

Treatment of Iodine Deficiency in School-Age Children Increases Insulin-Like Growth Factor (IGF)-I and IGF Binding Protein-3 Concentrations and Improves Somatic Growth

Michael B. Zimmermann, Pieter L. Jooste, Ngoako Solomon Mabapa, Xikombiso Mbhenyane, Serina Schoeman, Ralf Biebinger, Nouredine Chaouki, Maksim Bozo, Lindita Grimci, and John Bridson

Laboratory for Human Nutrition (M.B.Z., R.B.), Swiss Federal Institute of Technology, CH-8092 Zürich, Switzerland; Medical Research Council (P.L.J., S.S.), Cape Town 7505, South Africa; University of Venda (N.S.M., X.M.), Thohoyandou 0950, South Africa; The Ministry of Health (N.C.), Rabat, Morocco; The Ministry of Health (M.B.), Tirana, Albania; University Hospital (L.G.), 372 Tirana, Albania; and Child Advocacy International (J.B.), Newcastle under Lyme ST5 1ND, United Kingdom

Context: Iodine deficiency *in utero* impairs fetal growth, but the relationship between iodine deficiency and postnatal growth is less clear.

Objective: The objective of the study was to determine whether iodine repletion improves somatic growth in iodine-deficient children and investigate the role of IGF-I and IGF binding protein (IGFBP)-3 in this effect.

Design, Participants, and Interventions: Three prospective, double-blind intervention studies were done: 1) in a 10-month study, severely iodine-deficient, 7- to 10-yr-old Moroccan children (n = 71) were provided iodized salt and compared with children not using iodized salt; 2) in a 6-month study, moderately iodine-deficient, 10- to 12-yr-old Albanian children (n = 310) were given 400 mg iodine as oral iodized oil or placebo; 3) in a 6-month study, mildly iodine-deficient 5- to 14-yr-old South African children (n = 188) were given

two doses of 200 mg iodine as oral iodized oil or placebo. At baseline and follow-up, height, weight, urinary iodine (UI), total T₄ (TT4), TSH, and IGF-I were measured; in Albania and South Africa, IGFBP-3 was also measured.

Results: In all three studies, iodine treatment increased median UI to more than 100 µg/liter, whereas median UI in the controls remained unchanged. In South Africa, iodine repletion modestly increased IGF-I but did not have a significant effect on IGFBP-3, TT4, or growth. In Albania and Morocco, iodine repletion significantly increased TT4, IGF-I, IGFBP-3, weight-for-age z scores, and height-for-age z scores.

Conclusion: This is the first controlled study to clearly demonstrate that iodine repletion in school-age children increases IGF-I and IGFBP-3 concentrations and improves somatic growth. (*J Clin Endocrinol Metab* 92: 437–442, 2007)

SEVERE IODINE DEFICIENCY *in utero* causes cretinism and dwarfism (1). Iodized oil given during pregnancy in areas of moderate iodine deficiency increases birth weight by 100–200 g (2, 3). Less clear is the relationship between iodine deficiency and postnatal growth. Data from cross-sectional studies on iodine intake and child growth are mixed (4–11), with most studies finding modest positive correlations. In five Asian countries, household access to iodized salt was correlated with increased weight for age and mid-upper arm circumference in infancy (10). However, controlled intervention studies of iodized oil alone (12, 13) and iodine given with other micronutrients (14–16) have generally not found effects on child growth.

Iodine status may influence growth through its effects on the thyroid axis. Administration of T₄ to hypothyroid children increases their growth (17). Thyroid hormone promotes GH secretion and modulates the effects of GH at its receptor

(18–20). IGF-I and IGF binding protein (IGFBP)-3 are also dependent on thyroid status (21–25). In humans, hypothyroidism decreases circulating IGF-I and IGFBP-3 levels, and thyroid hormone replacement increases them (26, 27).

In iodine-deficient children, impaired thyroid function and goiter are inversely correlated with IGF-I and IGFBP-3 concentrations (28–30). However, in an uncontrolled trial, oral iodized oil decreased IGF-I and IGFBP-3 concentrations in Turkish children (31). Thus, our study aim was to determine whether iodine repletion improves growth in school-age children and investigate the potential role of IGF-I and IGFBP-3 in this effect.

Subjects and Methods

Intervention study of iodized salt

The study was done in the Brikcha Rural Commune, an area of endemic goiter in the Rif Mountains of northern Morocco (32). A small cooperative supplies local salt produced in drying ponds using water from a salty spring. The salt is not washed or ground, and it contains less than 2 ppm iodine. For the intervention trial, salt was iodized at a level of 25 µg iodine per gram salt with reagent-grade potassium iodate (Sigma & Aldrich, Buchs, Switzerland) mixed into the local salt using a rotating drum mixer (ELTE 650; Engelsmann, Ludwigshafen, Germany). The subjects were 7- to 10-yr-old children from primary schools. In-

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Abbreviations: HAZ, Height-for-age z score; IGFBP, IGF binding protein; TT4, total T₄; UI, urinary iodine; WAZ, weight-for-age z score.

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formed oral consent was obtained from parents, and oral assent from the children. The Ethical Committee of the Swiss Federal Institute of Technology in Zürich and the Ministry of Health in Rabat gave ethical approval for the study. All children from the schools were invited to participate in the 10-month study. At baseline, height and weight of the children were measured in duplicate using standard anthropometric technique (33). For the measurements, children removed their shoes, emptied their pockets, and wore light indoor clothing. Body weight was measured to the nearest 0.1 kg using a TANITA digital scale HD-313 (Itin scale, Brooklyn, NY) calibrated with standard weights. Height was measured to the nearest 0.1 cm using a pull-down metal measuring tape (person-check REF 44 444; Medizintechnik KaWe, Kirchner & Wilhelm, Germany) held perpendicular to the ground. A spot morning urine sample and a venous blood sample were collected. For 10 months, each participating family was given 2 kg salt monthly for use in the household. The salt was dispensed directly to the head of the household from a central supply at the local health center. Salt was offered to all households, but use of the salt was not compulsory, and of 45 households enrolled in the study, 34 used the iodized salt over the 10-month study and 11 did not, based on both monitoring of urinary iodine concentrations in the participating children and a household interview; the main reason given for not using the salt was that it changed food flavor. Examined retrospectively, children from households using the iodized salt ($n = 47$) were compared with those from households not using it ($n = 24$). At 5 and 10 months, a spot urine sample and a venous blood sample were collected, and weight and height were measured.

Intervention studies of oral iodized oil

The first study was done in rural schools in the Korçë/Pogradec district of southeastern Albania. The primary outcome of this study was cognitive function; these data have been previously reported (34). Most household salt is not iodized, and the region is severely iodine deficient. All 10- to 12-yr-old children at the schools were invited to join the study ($n = 310$). Ethical approval for the study was given by the Swiss Federal Institute of Technology Zürich and the Ministry of Health of Albania. Informed written consent was obtained from their parents, and oral assent from the children.

The second study was done in rural schools in Limpopo Province in South Africa, where many households use noniodized agricultural salt, and children are mildly iodine deficient. All children at the schools ($n = 188$) were invited to participate in the study. Ethical approval for the study was given by the Swiss Federal Institute of Technology in Zürich and, in South Africa, by the University of Venda in Thohoyandou and the Provincial Department of Education. Informed written consent was obtained from the parents and oral assent from the children.

At both sites, height and weight of the children were measured in duplicate using standard anthropometric technique (33). For the measurements, children removed their shoes, emptied their pockets, and wore light indoor clothing. In Albania, body weight was measured to the nearest 0.1 kg using a TANITA digital scale HD-313 (Itin scale) calibrated using fixed weights; in South Africa, it was measured using a TANITA digital scale 1631 (Itin scale). In Albania, height was measured to the nearest 0.1 cm using a pull-down metal measuring tape (person-check REF 44 444; Medizintechnik KaWe, Kirchner & Wilhelm, Germany) held perpendicular to the ground; in South Africa, it was measured using a rigid stadiometer. Pubertal staging was not done. A spot morning urine sample and a venous blood sample were collected.

In Albania, the children were randomly assigned to receive at baseline a single oral dose of 400 mg iodine as iodized poppyseed oil (Lipiodol, Guerbet; Roissy CdG Cedex, France) or a sunflower oil-containing placebo. In South Africa, the children were randomly assigned to receive at baseline and 3 months an oral dose of 200 mg iodine as iodized oil (Lipiodol; Guerbet) or a sunflower oil-containing placebo. At both sites, the capsules were swallowed with water under direct supervision. In Albania, all baseline measures were repeated after 6 months. In South Africa, all baseline measures were repeated after 3 and 6 months. Both studies were double blind.

Laboratory analysis

Serum and urine samples were aliquoted and frozen at -20 C until analysis in Zürich. Urinary iodine concentration (UI) was measured

using the Pino modification of the Sandell-Kolthoff reaction (35). Whole-blood TSH and serum total T_4 (TT4) were measured using immunoassays (36); normal reference values are: TSH, less than 3.7 mU/liter; and TT4, 65–165 nmol/liter. IGF-I and IGFBP-3 were measured using enzyme-labeled chemiluminescent immunometric assays (Immulite IGF-I, IGFBP-3; Diagnostics Products Corp., Los Angeles, CA).

Statistical analysis

Data were analyzed using Prism (version 3; GraphPad, San Diego, CA) and Excel (XP 2002; Microsoft, Seattle, WA). Epiinfo (version 3.3.2, CDC, Boston, MA) was used to calculate height-for-age z (HAZ) scores and weight-for-age z (WAZ) scores using World Health Organization references (37). The z -scores are derived by subtracting the population mean from an individual (raw) score and then dividing the difference by the population SD (37). Nonnormally distributed data (HAZ and WAZ scores, concentrations of UI, TSH, IGF-I, and IGFBP-3) were log transformed for comparisons. Baseline data from children who did not complete the biochemical retesting were not included in the analysis. A two-way ANOVA was used to determine the interaction between time and treatment on HAZ and WAZ scores, UI, TSH, TT4, IGF-I, and IGFBP-3. *Post hoc* comparisons were done using paired Wilcoxon tests within groups and unpaired Wilcoxon tests between groups. Significance was set at $P < 0.05$.

Results

In Morocco, 71 children were enrolled, and all children completed the study. Table 1 shows the age, sex ratio, HAZ and WAZ scores, and concentrations of UI, TSH, TT4, and IGF-I in the groups at baseline and 5 and 10 months. At baseline, the children were severely iodine deficient as indicated by a median UI concentration of 14–18 $\mu\text{g/liter}$ (1). Mean TT4 concentration was in the low-normal range, and 21% of children were hypothyroxinemic. In the group receiving the iodized salt, there was a significant increase in median UI concentration ($P < 0.001$), and at 10 months, the median UI indicated iodine sufficiency ($>100\ \mu\text{g/liter}$) (1). There was a significant increase in mean TT4 concentration in the treatment group ($P < 0.01$). In the treated group, there were significant increases in median HAZ and WAZ scores ($P < 0.01$), and median IGF-I concentration ($P < 0.01$), compared with baseline, median IGF-I in the treated group increased greater than 100% at 10 months.

In Albania, 310 children began the study, and at 6 months, six children had moved away; 4 in the iodine group and 2 in the placebo group. Twelve percent of children refused to repeat the blood sampling at 6 months. Table 2 shows the age, sex ratio, HAZ and WAZ scores, and concentrations of UI, TSH, TT4, IGF-I, and IGFBP-3 in the groups at baseline and 6 months. At baseline, the children were moderately iodine deficient as indicated by a median UI concentration of 42–44 $\mu\text{g/liter}$ (1). Mean TT4 concentration was in the low-normal range, and 30% of children were hypothyroxinemic. In the group receiving the iodized oil, there was a significant increase in median UI concentration ($P < 0.001$), and at 6 months, the median UI indicated iodine sufficiency ($>100\ \mu\text{g/liter}$) (1). There was a significant increase in mean TT4 concentration in the treatment group ($P < 0.01$). In the treated group, there were significant increases in median HAZ and WAZ scores ($P < 0.05$) and median IGF-I and IGFBP-3 concentrations ($P < 0.05$).

In South Africa, 188 children began the study, and at 6 months, 17 children were absent on the testing day; seven in the iodine group and 10 in the placebo group. Table 3 shows the age, sex ratio, HAZ and WAZ scores, and concentrations

TABLE 1. Age, sex ratio, HAZ and WAZ scores, and concentrations of UI, whole-blood TSH, serum TT4, and IGF-I in 7- to 10-yr-old Moroccan children given iodized salt (25 ppm iodine) or noniodized salt at baseline and 5 and 10 months

Variable	Time (months)	Iodine	Control
n		47	24
Age (yr) ^a		8.4 ± 1.1	8.5 ± 1.1
Sex ratio (M/F)		24/23	13/11
HAZ score ^{b,c}	0	-0.98 (-2.68 to 0.75)	-0.93 (-2.74 to 1.00)
	5	-0.81 (-2.66 to 0.96)	-0.85 (-2.66 to 0.75)
	10	-0.69 (-2.45 to 1.15) ^{d,g}	-1.04 (-2.63 to 0.83)
WAZ score ^{b,c}	0	-0.81 (-2.47 to 0.95)	-0.82 (-1.93 to 0.88)
	5	-0.60 (-2.30 to 1.01)	-0.65 (-1.79 to 0.94)
	10	-0.24 (-1.93 to 1.10) ^{e,h}	-0.76 (-1.62 to 1.01)
UI (μg/liter) ^{b,c}	0	14 (4 to 64) ^d	18 (2 to 61)
	5	74 (39 to 221) ⁱ	19 (4 to 79)
	10	104 (31 to 781) ^{f,i}	26 (4 to 71)
TSH (mU/liter) ^b	0	1.9 (0.6 to 5.4)	1.8 (0.7 to 5.3)
	5	1.4 (0.3 to 5.1)	1.6 (0.8 to 5.5)
	10	1.3 (0.4 to 5.0)	1.6 (0.7 to 4.9)
TT4 (pmol/liter) ^{a,c}	0	81 ± 19	74 ± 22
	5	114 ± 21 ^{e,g}	81 ± 24
	10	118 ± 24 ^{e,g}	87 ± 23
IGF-I (ng/ml) ^{b,c}	0	90 (29 to 368)	104 (25 to 217)
	5	184 (54 to 507) ^e	120 (34 to 220)
	10	202 (81 to 666) ^{e,g}	134 (60 to 196) ^d

M, Male; F, female.

^a Mean ± SD.^b Median (ranges).^c Significant interaction (time × treatment) (ANOVA) ($P < 0.0001$).Different from baseline (paired Wilcoxon test); ^d $P < 0.05$; ^e $P < 0.01$; ^f $P < 0.001$.Different from control (unpaired Wilcoxon test); ^g $P < 0.05$; ^h $P < 0.01$; ⁱ $P < 0.0001$.

of UI, TSH, TT4, IGF-I, and IGFBP-3 in the groups at baseline and 3 and 6 months. At baseline, the children were mildly iodine deficient as indicated by a median UI concentration of 70–78 μg/liter (1). Mean TT4 concentration was near the midpoint of the normal range. In the group receiving the iodized oil, there was a significant increase in median UI concentration ($P < 0.001$), and at 3 and 6 months, the median UI indicated iodine sufficiency (>100 μg/liter) (1). There was no significant change in mean TT4 concentration in the treat-

ment group. In the treated group, there were no significant changes in median HAZ and WAZ scores, or median IGFBP-3 concentration. However, median IGF-I concentration increased significantly ($P < 0.05$) with treatment.

Discussion

Cross-sectional studies on iodine deficiency and child growth have reported mixed results. In Greece (4), school-

TABLE 2. Age, sex ratio, HAZ and WAZ scores, and concentrations of UI, whole-blood TSH, serum TT4, IGF-I, and IGFBP-3 in 10- to 12-yr-old Albanian children at baseline and 6 months after receiving either 400 mg iodine as oral iodized oil or placebo

Variable	Time (months)	Iodine	Control
n		159	151
Age (yr) ^a		11.3 ± 0.8	11.5 ± 0.8
Sex ratio (M/F)		89/70	77/74
HAZ score ^{b,c}	0	-1.17 (-4.33 to 1.22)	-1.08 (-3.69 to 2.23)
	6	-0.82 (-3.94 to 1.48) ^{d,g}	-1.03 (-3.61 to 1.83)
WAZ score ^{b,c}	0	-0.77 (-2.77 to 0.91)	-0.83 (-2.68 to 1.92)
	6	-0.53 (-2.74 to 1.36) ^{d,g}	-0.70 (-2.58 to 2.22)
UI (μg/liter) ^{b,c}	0	42 (0 to 186)	44 (0 to 215)
	6	172 (18 to 724) ^{e,h}	49 (3 to 221)
TSH (mU/liter) ^b	0	1.6 (0.6 to 5.0)	1.8 (0.8 to 5.2)
	6	1.4 (0.4 to 5.2)	1.6 (0.4 to 15.4)
TT4 (pmol/liter) ^{a,c}	0	76 ± 17	75 ± 17
	6	106 ± 18 ^{f,i}	81 ± 19
IGF-I (ng/ml) ^{b,c}	0	147 (25 to 587)	139 (25 to 540)
	6	229 (71 to 627) ^{f,g}	178 (73 to 497) ^d
IGFBP-3 (μg/ml) ^{b,c}	0	3.1 (1.8 to 5.5)	3.3 (1.9 to 5.4)
	6	4.5 (1.0 to 7.2) ^{d,g}	3.7 (1.9 to 5.7)

M, Male; F, female.

^a Mean ± SD.^b Median (range).^c Significant interaction (time × treatment) (ANOVA) ($P < 0.0001$).Different from baseline (paired Wilcoxon test); ^d $P < 0.05$; ^e $P < 0.001$; ^f $P < 0.01$.Different from control (unpaired Wilcoxon test); ^g $P < 0.05$; ^h $P < 0.001$; ⁱ $P < 0.01$.

TABLE 3. Age, sex ratio, HAZ and WAZ scores, and concentrations of UI, whole-blood TSH, serum TT4, IGF-I, and IGFBP-3 in 5- to 14-yr-old South African children at baseline and 3 and 6 months after receiving either 200 mg of iodine as oral iodized oil at baseline and 3 months or placebo

Variable	Time (months)	Iodine	Control
n		100	88
Age (yr) ^a		9.1 ± 2.3	9.2 ± 2.5
Sex ratio (M/F)		52/48	49/39
HAZ score ^b	0	−0.62 (−3.18 to 3.96)	−0.46 (−2.61 to 2.26)
	3	−0.43 (−2.71 to 3.07)	−0.41 (−2.73 to 6.20)
	6	−0.59 (−3.08 to 3.02)	−0.44 (−2.78 to 1.82)
WAZ score ^b	0	−0.65 (−2.54 to 2.53)	−0.52 (−2.48 to 1.29)
	3	−0.63 (−2.65 to 2.61)	−0.46 (−2.33 to 5.33)
	6	−0.57 (−2.16 to 2.56)	−0.49 (−2.33 to 1.51)
UI (μg/liter) ^{b,c}	0	70 (17 to 609)	78 (21 to 299)
	3	727 (140 to 12,288) ^{d,g}	93 (4 to 265)
	6	149 (1 to 1044) ^{e,h}	88 (13 to 455)
TSH (mU/liter) ^b	0	0.9 (0.5 to 2.8)	1.0 (0.6 to 3.0)
	3	0.7 (0.4 to 2.2)	1.1 (0.4 to 3.2)
	6	0.7 (0.4 to 2.1)	1.0 (0.4 to 3.9)
TT4 (pmol/liter) ^a	0	101 ± 22	99 ± 22
	3	106 ± 20	104 ± 20
	6	105 ± 24	97 ± 24
IGF-I ^{b,c}	0	130.0 (25.0 to 591.0)	128.0 (25.0 to 566.0)
	3	148.0 (25.3 to 533.0)	139.5 (49.6 to 449.0)
	6	169.0 (47.9 to 636.0) ^{f,i}	148.5 (45.3 to 466.0)
IGFBP-3 ^b	0	3.3 (1.6 to 5.6)	3.2 (1.6 to 5.9)
	3	3.8 (1.4 to 6.7)	3.5 (2.0 to 7.0)
	6	3.9 (1.8 to 7.0)	3.6 (1.0 to 6.5)

M, Male; F, female.

^a Mean ± SD.^b Median (range).^c Significant interaction (time × treatment) (ANOVA) ($P < 0.0001$).Different from baseline (paired Wilcoxon test); ^d $P < 0.0001$; ^e $P < 0.01$; ^f $P < 0.05$.Different from control (unpaired Wilcoxon test); ^g $P < 0.001$; ^h $P < 0.01$; ⁱ $P < 0.05$.

age children in areas of endemic goiter had decreased height and weight and delayed bone maturation, compared with children in nonendemic areas, but there was no correlation of goiter with somatic growth. Goiter was also not associated with growth in children in Bolivia (5) and Malaysia (6). Children in iodine-deficient areas in Iran (7) and India (9) showed retarded height and bone maturation; in Iran, impaired growth was inversely correlated with TSH (7). Mason *et al.* (10), reviewing studies from Sri Lanka, Nepal, Bangladesh, India, and the Philippines, found use of iodized salt was correlated with increased weight-for-age and mid-upper arm circumference in children less than 3 yr of age. Similarly, household use of iodized salt was directly correlated with height in preschool children in Kenya (8). In contrast, a study in 6- to 12-yr-old Thai children found an inverse correlation between UI concentration and HAZ score (11). However, these cross-sectional data have limitations. They compare current anthropometry with current iodine status, but because body size reflects earlier conditions, they assume iodine status at the time of survey reflects earlier iodine status. Also, households with access to iodized salt may have better socioeconomic and environmental conditions that would favor better child growth.

There are few intervention studies examining the effect of iodine repletion on growth of school-age children. In 5-yr-old Chinese children, median UI increased from less than 10 to 176 μg/liter after iodine addition to irrigation water, and this reduced childhood stunting (38). As part of a selenium supplementation trial in Tibet, 5- to 15-yr-old children with

Kashin-Beck disease received intramuscular iodized oil before being randomly assigned to receive selenium or placebo, and a control group did not receive iodine. Iodine treatment increased median UI from 10 to 50 to 250 μg/liter and increased HAZ score, whereas weight-for-height and WAZ scores decreased, suggesting that linear growth was not accompanied by appropriate weight gain (16). In a 1-yr, placebo-controlled Mexican study of a daily multiple-micronutrient food supplement containing 90 μg iodine, there was no increase in length gain in treated children older than 1 yr of age (15). In a controlled trial in South Africa, a daily multiple-micronutrient-fortified biscuit containing 60 μg iodine was given to iodine-deficient children aged 6–11 yr for 43 wk (14). Median UI increased to greater than 100 μg/liter in both treated and control groups, and the intervention had no significant effect on growth. In moderately iodine-deficient Bangladeshi schoolchildren, a 4-month controlled trial of 400 mg of iodine as oral iodized oil did not affect weight gain, but the treated children remained iodine deficient (13). In 22-month, placebo-controlled trial in iodine-deficient Bolivian schoolchildren, 475 mg iodine as oral iodized oil had no significant effect on growth; however, iodine status significantly improved in the placebo group (12). Compared with previous studies, strengths of the present study were: 1) no confounding by adventitious sources of iodine; 2) randomized, double-blind, placebo-controlled designs (in Albania and South Africa); and 3) reasonably large samples of children with poor thyroid function (in Morocco and Albania).

Improved growth in iodine-deficient children receiving

iodine is likely due to improved thyroid function; both thyroid hormone and GH are essential for normal growth and development (39, 40). Thyroid hormone is required for normal GH expression *in vitro* (41, 42) and *in vivo* (19), and, in animal studies, promotes GH secretion and modulates the effects of GH at its receptor (18–20). Thyroid hormone also directly affects epiphyseal growth, bone maturation, and stature (40, 43). Hypothyroidism is a well-recognized cause of short stature in children, and in hypothyroid Colombian children with minimal thyroid dysfunction, T₄ administration increased growth (17). In the present study, in the children who were moderate to severely iodine deficient, iodine repletion increased mean TT₄ concentrations by 40–50% and somatic growth improved. In contrast, in the children who were only mildly iodine deficient, there was no significant change in TT₄ with iodine repletion and no measurable effect on growth.

IGF-I is a growth factor that mediates many of the effects of GH (44, 45). Approximately 95% of circulating IGF-I is bound to IGFBP-3; binding prolongs the half-life of circulating IGF-I and may target IGF-I toward growth stimulation and away from glucose metabolism (44–46). IGFBP-3 can promote or inhibit growth, and its effects can be either IGF-mediated or IGF-independent (46). Circulating IGF-I and IGFBP-3 are dependent on thyroid status (21–24), both indirectly through effects on pituitary GH secretion and by a direct effect (25). In adults, hypothyroidism decreases serum levels of IGF-I and IGFBP-3, and thyroid hormone replacement increases them (26, 27). In malnourished, iodine-deficient Malaysian children, there was a positive correlation between T₄ concentrations and IGF-I and IGFBP-3 concentrations (28), and Turkish children from areas of endemic goiter had low IGF-I and IGFBP-3 concentrations (29, 30). In a previous study examining the effect of iodine supplementation on IGF-I and IGFBP-3 concentrations, 5- to 15-yr-old Turkish children who received 400 mg iodine showed decreased free T₄, IGF-I, and IGFBP-3 concentrations after 6 months (31). However, the study was not controlled, and many of the children remained iodine deficient after treatment (31). Use of a control group is important because IGF concentrations increase with age (44); an age effect was likely responsible for the significant increase in IGF-I in the control groups in the Moroccan and Albanian studies (Tables 1 and 2). In the present study, there was a significant increase in IGF-I and IGFBP-3 concentrations with iodine repletion over 6–10 months, particularly in the moderate to severely iodine deficient children, in which IGF-I concentrations increased 50–100%.

Our findings suggest impaired thyroid function adversely affects growth in iodine-deficient children, and this effect may be mediated, directly and/or indirectly, through effects on IGF-I and IGFBP-3 status. The World Health Organization estimates 285 million school-age children worldwide are iodine deficient (47). Our findings of a beneficial effect on growth underscore the importance of global efforts to eradicate iodine deficiency in this age group.

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Address all correspondence and requests for reprints to: Michael B. Zimmermann, M.D., Laboratory for Human Nutrition, Swiss Federal Institute of Technology, LFV E19, Schmelzbergstrasse 7, CH-8092 Zürich, Switzerland. E-mail: michael.zimmermann@ilw.agrl.ethz.ch.

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References

1. WHO/UNICEF/ICCIDD 2001 Assessment of iodine deficiency disorders and monitoring their elimination. WHO/NHD/01.1. Geneva: World Health Organization
2. Anwar US, Anwar ZR, Filteau SM, Sullivan KR, Tomkins AM 1997 The impact of maternal supplementation with a single dose of oral iodized poppy seed oil on infant thyroid status in rural Bangladesh. *Trans R Soc Trop Med Hyg* 91:499–501
3. Chaouki ML, Benmouli M 1994 Prevention of iodine deficiency disorders by oral administration of lipiodol during pregnancy. *Eur J Endocrinol* 130:547–551
4. Koutras DA, Christakis G, Trichopoulos D, Dakou-Voutetaki A, Kyriakopoulos V, Fontanares P, Livadas DP, Gatsios D, Malamos B 1973 Endemic goiter in Greece: nutritional status, growth, and skeletal development of goitrous and nongoitrous populations. *Am J Clin Nutr* 26:1360–1368
5. Bautista A, Barker PA, Dunn JT, Sanchez M 1977 Lack of correlation between thyroid size and body growth in an area of endemic goiter. *Am J Clin Nutr* 30:275–279
6. Ali O, Tan TT, Sakinah O, Khalid BA, Wu LL, Wan Nazaimoon WM, Ng ML 1994 Thyroid function and pubertal development in malnutrition. *Ann Acad Med Singapore* 23:852–855
7. Azizi F, Kalani H, Kimiagar M, Ghazi A, Sarshar A, Nafarabadi M, Rahbar N, Noohi S, Mohajer M, Yassai M 1995 Physical, neuromotor and intellectual impairment in non-cretinous school children with iodine deficiency. *Int J Vit Nutr Res* 65:199–205
8. Neumann CG, Harrison GG 1994 Onset and evolution of stunting in infants and children. Examples from the Human Nutrition Collaborative Research Support Program. Kenya and Egypt studies. *Eur J Clin Nutr* 48(Suppl 1):S90–S102
9. Lal RB, Srivastava VK, Chandra R 1996 A study of the spectrum of iodine deficiency disorders in rural area of Uttar Pradesh. *Indian J Public Health* 40:10–12
10. Mason JB, Deitchler M, Gilman A, Gillenwater K, Shuaib M, Hotchkiss D, Mason K, Mock N, Sethuraman K 2002 Iodine fortification is related to increased weight-for-age and birthweight in children in Asia. *Food Nutr Bull* 23:292–308
11. Thurlow RA, Winichagoon P, Pongcharoen T, Gowachirapant S, Boonpradern A, Manger MS, Bailey KB, Wasantwisut E, Gibson RS 2006 Risk of zinc, iodine and other micronutrient deficiencies among school children in North East Thailand. *Eur J Clin Nutr* 60:623–632
12. Bautista S, Barker PA, Dunn JT, Sanchez M, Kaiser DL 1982 The effects of oral iodized oil on intelligence, thyroid status, and somatic growth in school-age children from an area of endemic goiter. *Am J Clin Nutr* 35:127–134
13. Huda SN, Grantham-McGregor SM, Tomkins A 2001 Cognitive and motor

- functions of iodine-deficient but euthyroid children in Bangladesh do not benefit from iodized poppy seed oil (Lipiodol). *J Nutr* 131:72–77
14. van Stuijvenberg ME, Kvalsvig JD, Faber M, Kruger M, Kenoyer DG, Benade AJ 1999 Effect of iron-, iodine-, and β -carotene-fortified biscuits on the micronutrient status of primary school children: a randomized controlled trial. *Am J Clin Nutr* 69:497–503
 15. Rivera JA, Gonzalez-Cossio T, Flores M, Romero M, Rivera M, Tellez-Rojo MM, Rosado JL, Brown KH 2001 Multiple micronutrient supplementation increases the growth of Mexican infants. *Am J Clin Nutr* 74:657–663
 16. Moreno-Reyes R, Mathieu F, Boelaert M, Begaux F, Suetens C, Rivera MT, Neve J, Perlmutter N, Vanderpas J 2003 Selenium and iodine supplementation of rural Tibetan children affected by Kashin-Beck osteoarthropathy. *Am J Clin Nutr* 78:137–144
 17. Hernandez-Cassis C, Cure-Cure C, Lopez-Jaramillo P 1995 Effect of thyroid replacement therapy on the stature of Colombian children with minimal thyroid dysfunction. *Eur J Clin Invest* 25:454–456
 18. Crews MD, Spindler SR 1989 Thyroid hormone regulation of the transfected rat growth hormone promoter. *J Biol Chem* 261:5018–5022
 19. Samuels MH, Wierman ME, Wang C, Ridgway EC 1989 The effect of altered thyroid status on pituitary hormone messenger ribonucleic acid concentration in the rat. *Endocrinology* 124:2277–2282
 20. Hochberg Z, Bick T, Harel Z 1990 Alterations of human growth hormone binding by rat liver membranes during hypo- and hyperthyroidism. *Endocrinology* 126:325–329
 21. Burstein PJ, Draznin B, Johnson CJ, Schalch DS 1979 The effect of hypothyroidism on growth, serum growth hormone, the growth hormone-dependent somatomedin, insulin-like growth factor, and its carrier protein in rats. *Endocrinology* 104:1107–1111
 22. Geary ES, Lim M, Ceda GI, Ro S, Rosenfeld RG, Hoffman AR 1989 Triiodothyronine regulates insulin-like growth factor-I binding to cultured rat pituitary cells. *J Neuroendocrinol* 1:179–184
 23. Miell JP, Taylor AM, Zini M, Maheshwari HG, Ross RJ, Valcavi R 1993 Effects of hypothyroidism and hyperthyroidism on insulin-like growth factors (IGFs) and growth hormone- and IGF-binding proteins. *J Clin Endocrinol Metab* 76:950–955
 24. Angerva M, Toivonen J, Leinonen P, Valimaki M, Seppala M 1993 Thyroxine withdrawal is accompanied by decreased circulating levels of insulin-like growth factor binding protein-1 in thyroidectomized patients. *J Clin Endocrinol Metab* 76:1199–1201
 25. Nanto-Salonen K, Muller HL, Hoffman AR, Vu TH, Rosenfeld RG 1993 Mechanisms of thyroid hormone action on the insulin-like growth factor system: all thyroid hormone effects are not growth hormone mediated. *Endocrinology* 132:781–788
 26. Miell JP, Zini M, Quin JD, Jones J, Portioli I, Valcavi R 1994 Reversible effects of cessation and recommencement of thyroxine treatment on insulin-like growth factors (IGFs) and IGF-binding proteins in patients with total thyroidectomy. *J Clin Endocrinol Metab* 79:1507–1512
 27. Iglesias P, Bayon C, Mendez J, Gancedo PG, Grande C, Diez JJ 2001 Serum insulin-like growth factor type 1, insulin-like growth factor-binding protein-1, and insulin-like growth factor-binding protein-3 concentrations in patients with thyroid dysfunction. *Thyroid* 11:1043–1048
 28. Wan Nazaimoon WM, Osman A, Wu LL, Khalid BA 1996 Effects of iodine deficiency on insulin-like growth factor-I, insulin-like growth factor-binding protein-3 levels and height attainment in malnourished children. *Clin Endocrinol (Oxf)* 45:79–83
 29. Aydin K, Bideci A, Kendirci M, Cinaz P, Kurtoglu S 2002 Insulin-like growth factor-I and insulin-like growth factor binding protein-3 levels of children living in an iodine- and selenium-deficient endemic goiter area. *Biol Trace Elem Res* 90:25–30
 30. Alikasifoglu A, Özön A, Yordam N 2002 Serum insulin-like growth factor-I (IGF-I) and IGF-binding protein-3 levels in severe iodine deficiency. *Turk J Pediatr* 44:215–218
 31. Ozon A, Alikasifoglu A, Yordam N 2004 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* 46:303–308
 32. Zimmermann MB, Wegmüller R, Zeder C, Chaouki N, Biebinger R, Hurrell RF, Windhab E 2004 Triple fortification of salt with microcapsules of iodine, iron and vitamin A. *Am J Clin Nutr* 80:1283–1290
 33. World Health Organization 1995 Physical status: the use and interpretation of anthropometry. Report of a WHO Expert Committee. *World Health Organ Tech Rep Ser* 854:1–452
 34. Zimmermann MB, Connolly K, Bozo M, Bridson J, Rohner F, Grimci L 2006 Iodine supplementation improves cognition in iodine-deficient schoolchildren in Albania: a randomized, controlled, double-blind study. *Am J Clin Nutr* 83:108–114
 35. Pino S, Fang SL, Braverman LE 1996 Ammonium persulfate: a safe alternative oxidizing reagent for measuring urinary iodine. *Clin Chem* 42:239–243
 36. Torresani TE, Scherz R 1986 Thyroid screening of neonates without use of radioactivity: evaluation of time-resolved fluoroimmunoassay of thyrotropin. *Clin Chem* 32:1013–1016
 37. <http://www.cdc.gov/EpiInfo>
 38. Ren Q, Gr D, Cao X, Wang S, Jiang X, Jiang J, Ma E, O'Donnell K 2002 Effect of environmental supplementation of iodine on infant mortality and growth in children in Xinjiang, China (English abstract). *Zhonghua Liu Xing Bing Xue Za Zhi* 23:198–202
 39. Shapiro LE, Samuels HM, Yaffe BM 1978 Thyroid and glucocorticoid hormones synergistically control growth hormone mRNA in cultured GHI cells. *Proc Natl Acad Sci USA* 75:45–49
 40. Robson H, Siebler T, Shalet SM, Williams GR 2002 Interactions between GH, IGF-I, glucocorticoids, and thyroid hormones during skeletal growth. *Pediatr Res* 52:137–147
 41. Ceda PG, Fielder PJ, Donovan SM, Rosenfeld RG, Hoffman AR 1992 Regulation of insulin-like growth factor binding protein expression by thyroid hormone in rat GH3 pituitary tumor cells. *Endocrinology* 130:1483–1489
 42. Ezzat S, Laks D, Oster J, Melmed S 1991 Growth hormone regulation in primary fetal and neonatal rat pituitary cell cultures: the role of thyroid hormone. *Endocrinology* 128:937–943
 43. Nilsson A, Ohlsson C, Isakson OGP, Lindahl A, Isgaard J 1994 Hormonal regulation of longitudinal bone growth. *Eur J Clin Nutr* 48(Suppl 1):S150–S160
 44. Jones JJ, Clemmons DR 1995 Insulin-like growth factors and their binding proteins: biological actions. *Endocr Rev* 16:3–34
 45. Sjogren K, Jansson JO, Isaksson OG, Ohlsson C 2002 A model for tissue-specific inducible insulin-like growth factor-I (IGF-I) inactivation to determine the physiological role of liver-derived IGF-I. *Endocrine* 19:249–256
 46. Ferry Jr RJ, Cerri RW, Cohen P 1999 Insulin-like growth factor binding proteins: new proteins, new functions. *Horm Res* 51:53–67
 47. de Benoist B, Andersson M, Takkouche B, Egli I 2003 Prevalence of iodine deficiency worldwide. *Lancet* 362:1859–1860