

# Determination of urinary iodine excretion and iodine deficiency in school-age children aged 7–11 after mandatory iodization in Canakkale, Turkiye

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#### **ABSTRACT**

**OBJECTIVE:** The aim of this study is to determine the iodine deficiency status of school-age children in Canakkale, whose data were not known before.

**METHODS:** The population of the research was created from students in the 7–11 age group studying in primary schools. 316 students were selected for the study group by multi-stage stratified sampling method. Physical examinations and anthropometric measurements of the children were performed. A survey was conducted on their families regarding the use of iodized salt. Iodine level was measured spectrophotometrically from the collected spot urine sample.

**RESULTS:** One hundred forty-nine of the study group (47.2%) were male and 167 (52.8%) were female. Mean age was  $8.74\pm1.09$  years, mean height SDS was  $0.45\pm1.09$ , mean weight SDS was  $0.62\pm1.27$ . Iodine deficiency was detected in 25% (79) of the study group, and most of them (20.5%) had mild iodine deficiency and 51.8% of the children. The mean iodine level in Canakkale was  $15.8\pm8.43 \,\mu\text{g/dL}$ .

**CONCLUSION:** In our study, we showed that the average urinary iodine level in school-age children in Canakkale was sufficient. However, we showed that Canakkale is an endemic region for iodine deficiency due to its high rate of mild urinary iodine deficiency.

Keywords: Child; goiter; iodine; urine.

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I odine deficiency is the most common cause of preventable brain damage and mental retardation all over the world and affects 10–15% of the population [1]. Approximately 30% of the world population has insufficient iodine intake and the Iodine Global Network (IGN) of the World Health Organization (WHO) emphasizes that it is still an important deficiency for human health [1–3]. When iodine requirement is not enough daily, a group of mental, physical and developmental retardation symptoms called "iodine deficiency disorders" (IDD) occur [4]. Updating the iodine status, it is estimated that

there is deficiency in 32 countries and 29.8% of schoolage children [2, 3]. WHO's been presenting periodic reports on global iodine status since 2005. In the latest data, results were examined of school-age children in 196 countries; median urinary iodine levels in 132, insufficient for 28 and excessive for 14 countries [1]. And so, iodine deficiency is still a problem for humanity.

Iodization of table salt to eliminate iodine deficiency started in 1998 in Turkiye. While the prevalence of severe and moderate iodine deficiency in Turkiye was 58% in 1997, it decreased to 28.2% in 2008. In a study involving



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30 cities, iodine level was evaluated as sufficient in 20, and frequency of use of iodized salt was found to be 89.9% in urban and 71.5% in rural areas [2,5]. Global monitoring of iodine nutrition, collecting and reporting national, regional, and international data on iodine status are important for detecting iodine deficiency, planning prevention strategies, and monitoring effectiveness. As this information is updated, regions with insufficient or excessive iodine intake will be determined [6]. It is stated that if mild and moderate iodine deficiency is treated in primary school children, cognitive and motor functions will improve [7].

In this study, we aimed to perform iodine deficiency screening from urine samples of school-age children in the city center to examine the frequency of iodine deficiency in primary school children studying in Canakkale. In literature, there is no previous study to evaluate the prevalence of iodine deficiency in Canakkale, and so our study is the first.

## MATERIALS AND METHODS

This study was designed as a cross-sectional epidemiological study, covering students between the age of 7–11 years, from the city center of Canakkale in 2019–2020. There are 8689 students in this age range, according to the Provincial Directorate of National Education. When private schools and special education centers were excluded, 8007 students were evaluated. The minimum sample size was determined using the sample size formula used to estimate the population. In this formula, the population (N=8007), deviation (d) $\pm 0.05$ , with a 95% confidence interval, were calculated by using theoretical value  $(Z2\alpha/2)1.96$  from-table, using sampling formula. The sampling formula is used when the population number is known  $[n=N [Z2\alpha/2 P (1-P)] / d2 (N-1) + Z2\alpha/2 P]$ (1-P)]. The prevalence used for sample calculation in this study was accepted as 50% since more than one health problem will be investigated. As a result, the required sample size (n) was calculated as 367. Samples were collected from a total of 328 students. As 12 families left the study voluntarily, analyses were made on 316 students. Multistage stratified sampling was used as the sampling method. In the first stage, a stratification was made between schools, and in the second stage, stratification was made between classes in each school. In the selection of schools, less than 200 students were not included in the stratification. Inclusion criteria: Students between 7-11 years, in Canakkale central primary schools, who agreed to participate in the study or whose parents gave consent

# **Highlight key points**

- Iodine deficiency is still endemic in Canakkale, a seaside settlement, among school-age children.
- The mean urinary iodine level of the study group was 15.80±8.43 μg/dL, and the median iodine level was 14.8 μg/dL (3.9–48).
- The group with mild iodine deficiency is 20.5% and the rate of goiter in school-age children is over 5%.
- This is found to be the first study that evaluated urine iodine levels and parameters like children's goiter frequency, iodine deficiency and iodine use in Canakkale.

were included; exclusion criteria were using iodine-containing drugs, having a doctor-diagnosed thyroid disease, not agreeing to participate in the study by one's parent or legal guardian and having a chronic disease.

For the study, the necessary permission was obtained from the Canakkale Governorship Provincial Directorate of National Education between 01 March and 01 June 2019. Teachers and students were informed, consent forms were sent to the families to be included. Collected urine samples were appropriately collected for the study. When parents had questions, they were allowed to contact the researchers by phone until the end of the study. The child information form included demographic questions, nutrition and salt use status, a questionnaire including symptoms related to thyroid diseases and registration form. Height, weight measurements and goiter examination were implemented in the appropriate area determined by the school administration. Height was measured with his back against the wall after shoes were removed and portable height measurement rulers were used. Weight measurement was made with medical scales after removing shoes and thick clothes. Thyroid examinations were performed by the researchers. Goiter grading was done by two different researchers according to the WHO classification [1].

#### **Urine Iodine Test**

Urine samples were collected the next morning after urine containers were distributed to students. 5 ml of these samples were placed in deiodinase test tubes. After being separated and sealed with paraffin, they are placed in light-proof containers. On the same day in our clinic iodine was frozen until -20°C and was hidden in a deep freezer. Specimens were transferred from healthcare institutions in Istanbul to Development Medical Laboratories and analyzed directly or stored at -20°C until tested. Urine iodine results according to the Sandell-Coldhoff

**TABLE 1**. Demographic and laboratory characteristics of the study group

	Mean±SD	Median (min-max)
Age	8.70±1.09	9.0 (7.0–11.0)
Female	8.67±1.12	9.0 (7.0-11.0)
Male	8.81±1.06	9.0 (7.0-11.0)
Height (SDS)	0.45±1.09	0.41 (-5.17) -(3.35)
Weight (SDS)	0.62±1.27	0.35 (-1.74) -(5.1)
Urine iodine level (µg/dL)	15.80±8.43	14.18 (3.9–48.0)
Female	15.59±7.99	14.7 (3.9–48)
Male	16.04±8.92	13.7 (3.9–48)

Min: Minimum; Max: Maximum; SDS: Standard deviation score; SD: Standard deviation.

method were missing (<2  $\mu$ g/dL), moderately deficient (2–4.9  $\mu$ g/dL), slightly deficient, (5–9.9  $\mu$ g/dL), sufficient (10–19  $\mu$ g/dL), excess iodine level (20–29  $\mu$ g/dL) and extreme iodine level ( $\geq$ 30  $\mu$ g/ dL) [8].

Ethical approval was obtained from the Canakkale Onsekiz Mart University Clinical Research Ethics Committee (date: 27.03.2019, number: 2019-07). The study was carried out in accordance with the Helsinki Declaration.

#### Statistical Analysis

Data were analyzed with SPSS version 19.0 software (SPSS/Windows version 19.0; SPSS, Inc., Chicago, Ill., USA). Descriptive data in his presentation number, percentage, average, standard deflection, hydrangea, minimum, maximum values were used. Categorical data Chi-Square analysis test was used. In normal distribution in the analysis of quantitative data Kolmogorov-Smirnov and Shapiro-Wilk tests were also used. Significance tests were evaluated by the mean and Mann-Whitney U tests and analyzed with Kruskal-Wallis tests. P<0.05 accepted as statistical significance.

## **RESULTS**

A total of 316 students, 149 (47.2%) boys and 167 (52.8%) girls were included in the study. Demographic data are given in Table 1. The mean urinary iodine level of the study group was  $15.80\pm8.43~\mu g/dL$ , and the median iodine level was  $14.8~\mu g/dL$  (3.9–48) (Table 1). Iodine deficiency was detected in 79 (25%) of the study group. 51.89% of those were found to have iodine defi-

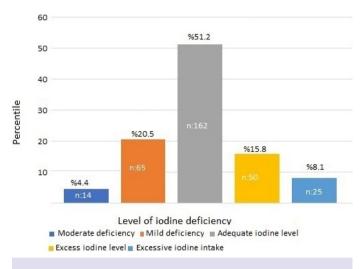


FIGURE 1. Distribution of urinary iodine deficiency level of the study group.

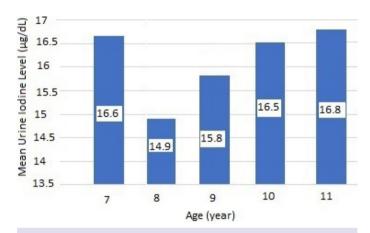


FIGURE 2. Distribution of the mean iodine level of the study group by age.

ciencies, and 48.11% were males. No serious iodine deficiency was found in our study (Fig. 1). Comparisons between the sufficient and insufficient urine iodine groups are given in Table 2. No statistically significant difference was found between the demographic characteristics of these two groups (Table 2).

The distribution of iodine in the study group by age is given in Figure 2. When the urinary iodine levels of the children with goiter according to age, the mean iodine level is  $22.60\pm16.2~\mu g/dL$  for 7 years,  $15.22\pm6.6~\mu g/dL$  for 8 years,  $15.55\pm9$  for 9 years,  $6~\mu g/dL$  was  $17.41\pm9.0~\mu g/dL$  for 10 years and  $17.12\pm6.8~\mu g/dL$  for 11 years. When urine iodine levels of the patients with goiter were examined according to age groups, no statistically significant difference was found between them with the Kruskal Wallis test (p=0.822).

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TABLE 2. Comparison of the group with low and sufficient urine iodine levels

		Urine iodine level is low (<10 μg/dL) (n=79)		Urine iodine level is sufficient (>10 µg/dL) (n=237)	
	Mean±SD	Median (min-max)	Mean±SD	Median (min-max)	
Age	8.69±1.12	9 (7–11)	8.75±1.08	9 (7–11)	0.594
Weight (SDS)	0.50±1.29	0.34 (-1.69-4.48)	0.66±1.27	0.38 (-1.74–5.1)	0.309
Height (SDS)	$0.30 \pm 1.00$	0.34 (-2.18–2.97)	$0.50 \pm 1.42$	0.48 (-5.17-3.35)	0.105*
Urine iodine level (µg/dL)	7.08±1.77	7.4 (3.9–9.92)	18.71±7.74	16.4 (10.10-48)	0.001

P: Mann-Whitney U Test; \*: Student-t Test; Min: Minimum; Max: Maximum; SDS: Standard deviation score; SD: Standard deviation.

Salt preferences of the children were 179 (56.64%) using iodized salt, 29 (9.17%) non-iodized salt and 108 (34.19%) mixed salt (iodized+non-iodized). Of the patients with iodine deficiency, 44 (55%) used iodized salt, 9 (11%) rock salt, and 26 (32%) mixed salt. Those who use iodized salt; moderate iodine deficiency was found in 3.3%, mild iodine deficiency in 20%, adequate iodine level in 51.9%, and excess iodine level in 24.8%. Those who use non-iodized salt; moderate iodine deficiency was found in 3.4%, mild iodine deficiency in 24.1%, adequate iodine level in 48.4%, and excess iodine level in 24.1%. Number of participants using iodized salt was 179, mean age 8.82±1.07 years, mean weight  $0.63\pm1.26$ , mean height  $0.37\pm1.11$ , mean urinary iodine level 15.46±8 was detected. The number of participants in the non-iodized salt group was 29, mean age  $8.65\pm1.07$  years, mean weight  $0.66\pm1.43$ , mean height 0.68±1.15 and mean urine iodine level was 16.55±10.28 μg/dL. No statistically significant difference was found between age, height, weight, and urinary iodine levels of children using iodized and non-iodized salt (p>0.05).

The results and analysis of the questionnaire in terms of nutrition according to the consumption weight of goitrogen foods, drinking water preference, feeding with seafood, feature of salt container, time to add salt to food, property of the salt storage container are given in Table 3. There was no statistically significant difference between the groups. When the goiter status of the study group and urinary iodine level were compared, the mean urinary iodine value with goiter was  $16.36\pm8.65~\mu g/dL$ , the median urinary iodine value was 15.05~(4.5-39.6), the mean urinary iodine value without goiter was  $15.67\pm8.39~\mu g/dL$ , and the median value was 14.00~(3.9-48). When the groups were evaluated with the Mann-Whitney U test,

no statistically significant difference was found. When we examine the gender distribution of the group with goiter, 54% were female and 46% male. When the participants with goiter were divided into groups according to male and female gender and urinary iodine levels were compared, the mean urinary iodine value of the girls with goiter was  $17.29\pm9.23~\mu g/dL$ , the median urinary iodine value was 17.45~(4.6-39.6), the urinary iodine average of the male group with goiter was  $15.30\pm7.97~\mu g/dL$ , and the median value was 13.75~(4.5-36.7). The groups were evaluated with the Mann-Whitney U test, no statistically significant difference was found.

### **DISCUSSION**

Iodine is one of the essential elements necessary for the body, which has an important role in normal growth and development. WHO, UNICEF/ICCIDD Study Group recommends that iodine levels should be monitored more effectively in children group of ages between 6-12 years [1, 9]. In our study, which we aimed to screen for iodine deficiency in school-age children, we found iodine deficiency at a rate of 25%. When the epidemiological studies showing iodine deficiency in the world are examined, serious iodine deficiencies are seen especially in the Himalaya region, Andes Mountains, South America, mountain ranges in China and Africa. India and Bangladesh are among the countries with a serious goiter rate [1, 2, 6, 10]. Countries that have achieved success in terms of IDD with the effective use of iodized salt are Switzerland, Mexico, Peru and Paraguay [2, 6]. Some countries where iodine deficiency remains a problem and the iodized salt program has not become widespread are the Russian Federation, Romania, and the Philippines [1, 2, 6]. When we look at Europe, although iodine deficiency

TABLE 3. Comparison of urine iodine level with influencing factors

	Urin	ie iodine level (µg/dL)	р
	Mean±SD	Median (min-max) μg/dL	
Feature of salt container			0.084
Closed, opaque	16.06±8.52	14.5 (3.9–48)	
Coverless, translucent	12.03±6.38	10.10 (4.6–31.2)	
Open container	16.03±8.73	12.88 (4.5–37)	
Other	16.46±6.37	15.6 (5.1–39.6)	
Salt storage conditions			0.184
Cool, dry	15.74±8.33	14.18 (3.9–48)	
Hot, humid	17.17±0.01	15.50 (7.9–38)	
Other	16.36±12.48	12.48 (6.60–36.7)	
Time to add salt to food			0.181
Before cooking	15.54±8.24	14.48 (3.9–48)	
While cooking	11.25±3.88	11.25 (8.5–14)	
After cooking	15.89±8.53	13.50 (3.9–48)	
Other	24.09±10.64	22.45 (12.3–39.6)	
Water supply			0.58
Ready water	16.83±8.84	15.10 (3.9–48)	
Tap water	13.35±6.79	12.80 (4.1–35.9)	
Spring water	15.87±8.40	13.35 (3.9–41.0)	
Other	14.01±7.63	12.89 (4.1–39.6)	
Frequency of seafood consumption			0.96
≥3 per week	15.71±8.22	14.2 (3.9–48)	
2-weekly 2-monthly	12.79±7.64	10.70 (4.3–34.4)	
≤2 per month	16.72±8.82	15.20 (3.9 <del>-4</del> 8)	
Never consumed	14.85±9.59	13.48 (6.4–35.2)	
Goitrogen food intake			0.737
≥3 per week	15.85±8.35	14.00 (4.1–48)	
2-weekly 2-monthly	16.86±5.89	14.56 (8.1–27.8)	
≤2 per month	15.85±8.83	13.9 (3.9–48)	
Never consumed	14.6±6.89	15.20 (4.3–34.4)	

P: Kruskal-Wallis Test; Min: Minimum; Max: Maximum; SD: Standard deviation.

can be controlled in most countries, iodine deficiency is still seen as a serious problem in some regions of Spain, Greece, Italy, and Germany [1, 2, 6].

When we look at the research conducted in various regions of our country, Kutlu et al. [10]. In their study including 1847 school-age children in Konya, Aslan et al. [7] found the average urine iodine value to be 19.8 $\pm$ 4.66 µg/dL. In their study conducted in Isparta province in 2015, they found the average iodine value to be 10.78 $\pm$ 7.81 µg/

dL, but no iodine deficiency was detected in either study [7, 10]. As one of the studies conducted in Central Anatolia, Kurtoglu et al. [11] evaluated postnatal urinary iodine excretion in mothers and their children in Kayseri and measured the median urinary iodine level as 3.2  $\mu$ g/dL in mothers and 2.38  $\mu$ g/dL in their babies. These rates are below normal and correspond to moderate iodine deficiency [11]. In a large-scale study including 401 primary schools in Sivas province to demonstrate the negative ef-

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fects of iodine deficiency, the mean urinary iodine excretion was found to be 7.05±0.48 µg/dL. Findings related to mild iodine deficiency in primary school-age children were obtained [12]. Similarly, in a study conducted in Hatay, in children between 6-12 ages, there was no difference between genders and iodine levels [13]. In the first study conducted in Isparta, the median urinary iodine level was 7 µg/dL, indicating insufficient iodine status, and the frequency of goiter was 30.4% by palpation. In the study conducted by Aslan et al. [7] in the same province ten years later, an increase was found in urinary iodine excretion, but the expected decrease in the frequency of goiter was not detected. This moderate increase in urinary iodine level has been attributed to the recent increase in iodine nutrition in school-age children in the region [7, 14]. Similarly, Gur et al. [15], in Istanbul, determined that for 46.2% of the students the median urinary iodine value was below 10 μg/dL; and 5 years later, Barutcugil et al. [16] found the same value as 17.87% and the median urinary iodine value as 15.9 µg/dL, and they attributed the increases of urinary iodine level to the consumption of iodized salt after the mandatory iodization of salts in 1999. Also in other studies, Erdogan et al. [17] conducted with the Ministry of Health between the years 1997–1999, and evaluated the iodine levels in urine of the students every year; before the mandatory iodization of table salt began (1997), five years after the first measurement (2002) and in the tenth year (2007) evaluations were made, and the median urinary iodine excretion values increased to 25.5  $\mu g/L$ , 87  $\mu g/L$  and 117  $\mu g/L$ , respectively, over the years [2, 17, 18]. As a continuation of Erdogan et al.'s [17] collaborative work with the Ministry of Health covering 30 provinces in 2007, Balikesir, Kocaeli, Tekirdag, Bursa, Edirne and Istanbul from the Marmara region were included in the study conducted with school-age children (our province was included in the study) and the median urinary iodine concentration of all these provinces was found to be 14.8 µg/dl. When the data of these provinces for the years 1997, 2002 and 2007 are examined, the median iodine concentration in Bursa increased to 5.1 µg/dL, 7.3 μg/dL and 15.9 μg/dL, respectively, and similarly in Edirne, it increased to 8 µg/dL, 9.9 µg/dL and 12 µg/dL, and the urinary iodine concentration was sufficient. According to 2002 and 2007 data, the median iodine concentration for Tekirdağg increased to 10.7 µg/dL and 13.3 µg/dL, respectively, and for Istanbul, the values increased from 12.2 μg/dL to 16.4 μg/dL [6, 15, 16]. Studies conducted with the mandatory salt iodization action show that median urinary iodine levels increase when iodine uptake

increases in the region, as supported by our study [17]. Since there is no previous study data for our province, we do not have an idea about the changes over time. In this regard, the median iodine level we found most closely was 14.8 µg/dL, which is like the close field study conducted in 2007 [18]. However, there is a 12-year time difference between our results and that study. In another research, 16 years after the mandatory iodization of table salts in Antalya, the average urinary iodine concentration was found to be 17.46 µg/dL, and the rate of goiter decreased from 34% to 0.3% in 16 years, and it was shown that it became an iodine-sufficient region. In their study, although the median urinary iodine concentration was 17.46 µg/L, they found moderate iodine deficiency in 6.5% of the population [19]. Compared to our study, school children in Canakkale have sufficient iodine levels in terms of iodine with a median urinary iodine concentration of 14.18 (3.9-48.0) µg/dL, while samples with a urinary iodine concentration below 5 µg/dL were 4.4% (<20%), closer to the target value. When similar studies examining urinary iodine excretion and thyroid volume status, it was not find a relationship between age, gender, and urinary iodine levels [20-24] In our study, like the studies mentioned, no difference was found between urinary iodine concentration and age and gender.

Unlike our study, Topal and Soyturk [25] worked with commonly used local spring salt and evaluated urinary iodine levels, iodine volumes and school success of children using iodized salt. Iodine deficiency was observed in 133 (95.7%) of 139 students, using source salt iodine was present in 39 (84.8%) of the 46 students who used iodized table salt [25]. In our study, because there was no statistically significant difference between urinary iodine levels of children using iodized salt and non-iodized salt, we think this is due to the type of salt consumption, maybe since people prefer to use mixed salt (34.19%) instead of only rock salt (9.17%). Another reason suggests that because of the active fishing activities in Canakkale, which is a coastal city, the consumption of seafood is higher than in many other cities. In this regard, in a study in 2006 dealing with fish consumption in Canakkale, Turkiye's annual per capita fish consumption average is 6.7-9.8 kg/year, while the average fish consumption in Canakkale is approximately 13.8 kg/year in the world. It is close to the mean [26]. Considering all these data, it can be thought that the frequency of seafood use in Canakkale is higher than other parts of the country, contributing to the iodine intake in addition to the mandatory iodization of salts [27].

In our study, we did not find a significant relationship between urinary iodine concentrations and the way salt is stored, the characteristics of the storage container, the time it is added to the meal, and the urinary iodine concentrations. However, there are studies in the literature showing iodine deficiency despite the use of adequate iodized salt, and in those, researchers have stated that iodine loss may be caused by storage and usage conditions [28, 29].

When the relationship between drinking water preferences and iodine deficiency is evaluated, in the study of Darcan et al. [30] in Izmir, they determined the amount of iodine in drinking water to be 4.99 µg/dL, and the amount in rural areas as 3.74 μg/dL. Those results showed that Izmir, which is a province close to our study region, is a risk area for iodine deficiency [30]. In our study, although we did not evaluate the iodine level in drinking tap waters of Canakkale province, we could not detect a significant difference between iodine deficiency levels and drinking water preferences. That is thought, the amount of iodine in tap waters may not make a significant difference as much as the amount of iodine in other nutrients and iodized salt. In a study in India, the average urinary iodine value was found to be 6.16 µg/dL in children aged between 10–12 years in a region where the rate of using iodized salt is quite high and unsuitable salt storage conditions [29]. Similarly, we could not find a significant relationship between urinary iodine concentrations and did not investigate the way the salt is stored, the characteristics of the storage container, the time it is added to the food, and the urinary iodine concentrations.

When iodine deficiency and the presence of goiter were examined, the rate of goiter of stage 2 and above was found to be 1.9% in the study conducted by Gur et al. [15] among children aged 6-16 years after compulsory iodization of salts in Istanbul. In a study conducted in the province of Istanbul, Barutcugil et al. [16] found the rate of stage 2 and 3 goiters to be as low as 0.3% and the rate of goiter in girls to be higher than in boys, similar to our study. The absence of stage 2 and advanced goiter in our study, the absence of severe iodine deficiency, and the high rate of stage 1 goiter in the group support these studies. In our study, when we classified children with goiter according to their age, there was no significant relationship between the ages of those with goiter and their urinary iodine levels, but the group with low iodine levels clustered between the ages of 8 and 9 years, and most of the participants with

goiter were 8–9 years old. We found the frequency of goiter in these age groups to be high, although not statistically significant. Although the relationship between the stage 1 goiter status of children with a high rate and pubertal goiter is not the subject of our study, it is a subject that needs to be investigated in future studies due to the study age group.

#### Conclusion

We have shown for the first time that although urinary iodine levels are sufficient in school-age children in Canakkale, iodine deficiency continues as a mild and moderate problem in growing children. The fact that the group with mild iodine deficiency is more than 20% (20.5%) and the rate of goiter in school-age children is over 5% also shows that Canakkale is an endemic province. Our study is the first study to show the urinary iodine levels in Canakkale and will guide further studies to be conducted. Among the limitations of our study, the reasons for this include the fact that our number of cases was low compared to the literature and that the urinary iodine level was studied in spot urine, in a single urine sample. In addition, since no similar study has been conducted in our region before, the effects of iodized salt use on the results cannot be observed over time. Strong sides of our study are that it is the first study to be evaluating urine iodine levels and parameters like children's goiter frequency, iodine deficiency and iodine use in Canakkale and to be a guide for future research.

**Ethics Committee Approval:** The Canakkale Onsekiz Mart University Clinical Research Ethics Committee granted approv-al for this study (date: 27.03.2019, number: 2019-07).

**Informed Consent:** Written informed consents were obtained from patients who participated in this study.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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