Serum insulin-like growth factor-I (IGF-I) and IGF-binding protein-3 levels in severe iodine deficiency

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Iodine deficiency is an important public health problem worldwide. It is well known that it has severe consequences such as brain damage, developmental delay, deficits in hearing and learning and lower intellectual attainment. It also has a negative impact on growth. In this study, we aimed to address this issue and we assessed height standard deviation scores of children living in an area of severe iodine deficiency in comparison to those living in a mild iodine deficiency area. Serum levels of insulin-like growth factor-I (IGF-I), IGF-binding protein-3 (IGFBP-3), thyroxine (T_4), and thyroid stimulating hormone (TSH) were also analyzed to investigate the mechanisms by which iodine depletion leads to growth failure. Pubertal children in a severe iodine deficient SID area had lower height standard deviation scores (HSDS), IGF-I and IGFBP-3 levels than those living in mild iodine deficient MID area. Similar findings could not be elucidated in the prepubertal age group. The major determinants of HSDS were age, IGF-I, IGFBP-3 and TSH. IGF-I and IGFBP-3 were negatively correlated with T_4. These findings suggest that iodine deficiency has a negative impact on growth, as well as IGF-I and IGFBP-3 levels. This effect seems to be due to the derangements in thyroid hormone economy arising from iodine depletion. The degree of this impact may be related to the duration of iodine depletion or may be dependent on the developmental stage of the organism at the time of iodine depletion.

Key words: iodine deficiency, insulin-like growth factor-I, insulin-like growth factor-binding protein-3.

Normal growth and development in children are dependent on a number of factors, including growth hormone, the growth hormone insulin-like growth factor axis, thyroid hormones and nutritional status. The complex relationship between thyroid hormones and the growth hormone – insulin-like growth factor axis has not yet been completely understood. Although the mechanism of action has not been fully elucidated, thyroid hormones probably regulate expression of insulin-like growth factor-I (IGF-I) receptors and its binding protein[1]. In previous studies low levels of serum IGF-I and the major binding protein IGF-binding protein-3 (IGFBP-3) were reported in primary hypothyroidism[2-5]. The low IGF-I and IGFBP-3 levels in hypothyroidism both in humans and animals returned to normal with thyroxine replacement[1,5-6]. Iodine as a trace element is an important substrate for thyroid hormone synthesis. Although the thyroid gland can tolerate a wide range of iodine intake with only minute changes in thyroid hormone status, iodine is still an important factor for normal growth. This is proven in the case of cretenism or mild-to-moderate growth failure seen in areas of moderate-to-severe iodine deficiency.

In this study, we assessed serum levels of IGF-I, IGFBP-3, thyroxine (T_4), and thyroid stimulating hormone (TSH) in patients with severe iodine deficiency in various age groups and compared them with age-matched controls with mild iodine deficiency.

Material and Methods

A total of 78 children, aged 7-12 years, from a mountain village in the central part of Turkey (Büyükçakır-Kayseri) with severe iodine deficiency (SID) were included in the study. The children were assessed anthropometrically. Height standard deviation scores (HSDS) were calculated using the formula below:

$$HSDS = (X - \bar{X}) / SD$$

where X: height measurement, and $\bar{X}$ and SD the mean and standard deviation for the height appropriate for age and sex[7]. Levels of serum IGF-I, IGFBP-3 and urinary iodine were measured and compared to 75 age-matched controls living in a mild iodine deficient (MID) area in Ankara.

Urinary iodine was determined in randomly collected urine samples using the Sandell-Kolthoff reaction[8]. Urine was first digested with hydrochloric acid in a heating block and iodine was determined from its catalytic reduction of ceric ammonium sulfate in the presence of arsenious acid. Median urinary iodine/creatinine (μg/g creatinine) was used as a criteria of iodine status[9-11].

Serum IGF-I level was determined by coated tube IRMA (Diagnostic Systems Laboratories, Webster, TX, USA). The extraction procedure was performed after acidifying the serum to dissociate IGF-I from its binding proteins. Serum IGFBP-3 was measured using a double antibody radioimmunoassay (RIA) (Diagnositc Systems Laboratories, Webster, TX, USA).

Serum T_4 and TSH were measured using standard RIA and IRMA kits (ICN Pharmaceuticals, Costa Mesa, CA, USA; BRAHMS Diagnostica, Berlin, Germany).

Statistical evaluation was made using Statistical Package for Social Sciences (SPSS). Serum IGF-I and IGFBP-3 levels showed when logarithmic transformation was carried out. Student's t-test, Kruskal-Wallis and Mann-Whitney U tests were used in the comparisons. Correlation analysis and linear regression model was used where appropriate. $P<0.05$ was accepted as significant.

Results

The study group consisted of 78 children (43 boys, 35 girls), aged 7-12 years (9.3 ± 1.7 years, mean ± SD) living in an SID area (median iodine/creatinine: 19.7 μg/g creatinine). Their HSDS and IGF-I, IGFBP-3 levels were compared to 75 age-matched controls (40 boys, 35 girls) living in an area with MID (median iodine/creatinine: 60.8 μg/g creatinine).

In the prepubertal age group (7-9 years) HSDS, and serum IGF-I and IGFBP-3 levels did not differ between the children living in the SID and MID areas. In the pubertal age group, however, all parameters were significantly lower in children from the SID area than in those living in an MID area (Table I, $p<0.0001$).

IGF-I and IGFBP-3 correlated significantly with the HSDS of the children ($r=0.52$, $p<0.0001$, and $r=0.57$, $p<0.0001$, respectively). Serum IGF-I showed significant negative correlation to T_4 ($r=-0.42$, $p<0.0001$), whereas IGFBP-3 was only weakly correlated to T_4 ($r=-0.23$, $p=0.044$). There was negative correlation between T_4 and TSH as expected, although the correlation was not strong ($r=-0.34$, $p=0.003$).

Factors influencing HSDS were analyzed by multiple regression analysis. In the regression

Table I. Urinary iodine/creatinine, serum IGF-I, IGFBP-3 levels, and height standard deviation scores (HSDS) in children from mild and severe iodine deficient (ID) areas

	I/Creatinine (μg/g)*	IGF-I (ng/ml)	IGFBP-3 (mg/ml)	HSDS
Severe ID Area				
7-9 years (45)	18.1†	131.8 ± 14.4	2.8 ± 0.1	0.2 ± 0.4
10-12 years (33)	31.3‡	108.6 ± 19.3††	2.6 ± 0.1‡‡	-3.2 ± 0.4$
Mild ID Area				
7-9 years (28)	53.6†	108.1 ± 16.1	3.3 ± 0.3	0.0 ± 0.2
10-12 years (47)	64.6‡	337.8 ± 33.4††	3.4 ± 0.2‡‡	0.3 ± 0.1$

* Urinary iodine/creatinine ratio is given as median values; all other parameters are given as mean ± SEM
† $p<0.0001$ iodine/creatinine levels of MID vs SID area at the age of 7-9 years
‡ $p=0.005$ iodine/creatinine levels of MID ve SID area at the age of 10-12 years
†† $p<0.0001$ IGF-I levels of children in MID area were significantly higher than in children from SID area
‡‡ $p<0.0001$ IGFBP-3 levels of children in MID area were significantly higher than in children from SID area
$ $p<0.0001$ HSDS of children in MID area were significantly higher than in children from SID area
IGF-1: insulin-like growth factor-I; IGFBP-3: IGF-binding protein-3; SEM: standard error of the mean.

equation age, IGFBP-3, IGF-I, and TSH levels predicted the HSDS of the children in the SID area ($R^2=0.67$, $p<0.0001$).

Discussion

Iodine deficiency is an important public health problem for almost all countries worldwide. Turkey has long been known as a mild iodine deficiency area according to previous epidemiological studies. Urgancıoğlu and Hatemi[12] reported an overal goitre prevalence of 30.5%, and visible goitre was 6.7% in their study involving 73,757 subjects throughout Turkey. Our previous study revealed severe iodine deficiency in a mountain village in the central part of Turkey, and the prevalence of goitre was more than 90% in that study[13]. These results disclosed the presence of severe iodine deficient regions in Turkey in addition to mild-to-moderate iodine deficient areas. It is well known that iodine deficiency has severe consequences such as brain damage, developmental delay, deficits in hearing, and learning and lower intellectual attainment[9,14].Hypothyroidism is the major factor responsible for these consequences. The fundamental role that thyroid hormones play in normal growth and development is well established. In experimental studies, it has been shown that thyroid hormones play an important role in the regulation of insulin-like growth factors and their binding proteins[15]. Diminished serum IGF-I and IGFBP-3 concentrations have been reported in hypothyroidism and they returned to normal with thyroxine replacement[1,5-6]. There is much research investigating the impact of thyroid hormone status on IGF-I and IGFBP-3. On the other hand, research on the association of iodine status with IGF-I and IGFBP-3 is scarce, despite the well known relation between iodine status and growth. Nazaimoon et al.[16] investigated the effects of iodine depletion on these growth factors and growth in a group of children living in a SID area. But their study involved malnourished children who may have had other problems affecting their growth.

In this study, pubertal children from a SID area had significantly lower HSDS and serum IGF-I and IGFBP-3 levels when compared to those living in a MID area. This finding suggests that growth failure seen in iodine deficiency may be mediated by IGF-I and IGFBP-3 directly. The same difference could not be elucidated in the prepubertal age group, however. HSDS, as well as IGF-I and IGFBP-3 levels of prepubertal children living in a SID area were similar to controls. This may be explained either by the longer duration of iodine depletion in pubertal children leading to more severe or long-standing derangements in thyroid hormone status, or it may be related to the specific age period. Puberty is a stage of childhood where growth accelerates, and daily iodine requirements also increase. Iodine depletion at this stage of childhood may have more serious consequences on growth than in early childhood.

A strong correlation between serum IGF-I and IGFBP-3 levels with HSDS in this group of children supports the hypothesis that in these children growth is closely regulated by these growth factors. On the other hand, both IGF-I and IGFBP-3 levels were negatively correlated to serum T_4 levels. Also, on multiple regression analysis, the predictors of HSDS in addition to age were IGF-I, IGFBP-3 and TSH levels. These findings may support the hypothesis that the negative influence of iodine depletion on IGF-I and IGFBP-3 may be related to the derangements in thyroid hormone economy resulting from iodine deficiency.

In conclusion, our findings suggest that iodine deficiency has a negative impact on growth, as well as on IGF-I and IGFBP-3 levels. This effect seems to be due to the derangements in thyroid hormone economy arising from iodine depletion. The degree of this impact may be related to the duration of iodine depletion or to the age of the patient.

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