Thyroid status of iodine deficient newborn infants living in central region of Turkey: a pilot study

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Background: **Iodine deficiency (ID) during the fetal and neonatal periods can lead to neonatal hypothyroidism. This study was conducted to evaluate the effect of ID on the thyroid hormone level of newborns living in Turkey.**

Methods: **Between 1998 and 2013, 71 newborns with a urinary iodine concentration <100 μg/L were recruited into the study. Data on thyroid volume, free triiodothyronine (fT3), free thyroxine (fT4), thyroid stimulating hormone (TSH), and thyroglobulin (Tg) were collected from all newborns, and on breast milk iodine from their mothers. Infants who were classified as having congenital hypothyroidism (TSH >40 mU/L and fT4 <8.5 pmol/L) were treated with levothyroxine (*n*=26, T group), while the remaining infants remained untreated (*n*=45, UT group). Thyroid hormones were subsequently measured 7-14 days later in a sub-sample of both treated and untreated infants.**

Results: **The average values at the time of admission were as follows [median (min-max)]. fT3: 5.0 (2.8-7.1) pmol/L, fT4: 7.7 (0.13-19.1) pmol/L, TSH: 75 (14-426) mU/L, Tg: 464 (226-1100) ng/mL, urinary iodine concentration (UIC): 30 (0-61) μg/L, breast milk iodine levels: 21 (10-150) μg/L, thyroid ultrasound (USG): 1.10 (0.24-1.95) mL for the T group; and fT3: 5.7 (1.7-12.7) pmol/L, fT4: 16.2 (9.9-33.5) pmol/L, TSH: 5.4 (0.63-41.8) mU/L, Tg: 171 (15-2124) ng/mL, UIC: 39 (0-90) μg/L, breast milk iodine levels: 47 (10-120) μg/L, thyroid USG: 0.75 (0.35-1.72) mL for the UT group. A significant difference was found between groups in respect to fT3, fT4, TSH and Tg levels. No significant difference in thyroid ultrasonography, UIC, and breast milk iodine levels was found between the two groups. The Tg levels of 50 out of 71 patients were measured, 40 (80%) of whom had Tg levels above the normal range (101 ng/mL).**

Conclusions: **In our country, despite the use of iodized salt, congenital hypothyroidism due to ID remains a problem. The Tg level of newborns can be used as a good indicator of ID.**

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Introduction

Annually, 50 million infants are born from mothers with iodine deficiency (ID) worldwide; of these, 40% are adversely affected at varying degrees in terms of mental development.[1] ID is one of the causes of transient congenital hypothyroidism (CH), and CH is still the leading cause of preventable mental retardation. CH has an incidence of about one out of 2000-4000 births.[2,3] There are no clear figures as to what proportion of CHs are transient. In their study, Parks et al[4] diagnosed transient CH in 290 out of 1727 cases of CH (proportion of transient disease: 16.8%). Another study better demonstrates the importance of iodine supplementation in transient CH. In that study, the proportion of CH associated with ID was reduced from one in 3920 between 1985 and 1991 to one in 48 474 between 1992 and 2000, after the introduction of iodized salt.[4] In our country (Turkey), the Iodine Deficiency Diseases and Salt Iodization Program was first implemented in 1994 to prevent iodine deficiencies and a law was introduced in 1998 in an attempt to ensure that all table salts are manufactured with iodine.[5] Our study was conducted after iodized salt use was made obligatory by law in our country.

Our study attempted to define the treatment requirements of mature neonates who were transferred

to our hospital with thyroid dysfunction or with clinical suspicion thereof and were diagnosed with ID, and to emphasize the importance of thyroglobulin (Tg) measurements in diagnosing ID in the newborn.

Methods

By the end of 2014, Turkey's population is around 76.7 million. The annual number of live-born babies in Turkey is 1.3 million. Kayseri is located in the central area of Turkey. The population of Kayseri is around 1.3 million. According to data from the Turkish Statistical Institute, 23 304 infants were born in the Kayseri in 2014.[6] Turkey is located in an area of mild to moderate ID. In a study performed to determine the ID in Kayseri, moderate ID has been detected.[7]

The study was approved by the Ethics Board of Erciyes University Faculty of Medicine, Kayseri (approval number: 2014/14). This study was conducted in those living in Kayseri province between 1998 and 2013. The data of patients were collected from term newborns who presented to our neonatology and pediatric endocrinology units for thyroid dysfunction.

Newborn screening started in Turkey after 2006. Therefore, before 2006, patients with detected abnormalities in thyroid function tests due to symptoms of hypothyroidism were referred to our unit. After 2006, patients identified from newborn screening were enrolled. In our country, the cut-off value of capillary thyroid stimulating hormone (TSH) in newborn screening is considered as 15 mU/L.

All patients were investigated for abnormal thyroid functions tests including free triiodothyronine (fT3), free thyroxine (fT4), TSH, and Tg, urinary iodine level, maternal breast milk iodine level, and thyroid ultrasonography (USG). The study included patients with low urinary iodine level (<100 μg/L) regardless of hypothyroidism.[8] Significant CH was defined as either TSH >40 mU/L or fT4 <8.5 pmol/L or both. Premature infants (before 37 completed weeks of gestation), infants with congenital anomalies, chronic diseases, and infants born to mothers with a history of a thyroid disorder were excluded.

Levothyroxine (L-T4) in tablet form, with a dosage of 10-15 mcg/kg/day, was used in the treatment of patients with CH (Fig.). These patients formed the treatment group (T group). Patients without CH were included in the untreated group (UT group). In all subjects in T and UT groups, data regarding age, birth weight, actual weight, height, head circumference, baseline fT3, fT4, TSH and Tg levels, iodine levels in urine and breast milk, results of thyroid USG, and control fT3, fT4, TSH and Tg levels were recorded. Both treated and untreated groups had been recalled for clinical and biochemical reassessment at 7-14 days later and their thyroid status at this time was compared.

Urineiodine measurement

To measure the urine iodine level, urine samples from the newborns were obtained at the same time as blood samples were taken for measurement by the thyroid function test. Urine samples were taken with in a sterile adhesive bag. Urine samples were treated with concentrated HCl (one drop per 2.5 mL urine sample). Commercially available A & D GR-200 and WTW pH 330i were used for analytical balance and pH meter, respectively. These treated urine samples were stored at -70ºC without centrifugation. The frozen urine samples were defrosted before urine iodine levels were measured using the modified Sandell-Kolthoff method described by Dunn et al.[9]

Breast milk iodine measurement

Approximately 10 mL of fresh milk was collected from each mother. A few drops of HCl were added to each milk sample to achieve a pH value of 6 (±1).[10] Samples were then incubated at 35ºC for 60 minutes

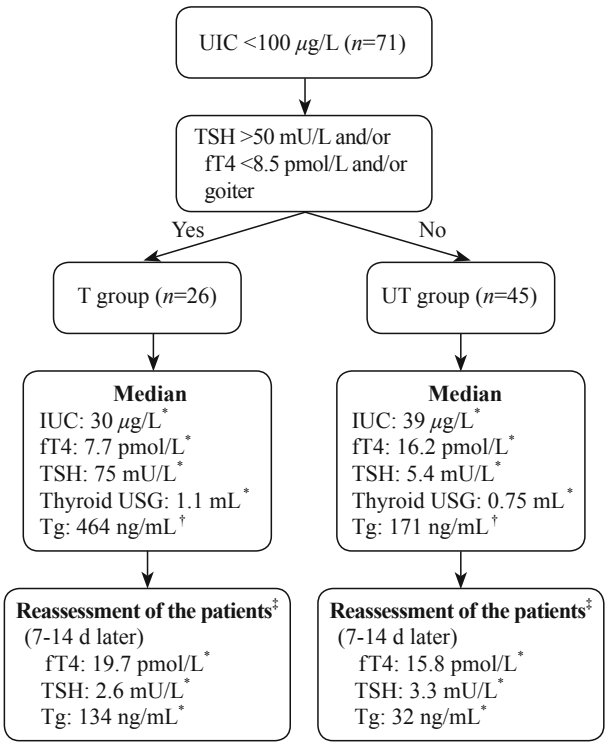

Fig. Distribution and results of the patients. UIC: urinary iodine concentration; TSH: thyroid stimulating hormone; fT4: free thyroxine; fT3: free triiodothyronine; Tg: thyroglobulin; USG: ultrasonography; T: treated with levothyroxine; UT: untreated. *: $P>0.05$, †: $P<0.05$; ‡: Both treated and untreated groups had been recalled for clinical and biochemical reassessment at 7-14 days later.

and centrifuged at 3000 rpm for 10 minutes to give serum (Sigma 3 K 30 trademark was used for cooled centrifuge).

Following this pre-treatment, iodine was measured in the supernatant by using the method described by Dunn et al.[9] Standard and sample tubes were measured at 405 nm absorbance (Shimadzu UV-Visible 1601 trademark was used for the spectrophotometer). Evaluation was carried out using the standard chart.

Iodine concentrations were measured in at least 2 occasions. In 95% of samples, there was no difference >5% between two measurements. Mean value of measurements were used in the analysis. Coefficient of variation was found as 3.48 and 2.64 for urinary iodine and breast milk iodine values, respectively.

Spot urine and breast milk iodine levels <100 μg/L were accepted as lower than normal and used for evaluation.[9,11]

fT3, fT4 and TSH levels

Measurements of the fT3, fT4 and TSH levels of the newborns were carried out by using a SIEMENS ADVIA CENTAUR XP machine with the chemiluminescent immunoassay method. The reference values shown in Table 1 were used.[12]

Tg level

Tg levels were measured using a SIEMENS IMMULITE 2000 machine with the chemiluminescent immunoassay method. Blood samples were drawn in the morning before taking the drug and measurements were carried out on the same day. The reference values shown in Table 1 were used.[13]

Thyroid USG

USG examination of the thyroid gland was carried out with the patient in a supine position by a radiologist experienced in the field of pediatric radiology by using an electronic multifrequency (5-13 Mhz) linear probe with "Siemens Antares (Siemens Medical Solutions USA, Inc.) and Toshiba Aplio (Toshiba America Medical Systems)" USG machines, while measuring both thyroid lobes separately. The Brunn formula (height×length×width×0.523) was used to calculate thyroid volume for both lobes.[14] Isthmus measurements were excluded. Values between 0.44-1.5 mL were accepted as normal.[15]

Statistical analysis

The data were analyzed using the SPSS 16.0 (IBM Corp., Armonk, NY) statistical package program. Distribution of the data was tested for normality using the Shapiro-Wilk normality test. Between groups, normally distributed variables (parametric data) were compared by using the independent sample *t* test; variables without normal distribution (nonparametric data) were compared by using Mann-Whitney *U* test. Additional tests were conducted: analysis of descriptive statistics, percentile values, distribution, and central tendency. A *P* value of <0.05 was accepted as statistically significant.

Results

Seventy-one patients with a urine iodine level <100 μg/L were included. Among them, 32 were girls and 39 boys. The average age was 16 days. There were no statistically significant differences between boys and girls for all values ($P>0.05$). The anthropometric measurements of the patients enrolled in the study are shown in Table 2.

Patients with CH due to ID who were treated (n=26, 37%) with L-T4 and those who were untreated (n=45, 63%) due to the absence of CH were compared and the two groups did not differ significantly with respect to anthropometric measurements ($P>0.05$).

The statistical comparison of fT3, fT4, TSH, Tg, thyroid volume, urinary iodine concentration (UIC) and breast milk iodine levels of the T and UT groups at the time of admission is summarized in Table 1 and Fig..

Table 1. Baseline data of 71 iodine deficient newborns who either received treatment with levothyroxine (T group) for TSH >40 mU/L and/or fT4 <8.5 pmol/L; or who were untreated (UT group) with TSH ≤40 pmol/L and/or fT4 ≥8.5 pmol/L

Variables	T group		UT group		*P* value	Reference values 0-1 mon*
	Median±SD (min-max)	*n*	Median±SD (min-max)	*n*		(2.5th-50th-97.5th percentiles)
Gender, M/F	18/8	26	21/24	45	0.0700	
Age (d)	16±6.1 (3-28)	26	16±7 (3-28)	45	0.3200	
fT3 (pmol/L)	5.0±1.1 (2.8-7.1)	18	5.7±2.5 (1.7-12.7)	43	0.0050	M 4.6-6.3-10.1/F 5.0-6.6-7.5
fT4 (pmol/L)	7.7±4.5 (0.13-19.1)	23	16.2±4.6 (9.9-33.5)	45	0.0001	8.5-20.1-30.5
TSH (mU/L)	75±88 (14-426)	26	5.4±8.7 (0.63-41.8)	45	0.0001	0.7-3.5-18.1
Tg (ng/mL)	464±244 (226-1100)	16	171±460 (15-2124)	34	0.0020	9-55-101
Urinary iodine levels (μg/L)	30±19 (0-61)	26	39±23 (0-90)	45	0.2600	
Breast milk iodine levels (μg/L)	21±53 (10-150)	8	47±36 (10-120)	14	0.5600	
Thyroid USG (mL)	1.10±0.54 (0.24-1.95)	22	0.75±0.41 (0.35-1.72)	23	0.1300	

*: Bayer Advia-Centaur thyroid hormone[10] and thyroglobulin[11] reference values. M: male; F: female; fT3: free triiodothyronine; fT4: free thyroxine; TSH: thyroid stimulating hormone; Tg: thyroglobulin; USG: ultrasonography; SD: standard deviation.

Of the 71 patients, 21 (29.6%) had TSH levels below 5 mU/L and all of them were in the UT group. Of the same patients, 4 had iodine levels between 50 and 90 μg/L, 7 had iodine levels between 25 and 49 μg/L and 10 had iodine levels below 25 μg/L. An infant with TSH 41.8 mU/L and fT4 13.2 pmol/l was followed up without treatment and improved with follow-up. Other infants with TSH >40 were treated.

The two groups were also compared for Tg levels. The T group had higher levels and the difference was statistically significant (P<0.05) (Table 1). The Tg levels of 50 out of 71 patients were measured, and of these, 40 (80%) had Tg levels above the normal range (101 ng/mL). Of these patients, 16 were in the T group and 24 were in the UT group. Ten patients had Tg levels below 101 ng/mL and all of these patients were in the UT group. Tg level was >75 ng/mL in 46 (92%) of 50 patients.

The breast milk iodine levels of the 22 participating mothers were measured. Of these, 17 (77%) were found to have levels <100 μg/L and 5 (23%) had levels between 100-200 μg/L. Six of the mothers with low levels were in the UT group. No statistically significant difference was observed between the breast milk iodine levels of the two groups (P>0.05).

The thyroid volumes of 45 patients were measured. The average thyroid volume was 0.90 mL which was within the normal range. Of the patients, 22 were in the T group and 23 were in the UT group. Eight (17.8%) (6 were in the T group and 2 were in the UT group) of the 45 patients who underwent thyroid ultrasonography had a thyroid volume of >1.5 mL; four (8.9%) patients, 2 in the T group and 2 in the UT group, had a volume of <0.44 mL. Tg values ranged from 109 to 430 ng/mL in patients with thyroid volume <0.44 mL. One patient was started on L-T4 treatment due to distinctive goiter associated with ID (patient's measurements, TSH: 14 mU/L, fT4: 19.1 pmol/L, UIC: 0, and thyroid volume: 1.95 mL). The groups did not differ statistically significantly with respect to thyroid volume (P>0.05). Treatment was initiated based on TSH measurements (>40 mU/L) in the absence of fT3 and fT4 results in 8 and 3 patients, respectively.

There were no correlations between urine iodine levels and Tg levels, or between urine iodine levels and TSH levels (P>0.05). There was a borderline positive correlation between Tg levels and TSH levels (P=0.048).

After 7-14 days of L-T4 treatment in the T group, there was a statistically significant increase in fT4 and a decrease in TSH and Tg. In contrast, the UT group showed a significant decrease in TSH but no significant change in fT3, fT4 and Tg levels. The statistical comparisons of the reassessment of the thyroid hormone status of newborns in both groups are summarized in Table 3 and Fig.

Discussion

One of the major causes of transient CH is ID.[16] Other common causes include the transplacental passage of maternal thyrotropin receptor-blocking antibodies; the transplacental passage of drugs used in maternal antithyroid medications, and iodine excess.[4] Transient CH is more common among preterm infants who are born with insufficient iodine stores compared with term neonates.[4] The very marked reduction in the frequency of transient CH following the introduction of iodized salt in the country underlines the importance of iodine

Table 2. Anthropometric measurements of the patients with urinary iodine deficiency (n=71)

Variables	Age (d)	Birth weight (g)	Weight* (g)	Length* (cm)	Head circumference* (cm)
Median±SD (min-max)	16±6.6 (3-28)	3320±505 (2570-4500)	3525±593 (2600-5350)	51.5±2.1 (46-55)	35.3±1.7 (32-38)
Percentiles					
25	12	2838	3200	50.0	34.0
50	16	3320	3525	51.5	35.3
75	21	3713	3850	52.9	36.9

*: measurements of patients on admission to the Erciyes University Medical Faculty in Kayseri for thyroid dysfunction; SD: standard deviation.

Table 3. Re-assessment of thyroid hormone status of newborns who either received treatment (T group) or who were untreated (UT group)

Variables	T group		UT group		P value
	Median±SD (min-max)	n	Median±SD (min-max)	n	
fT3 (pmol/L)	5.9±1.5 (0.93-7.4)	16	5.2±1.7 (1.7-7.3)	15	0.250
fT4 (pmol/L)	19.7±8.6 (11.6-40.9)	16	15.8±3.4 (10.6-24.1)	18	0.004
TSH (mU/L)	2.6±3.8 (0.02-10.7)	17	3.3±2.6 (0.16-11.6)	18	0.860
Tg (ng/mL)	134±76 (7.85-208)	7	32±32 (13-111)	12	0.090

Both treated and untreated groups had been recalled for clinical and biochemical reassessment at 7-14 days later. T: treated with levothyroxine; UT: untreated; fT3: free triiodothyronine; fT4: free thyroxine; TSH: thyroid stimulating hormone; Tg: thyroglobulin; SD: standard deviation.

supplementation. This was shown by a study conducted in Poland.[17] The incidence of transient CH varies across countries. In Egypt, a neonate screening test including 731 743 neonates was performed between 2003 and 2011 and identified CH in 248 patients (prevalence: 1/2950 live births). Of these patients, 44 (17.7%) had transient (prevalence: 1/16 667 live births) and 204 (82.3%) had permanent CH (prevalence: 1/3587 live births).[18] According to the data from World Health Organization (WHO), Italy seems to have similar ID characteristics to our country.[19] In a 4-year study in Italy in which 8 of the 26 CH screening centers in the country participated, the proportion of transient CH was found as 10% (transient to permanent CH ratio 15:140).[20] We believe that the primary cause of inter-country variation in the incidence of transient CH is the difference in regional iodine levels.

Although the use of iodized salts was made obligatory by law in 1998 in our country, sufficient iodine intake has not been firmly established. This probably reflects demographic and cultural factors, with reluctance to give up using non-iodized rock salt despite government warnings.[7] According to WHO's data, our country is still included in the moderate ID area with iodization ratios (70%) of food and commercial salts remaining below sufficient levels (iodization ratios; adequate iodine levels in food).[19] Future studies in our province will presumably show that ID remains to be a problem for us. ID leads TSH elevation. Since elevated TSH is directly associated to congenital malformation, ID will adversely affect congenital malformation prevalence in our country.[21]

There are inter-gender differences in permanent and transient CH. The female to male ratio is 2:1 in permanent CH whereas it is 1:1 or lower in transient CH.[20,22] In our study, the female to male ratio was 1:1.2 in ID and 1:2.3 in patients treated for CH. The results are somewhat consistent with previous reports when all patients evaluated in the study are considered. However, contrary to previous studies, the male proportion was rather high in the T group, (female:male=8/18, 69% male), which was a noteworthy finding.

The most frequent finding in ID areas is endemic goiter.[23] The upper limit of thyroid volume for newborns is 1.5 mL; values above this are accepted as goiter.[24] In our study, the thyroid functions of 45 patients were evaluated using USG and 8 of these patients had thyroid volumes above 1.5 mL. The mean UIC of these 8 patients was 22.7 μg/L (min-max: 0-40 μg/L). Six of these patients received L-T4 treatment.

Low mean iodine levels were observed in the breast milk of patients' mothers in the T and UT groups. This was an expected result as iodine is transferred to the infant via the placenta during the intrauterine period and through the breast milk following delivery. Low UIC levels measured for infants suggest that the mother will also have low iodine levels. The level of iodine that an infant receives can be increased by giving the mother iodine supplements. The appropriate amount of iodine in the breast milk of a mother with sufficient iodine supplementation will meet the infant's requirements. In regions with sufficient iodine amounts, the average breast milk iodine levels are 150-180 μg/L.[25,26] A mother breastfeeds the infant 700-1000 mL/day of milk between months 1 and 6 during the lactation period.[27] Considering an average content of 150 μg/L iodine in the milk, the mother's iodine loss associated with breastfeeding over the first six months would approximately be 105 to 150 μg. This amount satisfies the 90 μg/L criteria recommended by WHO for neonates.[8]

A TSH level of >5 mU/L (a value that is equivalent to a serum TSH concentration of 11.2 mIU/L) in the whole blood samples collected to assess neonatal ID is reported to be a good indicator in determining iodine status.[28,29] In our study, only 48% of the mature neonates with ID had high serum TSH levels (≥11.2 mIU/L), while the same ratio was 80% for Tg (based on serum Tg >101 ng/mL).[13] In addition, we observed high Tg levels in 78% of neonates with iodine overload in a previous study of our team.[29] In a study conducted in 12 countries to screen 2512 school-age children (6-12 years old), Tg level was found to be a sensitive biomarker for iodine excess or deficiency. Zimmermann et al[30] reported that elevated Tg level was significantly more common in children with ID (UIC <100 μg/L) and iodine excess (UIC >300 μg/L) when compared with iodine-sufficient children; in addition, they found no significant change in the prevalence of elevated Tg, TSH, T4 and thyroid antibodies between children with UIC levels 100-199 μg/L and 200-299 μg/L. The WHO/UNICEF/ICCIDD have recommended the measurement of Tg level in dried blood samples to evaluate iodine status among school-age children.[8] We believe that Tg measurements would be appropriate in assessing iodine status during the neonatal period, as was also recommended for older children. However, because the number of cases in our study was low, we are of the opinion that studies with large case series are needed to establish this.

It should be kept in mind that, regardless of receiving treatment, thyroid gland could shrink in children with enlarged gland at birth if thyroid function is normal at 3 years of age and L-T4 dose is modest.Some of these children might have transient CH due to ID and hence not need lifelong thyroxine.

In conclusion, the urine iodine levels of L-T4 therapy group, although not statistically significant, were lower. Therefore, ID is still a healthcare problem

in Turkey. UIC is the best indicator in screening ID. Where this is not applicable, we believe Tg should be used in screening ID in the newborn. In our opinion, all mature neonates with Tg levels above 75 ng/mL should be screened for ID.

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Original article

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