ORIGINAL ARTICLE

The investigation of effects of fluorosis on thyroid volume in school-age children

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ABSTRACT

Aim To compare the urine iodine, fluoride, and to measure thyroid volumes in 10-15-year-old children using ultrasonography, a gold standard in evaluating thyroid volume.

Methods A total of 261 children were enrolled into the study group from the 4-8th grades of 3 different primary schools, which were in the zone with high fluoride levels. The control group was formed by enrolling 298 children from the 4-8th grades of only one primary school. Age, gender, height, and weight values were recorded for the children. The urine iodine, fluoride, and thyroid volumes were measured with ultrasonography in 10-15-year-old children with fluorosis and controls and compared between two groups.

Results The mean urine fluoride level was 0.48±0.24 mg/L in the study group and 0.22±0.17 mg/L in the control group ($p<0.001$). The mean urine iodine level did not differ between two groups. The mean total thyroid volume was 8.60±3.11 mL and 8.73± 2.75 mL in the study and control group, respectively. The groups were also compared according to the echobody index, and the score was 6.94±2.14 ml/m² in the study group and 6.48±1.53 ml/m² in the control group ($p=0.003$). Mean thyroid volumes did not differ between two groups. However, the echobody index in the study group was higher than in the control group.

Conclusion A relation between fluoride concentration and thyroid gland with ultrasonographic examination was firstly evaluated, and it was concluded that fluoride affected thyroid gland although it was weakly significant. After puberty, echobody index in subjects with fluorosis was markedly high. Based on our results, we thought that fluorosis increases thyroid volume in children with fluorosis after puberty.

Key words: ultrasonography, fluorosis, echobody index

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INTRODUCTION

Thyroid diseases lead to alterations in thyroid size and form or irregularities in hormone secretion (1). Goiter, an expression used to describe an enlargement of the thyroid gland for any reason, can be diffuse or nodular (1). Endemic goiter is a term used to describe a condition in which > 10% of a certain population or > 5% of school-age children between the ages of 5 and 12 years are observed with goiter (2). Apart from iodine deficiency, thiocyanates in goitrogenic food and the amount of calcium and fluoride in water are also important. Of these, iodine deficiency has the most critical role, and the goitrogenic effects of other factors only become important when they are adjuvant to iodine deficiency (2,3).

Fluoride is one of the essential elements for the body and stored chiefly in bones and teeth (4). Under normal conditions, people are exposed to harmless amounts of fluoride daily (5). However, when the daily fluoride intake is above the safety range for an extended period of time, chronic fluoride poisoning, known as fluorosis, occurs (6). Fluorosis leads to pathologic changes in the liver, kidney, heart, muscle, and in gastrointestinal, skeletal, reproductive and endocrine systems (7). Although fluoride has an impact on various organ systems, the effects on the dental and skeletal system have been investigated most often (8,9). The studies examining the effects of fluoride on the thyroid have largely been carried out on animals (10,11), but a limited number of human studies have demonstrated that excessive fluoride leads to several pathologies in the thyroid and has a similar effect to that of iodine deficiency (12-15).

The purpose of the present study was to investigate the urine iodine, fluoride, and calcium levels, and to measure thyroid volumes in 10-15-year-old children using ultrasonography for the first time, a gold standard in evaluating thyroid volume. Isparta Province in which study was performed was endemic area for fluorosis. We also compared the groups in terms of physical development and dental aberrations.

EXAMINEES AND METHODS

The study design and population

The study was designed as cross-sectional and carried out in Isparta, Turkey. It was conducted by Division of Endocrinology, Internal Medicine Department, Suleyman Demirel University, Isparta, Turkey. Ethical issues were approved by the Ethic Committee of the Institution. To conduct the study, local permission was obtained from local Health and Education Directorate of Isparta. Informed consent was provided for children's parents.

Study population included school-age children between 10 to 15-year-old living in the quarters of Yenice, Dere, and Anadolu in Isparta. A total of 261 children between 10 and 15 years of age were enrolled into the study group from the 4-8th grades of 3 different primary schools, which were in the zone with high fluoride levels (Yenice and Dere). The control group was formed by enrolling 298 children between 10 and 15 years of age from the 4-8th grades of only one primary school in Anadolu quarter, which was the area with normal fluoride levels. The groups were divided into subgroups according to age, 10 to 11-year-olds, 12 to 13-year-olds, and 14 to 15-year-olds in order to minimize the variations in their physical development to evaluate thyroid volume and 'echobody index' in children of age groups.

The study and control groups were determined according to data obtained from a study conducted by the Local Health Directorate of Isparta in 2001. Accordingly, an analysis of samples from 18 major water reservoirs in Yenice and Dere quarters supplying water to the city center was performed and established the fluoride level to be 4.6 mg/L in Dere and 2.8 mg/L in Yenice, and the fluoride concentration in tap water in Anadolu quarter to be 0.19 mg/L.

Exclusion criteria were previous medical history and thyroidal disease, detection of nodule on USG, and signs of thyroiditis.

The socio-demographic and anthropometric measurement of subjects

Age, gender, height, and weight values were recorded for the children. Anthropometric values of all participants from the study and control group were measured as follows: weight and height were measured with subjects wearing light clothing and without shoes, height was recorded to the nearest 0.1 cm, stadiometer, weight was recorded to the nearest 0.1 kg using a balance-beam scale. Body surface area (BSA) and body mass index (BMI) calculations were made by using the following formula: BSA= (weight x 4) + 7 / kg + 90, and BMI= weight (kg) / height (m^2).

The biochemical analysis of fluoride, iodine, calcium

Spot urine was used for urine fluoride analysis consistent with the studies in the literature (16,17). The measurements were performed by using an Orion ion electrometer and an Orion fluoride-selective electrode (Orion Research Inc., Beverly, MA, USA) (18). A fluoride level in spot urine was evaluated according to WHO criteria (normal ≤0.6 mg/L, high >0.6 mg/L) (19). Iodine measurement in the urine was performed with an autoanalyzer spectrophotometrically according to the method described by Sandell and Kolthoff (20). To evaluate iodine elimination through the urine iodine spot test, the following criteria were employed: <20 µg/L, severe iodine deficiency; 20-49 µg/L, moderate iodine deficiency; 50-99 µg/L, mild iodine deficiency; and >100 µg/L, normal (21,22). Calcium measurement in urine was performed with an autoanalyzer spectrophotometrically. The normal range for calcium in spot urine for this method was 0.5-4 mg/dl.

Dental examination

Dental aberrations were classified according to Dean's index one by an expert observer. According to this, it is classified into 6 groups as normal, questionable, very mild, mild, moderate and severe.

The evaluation of thyroid volume

For the ultrasonographic evaluation of thyroid volume, neck is placed in hyperextension when the patient is in the supine position. Transverse, sagittal, and antero-posterior lengths of the isthmus and the right and left lobes of the thyroid are measured. Then, applying the ellipsoid formula (Volume = [π/6] x transverse x sagittal x antero-posterior length), the volume is calculated for each section. To yield the total volume for the thyroid (TTV), the volumes of two lobes were summed (23).

Thyroid volume is associated with age, weight, height, and body surface area (BSA). However, it has been reported to be more closely associated with BSA and weight (24). In recent years, the 'echobody index' (TTV/BSA ml/m²) has been used to assess thyroid volume more accurately (25).

Statistical analysis

Data was encoded and entered into a computer. Normal distribution of variables was tested with Kolmogorov-Smirnov test. A Student t-test for independent non-categorical and a chi-square test for categorical variables were used for comparisons. Spearman correlation analysis was used for correlation analyses. Significance was set at p<0.05.

RESULTS

A total of 582 children were enrolled into the study. Of them, 23 were excluded due to the exclusion criteria. Totally, data of 559 children were analyzed (Table 1). There were no statistically significant differences between two groups in terms of mean age and gender. The height (p=0.002), weight (p<0.001), BSA (p<0.001) and BMI (p<0.001) were significantly lower in the study group than in control group.

The mean urine fluoride level was 0.48±0.24 mg/L in the study group and 0.22±0.17 mg/L in the control group (p<0.001). Mean thyroid volumes did not differ between two groups. However, the 'echobody index' in the study group was higher than in the control group. The mean total thyroid volume was calculated to be 8.60±3.11 ml and 8.73±2.75 ml in the study and control group, respectively. The groups were also compared according to the 'echobody index', and the score was 6.94±2.14 ml/m² in the study group and 6.48±1.53 ml/m² in the control group (p=0.003) (Table 2).

The participants were re-assigned into two groups of normal (≤0.6 mg/L) and high (>0.6 mg/L) urinary fluoride level. The number of children

Table 1. Demographic characteristics of examinees

Measurements	Study Group (n=261) (Mean ± SD)	Control Group (n=298) (Mean ± SD)	p
Gender			
Male	122 (46.8%)	148 (49.6%)	>0.05
Female	139 (53.2%)	150 (50.4%)	>0.05
Age (year)	12.00±1.50	11.87±1.37	0.296
Weight (kg)	38.33±10.17	43.67±12.64	<0.001
Height (cm)	144.77±10.16	147.58±11.49	0.002
BSA (m²)	1.23±0.20	1.34±0.23	<0.001
BMI (kg/ m²)	17.99±3.09	19.82±3.71	<0.001

BSA, Body Surface Area; BMI, Body Mass Index; SD, Standard Deviation

Table 2. Thyroid measurements and urinary iodine and fluoride level of examinees

Measurements	Study Group (n=261) (Mean ± SD)	Control Group (n=298) (Mean ± SD)	p
TTV (ml)	8.60±3.11	8.73±2.75	0.624
Echobody index [TTV / BSA (ml/m²)]	6.94±2.14	6.48±1.53	0.003
Urinary fluoride (mg/L)	0.48±0.24	0.22±0.17	<0.001
Urinary iodine (µg/L)	93.12±38.51	98.41±33.40	0.083

BSA, Body Surface Area; TTV, Total Thyroid Volume; SD, Standard Deviation with normal and high urinary fluoride level was 466 (83.3%) and 93 (16.7%), respectively. Of 93 children, 81 (31.03 %) were in the study group and 12 (4.03%) were in the control group. The mean age was 11.80±1.43 years in the group with high urine fluoride levels. The mean age was 11.95±1.43 years in the group with normal urine fluoride levels (p=0.357). Height, weight, BSA, and BMI values were significantly lower in children with high urine fluoride levels. 'echobody index' values, TTV, and urine iodine levels were not different for the children with high and normal urine fluoride levels. Urine calcium levels for the children with high and normal urine fluoride levels were 3.35±2.93 mg/L and 4.96±4.84 mg/L, respectively (p=0.002) (Table 3).

The average daily iodine urinary excretion did not differ between the two groups. One hundred ten children in the study group (42.1%) and 133 (44.7%) children in the control group had normal urine iodine levels. Severe iodine deficiency was not observed within in any group. The urine fluoride level and 'echobody index' analysis revealed a weak positive correlation when the overall study population (n=559) was evaluated (r=0.084, p=0.047). The urine fluoride and urine calcium levels were significantly negatively correlated (r=-0.161, p<0.001). Urine fluoride and urine iodine levels were not correlated. While a significant correlation was not detected between the urine iodine level and the 'echobody index', the significant correlation between urine iodine and urine calcium levels was observed.

When the fluoride level and dental aberrations were analyzed together, it was noted that an elevated fluoride level had a significant impact on the increase in dental aberrations (r=-0.318, p<0.001). On the other hand, dental aberrations and 'echobody index' were not significantly correlated (r=-0.071, p=0.093).

Table 3. Parameters of subjects according to normal and high urinary fluoride level

Variables	High Urinary Fluoride Level (n=93) (Mean ± SD)	Normal Urinary Fluoride Level (n=466) (Mean ± SD)	p
Age (year	11.80±1.43	11.95±1.43	0.357
Height (cm)	144.15±10.90	146±10.95	0.041
Weight (kg)	38.26±9.63	41.76±12.17	0.009
BSA (m^2)	1.23±0.19	1.30± 0.22	0.006
BMI (kg/ m^2)	17.96±3.17	19.17±3.60	0.003
TTV (ml)	8.29±2.58	8.74±2.98	0.136
'Echobody' index	6.74±1.87	6.68±1.85	0.788
Urinary fluoride (mg/L)	0.75±0.18	0.26±0.15	<0.001
Urinary iodine (µg/L)	93.45±34.55	96.43±36.23	0.466
Urinary calcium (mg/L)	3.35±2.93	4.96±4.84	0.002

BSA, Body Surface Area; BMI, Body Mass Index; TTV, Total Thyroid Volume; SD, Standard Deviation

Table 4. Factors influencing thyroid volume and žechobody index' in children according to age groups

Age groups (years-old)	Variables	Study Group (n=109) (Mean ± SD)	Control Group (n=142) (Mean ± SD)	p
10-11	Weight (kg)	32.44±5.58	36.50±8.33	<0.001
	Height (cm)	137.48±6.59	139.80±8.66	0.021
	BMI (kg/ m2)	16.93±2.61	18.63±3.22	<0.001
	Urinary fluoride (mg/L)	0.50±0.22	0.21±0.14	<0.001
	'Echobody' index (TTV/ BSA ml/m2)	7.08±2.15	6.85±2.17	0.424
12-13	Weight (kg)	39.07±7.87	48.43±12.29	<0.001
	Height (cm)	147.03±7.46	152.40±8.06	<0.001
	BMI (kg/ m2)	18.01±2.55	20.81±3.77	<0.001
	Urinary fluoride (mg/L)	0.48±0.24	0.22±0.21	<0.001
	'Echobody' index (TTV/ BSA ml/m2)	6.27±1.48	6.25±1.35	0.910
14-15	Weight (kg)	50.12±11.91	54.14±11.75	0.099
	Height (cm)	156.43±8.75	159.77±8.56	0.062
	BMI (kg/ m2)	20.35±3.84	21.11±3.92	0.339
	Urinary fluoride (mg/L)	0.42±0.27	0.21±0.15	<0.001
	'Echobody' index (TTV/ BSA ml/m2)	7.40±1.73	6.54±1.52	0.011

BSA, Body Surface Area; BMI, Body Mass Index; TTV, Total Thyroid Volume; SD, Standard Deviation

Age subgroups were compared again with respect to all the parameters mentioned (Table 4).

DISCUSSION

This study has shown that fluoride can increase thyroid volume independently from iodine. However, this particular effect of fluoride is not very pronounced. The 'echobody index', which is an important parameter in assessing thyroid volume, was markedly increased with age along with exposure to fluorosis. This finding could be attributed to the inhibiting effect of fluoride on puberty, but not on physiological increase in volume of the thyroid gland (25).

An evaluation of the children in our study population for each age group revealed that their TTV values were higher than those reported by the WHO and in a study carried out by Kurtoglu et al. (26). The difference may be attributed to iodine concentrations in our region or fluorosis. We did not establish significant differences between the groups in terms of TTV values. However, height and weight values, and as a result BSA values, were significantly lower for the children in the study group when compared with children in the control group. As described earlier, there is a strong correlation between TTV and BSA (27).

Evaluation of our measurements with the 'echobody index' demonstrated that the latter was significantly higher in the study group compared with the control group. Consequently, a higher 'echobody index' in the study group when thyroid volumes were consistent with the BSA had been expected to be lower than the control group, implying that fluorosis had an impact on thyroid volume. Moreover, in support of this implication, the urine fluoride level and 'echobody index' were significantly positively correlated.

Fluoride was found to be associated with goiter in the study of Jooste et al., which had been performed in children aged between 6-15 years in six regions with different fluoride levels with normal iodine levels; thyroid size had been evaluated by palpation (3). In this present study, thyroid volumes of the children were evaluated ultrasonographically, and rather than fluoride levels of springs, urine fluoride excretion values of the children were measured.

One limitation of our study was the high number of children of the school in the control group area. Some children in the control group could have come to school in the control area from different regions of the city. Some of these regions could have had a higher level of fluoride in drinking water. Therefore, 12 children in the normally non-fluorosis area could have had high levels of fluoride in urine.

Several studies reported that high fluoride level could result in different influences on thyroid hormone level (13,19,28,29). However, since we were not able to obtain permission from parents and relevant authorities, the children's blood samples were not collected in the present study.

In the study conducted by Powell-Jackson et al. in 13 regions, high fluoride levels and high pH in spring waters were positively correlated with goiter prevalence (12). The investigators maintained that the goitrogenic effects of excessive fluoride were more pronounced if accompanied by iodine deficiency. As we did not have cases with significant iodine deficiency in this study, we were not able to evaluate whether iodine deficiency augmented the goitrogenic effects of excessive fluoride.

The fact that in this study there were no 'echobody index' differences in urinary fluoride levels between the groups regarding the first two subgroups may be attributed to two main reasons. Firstly, a study demonstrated the negative effects of fluorosis on the reproductive system and development (30). Secondly, the mean age of children aged 10-11 years in the study group was lower when compared with the control group.

Isparta region has shown to be an endemic goiter area with different studies at different times, and it was also stated that the urinary iodine levels reached normal values in 2007 with iodine prophylaxis (31-33). Since the difference between the study and control groups in terms of urine iodine levels was not statistically significant, we maintain that iodine may not be accountable for the differences in thyroid volume in the present study.

In the present study, a correlation analysis did not reveal a correlation between urine fluoride and urine iodine levels. Similarly, the urine iodine level and the 'echobody index' were not correlated in the overall assessment and when the groups were evaluated with respect to age groups. Urine calcium is one of the indications of the pH level of water. The study carried out by Day et al. in 13 different regions of the UK established that the incidence of goiter increased with higher pH levels of water (12). In the present study, no correlation was observed between urine calcium levels and thyroid volume.

Previously it has been reported that very high level of fluoride concentrations could have an effect on calcium level through parathormone (34). The negative correlation based on results of our study was consistent with the finding that high level of fluoride concentrations can decrease calcium level.

Fluoride can have an effect on growth pattern along with thyroid volume particularly in early ages, but in later life of childhood, thyroid volume alone is usually affected. Further investigations are needed to find a possible correlation between fluoride and thyroid volume along with biochemical parameters related to puberty.

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