (13). A study involving 20 provinces of

Turkey measuring thyroid volume by means of US and iodine expulsion in urine. Among 5948 school age children aged between 9-11 in 1997 and 1999 reported the goiter incidence of 31.8% (14). That study also demonstrated moderate-severe iodine deficiency in 14 provinces based on median urinary iodine concentrations and mild iodine deficiency in another six. The authors concluded that iodine deficiency was most prevalent in the Black Sea and Eastern Anatolia regions, and that iodine deficiency was a significant public health problem across Turkey. The prevalence of severe and moderate iodine deficiency in Turkey was 58% in 1997. After 1998, the addition of iodine to table salt was made compulsory, and the prevalence contracted to 27.9% in 2007. Another study involving 30 provinces reported that a significant proportion of moderate-severe iodine deficiency derived from rural areas, with rates of iodized salt consumptions among household members being reported at 89.0% in urban areas and 71.5% in rural areas (15). In a study from a rural region of eastern Turkey, Özkan et al. determined goiter in 47.6% of school age children between seven and 14 years (24.8% of boys and 22.8% of girls), and reported mean urinary iodine levels of 20 µg/L in the goiter group and 50 µg/L in the non-goiter group. That study concluded that despite the salt iodization program, there were still regions of Turkey with severe iodine deficiency (16). In our study, iodine was the principal cause among children presenting with goiter (57%), and a significant female preponderance was observed among children with iodine deficiency-related goiter (female/male: 7.3/1). Various studies have evaluated the relationship between goiter and gender in children and adolescents, and in agreement with our findings, a higher prevalence of goiter has been shown in girls than in boys (17-19). Workie et al. (18). suggested that an increase in iodine requirements deriving from the development of secondary sex characteristics and the menstrual burden in adolescent girls may cause goiter to be seen in female gender, while Ahmed et al. (19). proposed a genetic disposition to increased thyroid gland dimensions in response to iodine deficiency in girls. Malboosbaf et al. (17). showed that goiter is more common in female gender than in males in individuals with grade II goiter and in regions with long-term iodine insufficiency. The marked female dominance determined in patients with iodine deficiency-related goiter in our study may be

associated with the severity of iodine deficiency in our region. Moderate deficiency was most common (46.5%) among children with iodine deficiency-related goiter in Adiyaman province and its districts. This finding corroborates the idea that iodine deficiency is still a significant public health problem in our region. Some studies have reported varying thyroid hormone levels in cases living in regions with endemic iodine deficiency, from isolated TSH elevation to biochemical hypothyroidism levels (16, 20). Isolated TSH elevation (compensated hypothyroidism) was present in one child with iodine deficiency-related goiter in our study, and hypothyroidism in eight (18%).

Thyroid gland volume and thyroglobulin levels are important parameters indicating chronic iodine deficiency (21). Studies have shown negative correlation between urinary iodine levels and thyroid volume, and that cases with the lowest urinary iodine expulsion have the largest thyroid volumes (16, 22). In addition, one study from western Nepal, an iodine deficient region, reported significant correlation between urinary iodine levels and thyroglobulin levels in school age children (23). We observed weak negative correlation between urinary iodine levels and goiter grade in our cases of goiter with iodine deficiency, and moderate negative correlation between urinary iodine levels and serum thyroglobulin levels, findings compatible with the previous literature.

Autoimmune thyroiditis represents a significant proportion of goiter in children. HT, also known as chronic autoimmune thyroiditis or chronic lymphocytic thyroiditis, most commonly presents in adolescence, although the disease can be seen at any time, even rarely in children under one year (24). Dündar et al. reported a mean age at presentation of patients with HT of 12.20±0.31 years (25). HT is more common in girls, with a reported female/male ratio in the literature of 2-9/1 (26, 27). The mean age of our HT patients was 13.3±2.8 years, and female gender was significantly predominant (female/male 24/1). Patients with HT generally present with asymptomatic goiter, and euthyroidism, subclinical hypothyroidism, significant hypothyroidism or hyperthyroidism may be present (26). Similarly, euthyroidism was determined in nine of our HT patients presenting with goiter, hypothyroidism in six, subclinical hypothyroidism in six, and hyperthyroidism in four. Studies have reported accompanying other

autoimmune disease in between 10.3% and 13.9% of children with HT (28, 29). Additional accompanying autoimmune disease was present in two (8%) of our HT patients, T1DM in one and comorbid T1DM and celiac disease in another.

Graves' disease represents 10-15% of thyroid diseases in children. The clinical manifestation involves diffuse goiter and hyperthyroidism. Similarly to HT, Graves' disease is more common in girls and in adolescence, and is very rare in children under five. Jurate Jankauskiene et al. (30). reported a mean age at presentation of  $13.3 \pm 2.3$  years. In our study, all our patients with Graves' disease were girls, with a mean presentation age of  $14.3 \pm 1.4$ .

THR syndrome was first described in 1967 and has an incidence of approximately 1/40,000 (31). It is seen equally among men and women. Genetic mutations in the THR $\beta$  gene have been shown in the majority of cases, and the disease is generally transmitted in an autosomal dominant manner (32). Goiter is the most common clinical finding. The disease is differentiated from Graves' disease by means of

no suppressed TSH despite an increase in fT3 and fT4 levels. In our study, THR was diagnosed in two euthyroid siblings with diffuse goiter, a girl and a boy.

As the thyroid measurements with US were performed using different devices and by different radiologists, the evaluation of goiter in children was made based on clinical findings according to WHO criteria.

## Conclusion

Iodine deficiency was the most common cause of goiter among children in the province of Adiyaman in our study, followed by autoimmune thyroid gland diseases such as HT and Graves' disease. This finding shows that iodine deficiency is still a problem in our region. Our study now needs to be supported by community screening studies aimed at evaluating iodine deficiency in our province and its districts. In addition, the salt iodization program needs to be re-assessed and applied effectively across the region.

**Conflict of interest:** The authors have not declared any conflict of interest in this study.

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