Iodine Treatment in Children with Subclinical Hypothyroidism Due to Chronic Iodine Deficiency Decreases Thyrotropin and C-Peptide Concentrations and Improves the Lipid Profile

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Background: Chronic iodine deficiency (ID) increases thyrotropin (TSH) concentrations and produces a thyroid hormone pattern consistent with subclinical hypothyroidism (ScH). ScH may be associated with cardiovascular disease risk factors. Thus, the study aim was to determine if iodine treatment of children with elevated TSH concentrations due to ID would affect their lipid profile, insulin (C-peptide) levels, and/or subclinical inflammation.

Methods: In controlled intervention trials of oral iodized oil or iodized salt, 5–14-year-old children from Morocco, Albania, and South Africa with TSH concentrations ≥2.5 mU/L ($n = 262$) received 400 mg iodine as oral iodized oil or household distribution of iodized salt containing 25 μg iodine/g salt. At baseline and after 5 or 6 months, urinary iodine (UI) and blood concentrations of total thyroxine, TSH, C-reactive protein (CRP), C-peptide, and lipids were measured.

Results: Median (range) UI at baseline was 46 (2–601) μg/L. Compared to the control group, iodine treatment significantly increased UI and total thyroxine and decreased TSH, C-peptide, and total and low-density lipoprotein cholesterol. The mean low-density lipoprotein/high-density lipoprotein cholesterol ratio fell from 3.3 to 2.4 after iodine treatment ($p < 0.001$). Iodine treatment had no significant effect on concentrations of high-density lipoprotein cholesterol, triglycerides, or C-reactive protein.

Conclusions: Correction of ID-associated ScH improves the insulin and lipid profile and may thereby reduce risk for cardiovascular disease. This previously unrecognized benefit of iodine prophylaxis may be important because ID remains common in rapidly developing countries with increasing rates of obesity and cardiovascular disease.

Introduction

SERUM THYROTROPIN (TSH) LEVELS often increase in chronic iodine deficiency (ID) to stimulate thyroidal uptake of circulating iodine and maintain euthyroidism (1,2). Iodine-deficient individuals typically demonstrate a variably elevated TSH with concentrations of serum thyroxine (T4) in the low-normal range and serum triiodothyronine in the high-normal range (3–8). Pituitary TSH reserves, as reflected in TSH response to TSH-releasing hormone, are elevated in chronically iodine-deficient children (8). Thus, chronic ID commonly produces a biochemical pattern consistent with subclinical hypothyroidism (ScH) (9). Because ID continues to affect one-third of the global population (1), it is likely to be the most common cause of ScH (and overt hypothyroidism) worldwide (10,11).

In adults, ScH may increase risk of dyslipidemia, insulin resistance, and subclinical inflammation (12,13), and thereby increase risk for coronary heart disease (14). Moreover, even within the reference range for TSH, higher TSH is associated with dyslipidemia (15), higher body mass index (BMI) (16), and death caused by coronary heart disease (17). T4 replacement

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in adults with ScH or with high-normal TSH may improve cardiovascular disease risk factors (18–20). The impact of ScH in children is uncertain: it may impair growth in diabetic children (21) and may be associated with a more atherogenic lipid profile (22).

Iodized oil rapidly normalizes the increased TSH concentrations found in iodine-deficient individuals (23–25) and thus corrects ScH. An uncontrolled study reported that iodine treatment of goitrous German adolescents decreased plasma cholesterol concentrations (26). Therefore, our study aim was to determine if iodine treatment of children with increased TSH due to ID would improve risk factors for cardiovascular disease, specifically, lipid concentrations, insulin levels, and/ or subclinical inflammation.

Subjects and Methods

This study is a secondary analysis of pooled data from three controlled intervention trials of iodized oil and/or iodized salt (27–29). For this study, we included data from all children with a serum TSH concentration ≥ 2.5 mU/L, as TSH values above this level have been suggested to indicate early or mild thyroid dysfunction (30,31). Total T4 (TT4) values were measured in all children, but free T4 values were not measured. We included children from the three studies to determine the effect of iodine repletion on children with elevated TSH values from different backgrounds and degrees of ID. The first study was a randomized, placebo-controlled trial done in rural Albania in moderately iodine-deficient 10–12-year-old primary school children ($n = 310$) with a median urinary iodine (UI) of 45 μg/L (27). Intervention was a single oral dose of 400 mg iodine as iodized poppyseed oil (Lipiodol®; Guerbet, Roissy CdG Cedex, France); placebo control was an identical-appearing capsule of sunflower oil. Based on the inclusion criteria of a serum TSH concentration ≥ 2.5 mU/L, 171 children were included. The second study was a randomized, placebo-controlled trial done in mildly iodine-deficient 5–14-year-old children ($n = 188$) in rural South Africa with a median UI of 76 μg/L. Intervention was an oral dose of 200 mg iodine as iodized oil (Lipiodol) given at baseline and 3 months (28); placebo control was an identical-appearing capsule of sunflower oil. Based on the inclusion criteria of a serum TSH concentration ≥ 2.5 mU/L, 39 children were included. The third study was done in rural northern Morocco in severely iodine-deficient 7–10-year-old children ($n = 71$) with a median UI of 19 μg/L (29). For the intervention trial, local salt was iodized at a level of 25 μg iodine/g salt with reagent-grade potassium iodate (Sigma & Aldrich, Buchs, Switzerland). Randomization was at the household level. A spot morning urine sample and a venous blood sample were collected. Each participating family was given 2 kg of salt monthly for use in the household. Children from households using the iodized salt were compared to those from households not using it. Based on the inclusion criteria of a serum TSH concentration ≥ 2.5 mU/L, 52 children were included. In all studies, a nonfasting morning spot urine sample and blood sample were collected at baseline and after 6 months. Informed written consent was obtained from the parents of the children in the study, and oral assent from the children. Ethics approval for the studies was given by the Swiss Federal Institute of Technology Zürich and the local ethics review boards.

Laboratory analysis

Serum and urine samples were aliquoted and frozen at -20°C until analysis. UI concentration was measured using the Pino modification of the Sandell-Kolthoff reaction (32). Serum TSH and TT4 were measured using immunoassays (33); all measurements were done in the same laboratory in Zürich. ScH was defined as TSH ≥ 2.5 mU/L (31) and normal TT4 (65–165 nmol/L). Triglycerides and total cholesterol were measured on Roche Modular (Roche Diagnostics, Mannheim, Germany), high-density lipoprotein (HDL) cholesterol was measured on Roche Integra (HDL cholesterol plus third generation; Roche Diagnostics), and low-density lipoprotein (LDL) cholesterol concentrations were calculated using the Friedewald equation. C-peptide and C-reactive protein (CRP), as measures of endogenous insulin production and subclinical inflammation, respectively, were measured by chemiluminescent immunometry on Immulite (Bühlmann Laboratories AG, Allschwil, Switzerland); reference values were as follows: total cholesterol <5.0 mmol/L; triglycerides <1.7 mmol/L; HDL cholesterol >0.9 mmol/L; LDL cholesterol <2.6 mmol/L; CRP <3 mg/L; C-peptide <7.8 ng/mL (34).

Statistical analysis

Data were analyzed using Prism (version 3; GraphPad, San Diego, CA) and Excel (XP 2002; Microsoft, Seattle, WA) and SPSS 16.0 for Windows (version 13.0; SPSS, Chicago, IL). Age- and sex-specific criteria from the World Health Organization (35) were used to calculate BMI Z-scores. Normally distributed data were expressed as means $\pm$ standard deviation, and nonnormally distributed data as medians (ranges). Nonnormally distributed data were log-transformed for comparisons. A two-way analysis of variance was used to determine the interaction between time and treatment on all variables, and *post hoc* comparisons were done using unpaired *t*-tests. Multiple regressions were done to test for associations between baseline variables. Significance was set at $p < 0.05$.

Results

The study included 262 primary school children, aged 5–14 years. Table 1 shows the sex ratio and age of the children at baseline, as well as the changes in weight and height, and concentrations of UI, TSH, and TT4 during the study. The median UI at baseline was 46 μg/L, indicating moderate ID. Compared to the control group, treatment significantly increased UI and TT4 and decreased TSH ($p < 0.001$). In the treated group at 5–6 months, the median UI indicated clear iodine sufficiency, and only two children had a TSH ≥ 2.5 mU/L.

Table 2 shows the changes during the study in concentrations of total, HDL, and LDL cholesterol, triglycerides, C-peptide, and CRP. At baseline, 8% and 27% of children had an elevated total and LDL cholesterol, respectively, and 12% had an elevated CRP, but none had an elevated C-peptide concentration. Iodine treatment significantly decreased C-peptide ($p < 0.01$), as well as total and LDL cholesterol ($p < 0.001$). Mean LDL/HDL cholesterol ratio significantly decreased with iodine treatment, from 3.3 to 2.4 ($p < 0.001$). Treatment did not significantly affect mean CRP concentrations in the groups (Table 2), and there was no significant

TABLE 1. SEX RATIO, AGE, WEIGHT, AND HEIGHT AT BASELINE, AND CHANGES IN CONCENTRATIONS OF URINARY IODINE, SERUM THYROTROPIN, AND TOTAL THYROXINE AFTER IODINE REPLETION IN 5–14-YEAR-OLD CHILDREN ($N=262$) WITH INCREASED THYROTROPIN ($\geq$2.5 mU/L) DUE TO IODINE DEFICIENCY

Variable	Time	Control	Iodine
Number of children		133	129
Girls/boys		62/71	58/71
Age (year)		10.1 ± 2.4[a]	9.7 ± 2.3
Weight (kg)	0 month	30.6 ± 8.8	29.1 ± 8.1
	5–6 months	31.9 ± 8.9	31.3 ± 8.3
Height (cm)	0 month	134.9 ± 13.0	132.7 ± 13.0
	5–6 months	136.0 ± 12.8	134.4 ± 13.1
Urinary iodine (μg/L)	0 month	45 (2–292)[b]	46 (7–602)
	5–6 months	60 (7–442)	158 (1–1045)[c]
Serum TSH (mU/L)	0 month	3.0 (2.5–10.8)	3.0 (2.5–10.2)
	5–6 months	3.2 (0.3–30.6)	1.4 (0.2–11.0)[c]
Serum total thyroxine (nmol/L)	0 month	74 ± 21	83 ± 25
	5–6 months	77 ± 21	101 ± 17[c]

As [a]mean $\pm$ standard deviation or [b]median (range) (all such values).
[c]$p<0.001$ versus control.
TSH, thyrotropin.

change in the prevalence of elevated CRP values among the groups (data not shown).

At baseline, both UI and TSH were correlated with TT4 (<0.01), but none of these three variables were significantly correlated with any of the lipid parameters. C-peptide correlated with triglyceride concentrations ($p<0.001$) and CRP correlated with TSH ($p<0.001$). In multiple regressions of baseline variables, with the lipid parameters and C-peptide as dependent variables and UI, TSH, and T4, as well as country of original study as independent variables, there were no significant correlations after controlling for BMI Z-scores and age.

Discussion

The relationship between ID and ScH in a population varies: it depends on the severity of the deficiency, age group

studied, and/or other local dietary and environmental factors. In areas of chronic ID, such as in our study, many children have a thyroid profile consistent with ScH (1–8). In contrast, there may be a decreased prevalence of ScH in populations with mild-to-marginal ID compared to populations with higher iodine intakes (36). In a cross-sectional study of Chinese children ($n=338$) from areas of mild deficiency, more than adequate, or excessive intake of iodine (median UI: 83, 243, and 651 μg/L, respectively), the prevalences of ScH were 4.3%, 14.5%, and 20.5% (37). In areas of marginal ID in southern Europe, prevalences of ScH in children range from <1% to 6% (38–40).

ScH in our iodine-deficient children may have been caused by the effects of *in utero* and/or current ID. Transient newborn hyperthyrotropinemia is more common in iodine-deficient populations, and infants with elevated serum TSH at newborn

TABLE 2. CHANGES IN SERUM CONCENTRATIONS OF TOTAL, HIGH-DENSITY LIPOPROTEIN, AND LOW-DENSITY LIPOPROTEIN CHOLESTEROL, TRIGLYCERIDES, C-PEPTIDE, AND C-REACTIVE PROTEIN AFTER IODINE REPLETION IN 5–14-YEAR-OLD CHILDREN ($N=262$) WITH INCREASED THYROTROPIN ($\geq$2.5 mU/L) DUE TO IODINE DEFICIENCY

Variable	Time	Control	Iodine
Total cholesterol (mmol/L)	0 month	3.7 ± 1.2[a]	3.8 ± 1.0
	5–6 months	3.9 ± 1.5	3.2 ± 0.7[c]
HDL cholesterol (mmol/L)	0 month	0.7 ± 0.2	0.8 ± 0.2
	5–6 months	0.8 ± 0.2	0.8 ± 0.2
LDL cholesterol (mmol/L)	0 month	2.5 ± 1.0	2.6 ± 0.9
	5–6 months	2.7 ± 1.2	1.9 ± 0.7[c]
Triglycerides (mmol/L)	0 month	0.9 ± 0.6	0.9 ± 0.5
	5–6 months	1.0 ± 0.8	1.0 ± 0.9
C-Peptide (ng/mL)	0 month	1.1 (0.3–3.8)[b]	1.0 (0.2–4.7)
	5–6 months	1.0 (0.2–4.8)	0.7 (0.2–3.8)[d]
C-Reactive protein (mg/L)	0 month	0.4 (0.3–20.8)	0.4 (0.3–26.7)
	5–6 months	0.4 (0.3–100)	0.3 (0.3–19.4)

As [a]mean $\pm$ standard deviation or [b]median (range) (all such values).
[c]$p<0.001$ versus control.
[d]$p<0.01$ versus control.
LDL, low-density lipoprotein; HDL, high-density lipoprotein.

screening are at risk of persistent ScH in childhood (41). Although we did not measure antithyroid antibodies, and Hashimoto's thyroiditis is the most common cause of thyroid hypofunction in children in iodine-sufficient areas (13), it was unlikely to be a major cause in our study population as nearly all cases of ScH were corrected by iodine treatment.

ScH is often a benign and remitting process in childhood (22,42), and there are few data on whether ScH worsens the cardiovascular disease risk profile in children. Paoli-Valeri *et al.* (22) compared the lipid profile of 2–9-year-old Spanish children ($n = 36$) with ScH to healthy controls; mean HDL cholesterol was significantly lower in children with ScH. Studies that examined the effects of T4 treatment in children or adolescents with ScH (21,43,44) did not report its effect on risk factors for cardiovascular disease.

Iodine treatment in our study showed clear benefits on the lipid profile, particularly a significant reduction in LDL cholesterol. The effect of ScH on serum lipids in adults is equivocal (11–13). In a cross-sectional study of >30,000 individuals without known thyroid disease (15), total and LDL cholesterol and triglycerides increased with increasing TSH, while HDL cholesterol decreased across the entire reference range, with no indication of a threshold effect. There have been two metaanalyses on the effects of T4 therapy on lipid levels in patients with mild thyroid failure; both reported reductions in total cholesterol (45,46) and one reported lower LDL cholesterol (46). In an uncontrolled study, iodine-deficient German adolescents ($n = 106$) treated for goiter with 300 μg/day iodine or 100 μg/day iodine plus 100 μg/day levo-T4 showed a decrease in serum TSH and an increase in serum T4; both treatments significantly decreased total and LDL cholesterol (26).

Iodine treatment in our study reduced serum C-peptide concentrations. This suggests that treatment reduced levels of endogenous insulin production. Previous studies in adults linking ScH and insulin metabolism (47,48) are equivocal. Iodine treatment in our study did not significantly change CRP concentrations. Whether CRP levels are elevated in ScH is uncertain (12); controlled trials of levo-T4 replacement in ScH have generally not found effects on CRP (13), and in the present study, there was no significant effect of iodine treatment on CRP concentrations.

Our findings suggest that ID-associated thyroid hypofunction in children produces a more atherogenic lipid and insulin profile. This may be particularly important in rapidly developing countries (e.g., India and Russia), where ID remains common but adoption of the Western lifestyle has rapidly increased the prevalence of obesity and cardiovascular disease. In such areas, affected by the double burden of over- and undernutrition (49), correction of ID may not only improve growth and cognitive development but also help reduce cardiovascular disease risk.

Disclosure Statement

Each of the authors made substantial contributions to the study design, data collection, and data analyses, as well as to the writing and/or editing of the article. None of the authors have a personal or financial interest in the companies or organizations sponsoring this research, including advisory board affiliations.

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