

## Influence of iodine supplementation on serum insulin-like growth factor-I (IGF-I) and IGF-binding protein-3 (IGFBP-3) levels in severe iodine deficiency

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**SUMMARY:** Özön A, Alikasıfoğlu A, Yordam N. Influence of iodine supplementation on serum insulin-like growth factor-I (IGF-I) and IGF-binding protein-3 (IGFBP-3) levels in severe iodine deficiency. Turk J Pediatr 2004; 46: 303-308.

Iodine deficiency is an important public health problem worldwide. In addition to severe consequences such as brain damage, developmental delay, deficits in hearing and learning, it also has a negative impact on growth. The negative impact of severe iodine deficiency (SID) on insulin-like growth factor-I (IGF-I) and insulin-like growth factor binding protein-3 (IGFBP-3) was shown previously. In this study we aimed to analyze the impact of iodine supplementation on growth and growth factors of children with SID. One hundred and four children (63 boys and 41 girls) aged 5-15 years participated in the study. Height standard deviation scores (HSDS), and serum levels of IGF-I and IGFBP-3 were assessed both before and six months after a single dose of iodized oil. Serum levels of free thyroxine (FT<sub>4</sub>) and thyroid stimulating hormone (TSH) were also analysed to investigate the mechanisms by which alterations of iodine status may influence growth. Pubertal children had lower HSDS six months after iodine supplementation, while that of prepubertal children remained unchanged. IGF-I and IGFBP-3 levels decreased significantly and FT<sub>4</sub> levels were suppressed six months after the supplementation, while TSH was normalized. These findings suggest a negative impact of iodine supplementation on growth factors in the short-term, which may be a direct effect of iodine repletion or an indirect effect caused by alterations in thyroid function. It may also be related to the method of supplementation used. Further studies are necessary to resolve these issues, as well as to examine the impact of iodine supplementation on growth in the long-term.

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

Normal somatic growth is a complex process dependent on a number of factors, including growth hormone (GH), the GH-insulin-like growth factor (IGF) axis, thyroid hormones and nutritional status. In spite of abundant research on the subject, the complex relationship between thyroid hormone-IGF axis has not yet been fully elucidated. It is suggested that thyroid hormones may affect the GH-IGF axis in more than one way.

Thyroid hormone metabolism and action are dependent on a multitude of enzymes and proteins, the expression or function of which can be influenced by trace elements<sup>1</sup>. The elements most closely associated with the

thyroid are iodine and selenium. Iodine is a trace element essential for the synthesis of thyroid hormones. 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 cretinism or growth failure seen in areas of iodine deficiency<sup>2</sup>.

Since the growth-promoting action of growth hormone is mediated at least partly with insulin-like growth factor-I (IGF-I), the determination of IGF-I is widely used as a screening parameter in the evaluation of growth disorders. IGF-I in circulation is mostly bound to insulin-like growth factor binding proteins,

the predominant from being IGFBP-3. Serum IGFBP-3 is thus also used as a useful parameter to evaluate growth hormone status<sup>3</sup>. We and others have previously shown the negative impact of severe iodine deficiency (SID) on growth as well as on IGF-I and IGFBP-3<sup>2,4</sup>. In this study, we further analysed the effect of iodine supplementation in the form of iodized oil administered in a single dose on the serum levels of IGF-I, and IGFBP-3 and on the growth of children living in a SID region.

### Material and Methods

A total of 104 (63 boys, 41 girls) children, aged 5-15 years, from an area with SID in central Anatolia participated in the study. All participants were assessed clinically by anthropometric measurements. Standing height was measured using a stadiometer (Kabivitrum Stadiometer) to the nearest 0.1 cm, and weight was measured using Seca 708 digital scale to the nearest 100 g. Body mass index (BMI) was calculated using the formula below.

$$\text{BMI} = \text{weight/height}^2 \text{ (kg/m}^2\text{)}$$

Urinary iodine was measured in randomly collected urine samples using the Sandell-Kolthoff reaction<sup>5</sup>. Briefly, 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 ( $\mu\text{g I/g creatinine}$ ) was used as a criteria of iodine status.

Blood was withdrawn for the determination of thyroid hormones, IGF-I and IGFBP-3 in serum. Serum free thyroxine ( $\text{FT}_4$ ) and thyroid stimulating hormone (TSH) were measured using standard immunoradiometric assays with coated tube systems (Brahms, Hennigsdorf, Germany). Serum IGF-I level was determined by coated tube IRMA (Diagnostics Systems Laboratories, Webster, TX, USA). Serum was extracted following acidification to separate IGF-I from binding proteins prior to the assay. Serum IGFBP-3 was determined using a standard double antibody radioimmunoassay (RIA) (Diagnostic Systems Laboratories, Berlin, Germany).

Standard deviation scores (SDS) were used in the analysis of parameters known to vary with age and sex (i.e. height, BMI, IGF-I and IGFBP-3). SDS is calculated using the formula below:

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

where X: measured value, and  $\bar{\text{X}}$  and SD are the mean and standard deviation of the parameter in question for age and sex<sup>6,7</sup>.

After the initial assessment, all children were supplemented with iodine in the form of iodized oil (Lipiodol with 400 mg iodine) administered perorally in a single dose. Six months after the administration of Lipiodol, basal measurements were repeated. The analysis was made separately for prepubertal (aged 5-10 years, n: 57) and pubertal (aged 11-15 years, n: 47) children. Levels of thyroid hormones, IGF-I, and IGFBP-3, as well as height SDS (HSDS) at the end of the study were compared to basal levels to analyze the effect of iodine supplementation on growth and growth factors.

Statistical Package for Social Sciences (SPSS, v 10) was used in the statistical analysis. Serum IGF-I, IGFBP-3 and TSH levels showed log-normal distribution, and thus were transformed before analysis. Student's t-test, Kruskal-Wallis and Mann-Whitney U tests, and linear regression were used to analyze data.  $P < 0.05$  was considered significant.

### Results

The study group consisted of 104 children (63 boys, 41 girls) living in an area of SID with a median urinary iodine/creatinine ratio of 1.56  $\mu\text{g iodine/g creatinine}$ . Initial characteristics of the children are shown in Table I. Height and BMI SDS did not differ between prepubertal and pubertal subjects at the initiation of the study (Table I,  $p > 0.05$ ). Pubertal children had lower IGF-I SDS at the onset (Table I,  $p = 0.04$ ); however, their IGFBP-3 and thyroid hormones did not differ from those of prepubertal children.

Six months after the administration of Lipiodol, prepubertal children were replete, and pubertal children were only mildly deficient in iodine (Table II). Mean serum TSH normalized while  $\text{FT}_4$  levels decreased significantly in both prepubertal and pubertal children after six months when compared to initial levels (Table II,  $p < 0.0001$ ). IGF-I and IGFBP-3 SDS showed a similar decrease in both prepubertal and pubertal subjects (Table II,  $p < 0.0001$ ), although they did not fall 2 SD below the mean. Pubertal children had lower HSDS after supplementation, whereas HSDS of prepubertal

**Table I.** Initial Clinical and Laboratory Characteristics of the Study Group\*

	Prepubertal children (n: 57)	Pubertal children (n: 47)	p
Age	8.8±1.2	11.7±0.8	–
Male/Female	33/24	30/17	–
HSDS	-1.7±0.9	-2.0±1.0	0.18
BMI SDS	0.0±0.9	-0.5±0.6	0.004
U <sub>iodine/creatinine</sub> <sup>a</sup>	1.73	1.34	0.09
FT <sub>4</sub> (ng/dl)	1.1±0.2	1.0±0.2	0.08
TSH (mIU/L)	5.7±7.6	5.9±6.3	0.63
IGF-I SDS	-0.5±0.7	-0.2±0.8	0.04
IGFBP-3 SDS	-0.1±0.8	-0.03±0.7	0.59

\* Data are expressed as mean±SD.

<sup>a</sup>U<sub>iodine/creatinine</sub>: urinary iodine/creatinine (µg iodine/g creatinine) median values are represented (Normal: >100, 50-100 mild, 20-50 moderate, <20 severe iodine deficiency); FT<sub>4</sub> free thyroxine (0.78-1.94 ng/dl euthyroid, <0.62 ng/dl hypothyroid); TSH (Normal: 0.4-4.0 mIU/L); BMI SDS: body mass index standard deviation score; HSDS: height standard deviation score; IGF-I SDS: insulin-like growth factor-I standard deviation score; IGFBP-3 SDS: insulin-like growth factor binding protein-3 standard deviation score.

children did not differ significantly from the initial values (Table II,  $p<0.0001$  and  $p=0.36$  in pubertal and prepubertal subjects, respectively).

Throughout the study IGF-I and IGFBP-3 were strongly correlated to each other ( $r=0.79$ ,  $p<0.0001$  at the onset, and  $r=0.81$ ,  $p<0.0001$  6 months later). At the onset, both IGF-I and IGFBP-3 were also correlated weakly but significantly with HSDS ( $r=0.19$ ,  $p=0.026$  and  $r=0.23$ ,  $p=0.011$  for IGF-I and IGFBP-3, respectively), as well as with FT<sub>4</sub> ( $r=-0.20$ ,  $p=0.022$  and  $r=-0.28$ ,  $p=0.002$ , respectively). There was a strong negative correlation between FT<sub>4</sub> and TSH, as may be expected ( $r=-0.51$ ,  $p<0.0001$ ).

In the iodine replete stage only IGF-I was correlated to HSDS weakly ( $r=0.25$ ,  $p=0.005$ ). Serum levels of IGF-I and IGFBP-3 were no longer correlated to FT<sub>4</sub>, and the correlation between FT<sub>4</sub> and TSH also disappeared.

## Discussion

Iodine deficiency is an important public health issue worldwide. It is well known that iodine deficiency in a given population leads to a series of functional and developmental abnormalities defined collectively as iodine deficiency disorders (IDD)<sup>8</sup>. In the pediatric age group, these include thyroid function abnormalities, endemic goiter and cretinism when iodine deficiency is severe, and impaired mental and

**Table II.** Clinical and Laboratory Findings Before and Six Months After the Administration of a Single Dose of Iodized Oil\*

	Prepubertal children (n: 57)			Pubertal children (n: 47)		
	Initial	6 months	p	Initial	6 months	p
HSDS	-1.7±0.9	-1.7±0.9	0.36	-2.0±1.0	-2.2±1.1	<0.0001
BMI	16.1±1.2	16.3±1.1	0.004	16.4±1.1	17.2±1.3	<0.0001
U <sub>iodine/creatinine</sub> <sup>a</sup>	1.73	107.12	<0.0001	1.34	87.50	<0.0001
FT <sub>4</sub> (ng/dl)	1.1±0.2	0.8±0.1	<0.0001	1.0±0.2	0.7±0.2	<0.0001
TSH (mIU/L)	5.7±7.6	2.3±1.8	<0.0001	5.9±6.3	2.3±1.3	<0.0001
IGF-I (ng/ml)	171.4±70.4	117.4±62.3	<0.0001	262.6±123.2	167.2±93.9	<0.0001
IGFBP-3 (ng/ml)	3599.7±681.2	3044.3±510.0	<0.0001	4023.1±665.4	3186.7±580.2	<0.0001
IGF-I SDS	-0.5±0.7	-0.9±0.9	<0.0001	-0.2±0.8	-1.3±0.9	<0.0001
IGFBP-3 SDS	-0.1±0.8	-0.8±0.7	<0.0001	-0.03±0.7	-0.9±0.6	<0.0001

\* Data are expressed as mean±SD.

<sup>a</sup>U<sub>iodine/creatinine</sub>: urinary iodine/creatinine (µg iodine/g creatinine) median values are represented (Normal: >100, 50-100 mild, 20-50 moderate, <20 severe iodine deficiency); FT<sub>4</sub> free thyroxine (0.78-1.94 ng/dl euthyroid, <0.62 ng/dl hypothyroid); TSH (Normal: 0.4-4.0 mIU/L); BMI: body mass index; HSDS: height standard deviation score; IGF-I SDS: insulin-like growth factor-I standard deviation score; IGFBP-3 SDS: insulin-like growth factor binding protein-3 standard deviation score.

physical development<sup>8,9</sup>. Impairment in somatic growth due to iodine deficiency is explained on the basis of alterations in thyroid function. Since iodine is a trace element essential for synthesis of thyroid hormones, its deficiency has a negative impact on thyroid hormone economy, leading to hypothyroidism, and as normal somatic growth depends on thyroid hormones, alteration of thyroid function may have an impact on growth.

Interaction of thyroid hormones with the growth axis is complex and may involve more than one stage. Previous work has established evidence indicating that thyroid hormones not only promote GH secretion<sup>10,11</sup>, but regulate GH effects at the level of the GH receptor as well<sup>12</sup>. A number of studies have shown that IGF-I and IGFBP-3 levels in serum are dependent on thyroid hormone status<sup>13,14</sup>. This may be secondary to the effects of thyroid hormones on the pituitary-GH secretion; however, there is data which supports that some of the effects are direct<sup>15</sup>. Although the exact mechanisms and relationship between the thyroid hormones and GH-IGF-I axis have not yet been elucidated completely, alterations in thyroid hormones due to iodine deficiency as well as its correction may be expected to have an impact on the IGF-I and IGFBP-3 status.

We have shown in a previous study that growth as well as IGF-I and IGFBP-3 levels were affected by the iodine status of the population<sup>2</sup>. In this study we examined the impact of iodine repletion on growth and growth parameters of children with SID in the short-term.

Children in prepubertal and pubertal age groups had mean HSDS 1.7 and 2 SDS below the mean, respectively. This was an expected finding in an area with SID. Six months after the administration of iodized oil, mean HSDS in pubertal children was significantly lower than the initial score, whereas that of prepubertal children did not change. The observation of lower HSDS in pubertal children may be related to the specific age group. Puberty is a stage of childhood where growth accelerates. It seems that the study group could not achieve the growth rates of their peers even when they were iodine repleted. These findings may be explained by failure of iodine repletion to increase growth velocity in the short-term. Alternatively, growth velocity may have increased significantly, albeit inadequately to

induce an alteration in HSDS in six months. Obviously six months is a short period for any increase in growth velocity to alter HSDS to a considerable extent. One of the constraints in this analysis is lack of data to calculate pre-treatment growth velocity.

Observation of a significant decrease in serum FT<sub>4</sub>, as well as in IGF-I and IGFBP-3 six months after repletion of iodine is the most interesting finding of this analysis, suggesting a third alternative. Thyroid function may be suppressed in the study group to an extent that may lead to a significant negative impact on growth factors, and thus growth. The adverse effect on growth may not be obvious enough to be reflected in HSDS in the prepubertal age group, but may become overt in a short time in the pubertal age group, where growth should normally accelerate. Lack of correlation between FT<sub>4</sub> and HSDS both at the onset and six months later suggests that the impact of thyroid hormones on growth of the study subjects may be indirect at best. Observation of a negative correlation between the growth factors and FT<sub>4</sub> at the study onset, as well as weak but positive correlation between HSDS and the growth factors, suggests that thyroid hormones may influence growth through their effect on growth factors. The weak correlation suggests that other factors too have an impact on growth factors. The fact that upon reexamination, six months after the administration of iodized oil, there was no correlation between growth factors and FT<sub>4</sub> makes it difficult to comment on how the alterations in thyroid hormones may affect growth factors and growth during iodine repletion.

The inhibitory effect of excess iodine on thyroid hormone synthesis is termed Wolff-Chaikoff effect, and is due to increased intrathyroid iodine concentrations<sup>16</sup>. It is a transient phenomenon, and thyroid hormone synthesis resumes normally despite continued administration of pharmacological quantities of iodine, most likely by a decrease in the thyroid iodide trap. Both T<sub>4</sub> and T<sub>3</sub> release from the gland, and FT<sub>4</sub> in serum decreases. TSH levels are expected to be elevated during Wolff-Chaikoff effect; however, and this is induced by excess iodine<sup>17</sup>.

The suppression observed in FT<sub>4</sub> levels in this study was not accompanied by the expected increase in TSH levels. On the contrary, mean

serum TSH normalized from mildly elevated levels to within normal levels, showing a small but significant decrement. Another unusual finding is the prolonged suppression of thyroid functions in this group of patients. It may be attributed to the method used in iodine supplementation, for administration of a single dose of iodized oil instead of salt iodization may lead to excess iodine in the short-term, which may suppress the thyroid gland. The decrement in TSH is difficult to explain without comparative data on other methods of iodine supplementation. The loss of the strong negative correlation between FT<sub>4</sub> and TSH after six months suggests that the negative feedback of thyroid hormone status on the hypothalamo-pituitary tropic hormone secretion may be lost. There is much research investigating the impact of iodine deficiency on thyroid size and function. In the last decade, data related to thyroid hormone status and serum IGF-I and IGFBP-3 also appeared in the literature. On the other hand, research on the association of iodine status with IGF-I and IGFBP-3 is scarce. We and others have analysed the serum levels of these factors in iodine depleted regions<sup>2,4,18</sup>; however, alterations in these growth factors during iodine supplementation has not been studied before. In this study, iodine supplementation in the form of iodized oil induced a small but significant decrement in both IGF-I and IGFBP-3 in the two age groups studied. This may be related to the thyroid suppressive effects observed in this group of subjects.

It is well established that hypothyroidism induces low circulating IGF-I concentrations<sup>19,20</sup>. This association between the thyroid axis and circulating IGF-I concentrations is most evident during the period of growth. In fact, the impaired growth observed in hypothyroid children may be in part due to the decrease in activity of the GH/IGF-I axis<sup>21</sup>. One study examining the relationship between thyroid hormones and IGF-I in healthy individuals showed that physiological variations in serum FT<sub>4</sub> levels were correlated to plasma IGF-I levels; however, the correlation coefficient<sup>10,11</sup> was too low to be considered significant. The researchers suggested that less than 2% of the variability in plasma IGF-I could be explained by the FT<sub>4</sub> concentration<sup>22</sup>. We observed a similar weak correlation between growth factors and serum FT<sub>4</sub> levels at the onset in this study, which

disappeared after iodine supplementation. These findings may be related to the fact that there is more than one factor influencing serum levels of IGF-I and IGFBP-3.

In conclusion, iodine supplementation in the form of iodized oil induced a negative impact on IGF-I and IGFBP-3 levels, and failed to improve the growth status of children with SID in the short-term. It may either be a direct effect of iodine repletion or, more likely, of alterations in thyroid function, alone or together with other factors that may be responsible for this effect. Further studies are necessary to elucidate both the long-term effects and underlying mechanisms of the observed impact of iodine supplementation on growth and growth parameters.

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