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Iodine Supplementation Decreases Hypercholesterolemia in Iodine-Deficient, Overweight Women: A Randomized Controlled Trial[1,2]

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Abstract

Background: In iodine deficiency, thyrotropin (TSH) may increase to stimulate thyroidal iodine uptake. In iodine-sufficient populations, higher TSH predicts higher total cholesterol. Whether higher TSH caused by iodine deficiency affects serum lipids is uncertain.

Objective: Our aim was to determine if iodine repletion decreases serum TSH and improves the lipid profile.

Methods: In this randomized controlled intervention, iodine-deficient, overweight or obese Moroccan women (n = 163) received 200 μg oral iodine or a placebo daily for 6 mo. Main outcomes were serum TSH and plasma total and LDL cholesterol. Secondary outcomes included thyroid hormones and measures of lipid and glucose metabolism and urinary iodine concentration (UIC). Data were compared by using mixed-model analysis.

Results: In the intervention group, median UIC increased from 38 (95% CI: 34, 45) μg/L to 77 (95% CI: 59, 89) μg/L ($P < 0.001$). After 6 mo of intervention, TSH was 33% lower in the treatment group than in the placebo group ($P = 0.024$). The triiodothyronine (T3) to thyroxine (T4) ratio and thyroglobulin decreased with treatment [−15% ($P = 0.002$) and −32% ($P < 0.001$), respectively], whereas T4 concentrations were higher in the treatment group ($P < 0.001$). Total cholesterol in subjects with elevated baseline cholesterol (>5 mmol/L) was reduced by 11% after the intervention ($P = 0.034$). At 6 mo, only 21.5% of treated women remained hypercholesterolemic (total cholesterol >5 mmol/L) vs. 34.8% of controls (baseline: 44.2% in the intervention and 36.8% in the control group; $P = 0.015$). The reduction in the prevalence of elevated LDL cholesterol (>3 mmol/L) seen in the intervention group (50.6% to 35.4% compared with 47.4% to 44.9% in the control group) was not significant (P-interaction = 0.23).

Conclusions: Our findings suggest that moderate to severe iodine deficiency in overweight women elevates serum TSH and produces a more atherogenic lipid profile and that iodine supplementation in this group reduces the prevalence of hypercholesterolemia. Thus, iodine prophylaxis may reduce cardiovascular disease risk in overweight adults. This trial was registered at clinicaltrials.gov as NCT01985204. *J Nutr* doi: 10.3945/jn.115.213439.

Keywords: obesity, iodine deficiency, subclinical hypothyroidism, cholesterol, Morocco, cardiovascular disease, lipid profile, double burden

Introduction

A common adaptation to chronic iodine deficiency is an increase in serum thyrotropin (TSH)[9] to stimulate thyroidal uptake of circulating iodine (1). In moderately to severely iodine-deficient areas, many adults demonstrate a variably elevated TSH with concentrations of serum thyroxine (T4) and triiodothyronine (T3) in the normal range (1–3), a biochemical pattern consistent with subclinical hypothyroidism. Because iodine deficiency continues to affect approximately one-third of the global population (4), it remains a common cause of subclinical hypothyroidism worldwide (5). Iodine repletion normalizes increased serum TSH in iodine-deficient individuals (6).

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[9] Abbreviations used: CRP, C-reactive protein; fT3, free triiodothyronine; fT4, free thyroxine; HbA1c, glycated hemoglobin; T3, triiodothyronine; T4, thyroxine; TSH, thyrotropin; UIC, urinary iodine concentration.

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Overt and subclinical hypothyroidism may increase the risk of dyslipidemia, and in some studies is associated with insulin resistance and subclinical inflammation (7, 8). Moreover, within the reference range for TSH, higher TSH is associated with dyslipidemia (9), higher BMI (10), and mortality from coronary artery disease (11). T4 replacement in adults with subclinical hypothyroidism or with high-normal TSH concentrations may improve cardiovascular disease risk factors, although not all studies agree (12–14).

In an uncontrolled study, iodine treatment of goitrous adolescents decreased total cholesterol concentrations (15). A secondary analysis of iodine supplementation studies in iodine-deficient children with subclinical hypothyroidism also found improvements in lipid and glucose metabolism (16). However, these were not randomized trials and they did not study adults at risk of cardiovascular disease. Overweight and obese adults are at high risk of subclinical hypothyroidism (17), as well as hyperlipidemia, insulin resistance, and subclinical inflammation (18).

Morocco has enacted national legislation mandating compulsory salt iodization, but because of poor compliance by the salt industry and a lack of enforcement many regions remain iodine deficient and the national median urinary iodine concentration (UIC) in children is only 69 μg/L (19). At the same time, there has been a rapid increase in recent years in Morocco in rates of overweight and obesity, as well as of hyperlipidemia and type 2 diabetes (20). We hypothesized that the correction of iodine deficiency would decrease serum TSH and thereby reduce elevated blood lipids. Our primary outcomes were serum total and LDL cholesterol.

Methods

Subjects. We carried out this study from December 2013 to May 2014 at the district health center of Amizmiz, in southern Morocco, in the foothills of the Atlas Mountains. Previous studies reported that young women in the region were iodine deficient (21). Inclusion criteria for the study were as follows: *1*) female sex; *2*) age from 20 to 50 y and premenopausal; *3*) overweight or obese, defined as a BMI (in kg/m^2) from 27 to 40; *4*) no thyroid nodularity by palpation (diffuse goiter was not an exclusion criterion); *5*) no major chronic diseases as judged by the study physician; *6*) no regular use of medication (except for oral contraceptives); and *7*) not pregnant or lactating. The study protocol was approved by the Ethical Committee of ETH Zurich, Switzerland, and the Regional Director of the Ministry of Health of the Marrakech-Tensift-Al Haouz region. The study was registered at clinicaltrials.gov (NCT01985204).

We based our sample size calculation on an expected 10% reduction in mean LDL-cholesterol concentration in the treatment group over time compared with the control, considering our previous study in iodine-deficient children selected for subclinical hypothyroidism in whom the reduction in LDL cholesterol after iodine supplementation was >25% (16). We expected the effect in this study to be less pronounced because we did not screen for subclinical hypothyroidism. With the use of a mean baseline LDL-cholesterol concentration of 3.2 mmol/L with an SD of 0.83, the expected reduction of 10%, a power of 95%, and an α error probability of 0.05, the required sample size was 72 subjects per group. We anticipated a drop-out rate of ~10% and thus planned to include 80 subjects per group.

Study design. The staff of the health clinic invited all overweight women in the community to a screening visit. At the screening, a study physician explained the study in detail, reviewed the medical history, and performed a brief medical examination, including thyroid palpation. Women who met the inclusion criteria were asked to participate in the study, and we obtained written informed consent. By using a random-number list generated in Excel (Microsoft) by one of the authors (IH-A), the study physicians randomly assigned women to either the treatment group or to a placebo control (**Figure 1**). The treatment group received 200 μg iodine daily as oral potassium iodide tablets (Merck). The control group received identical-appearing tablets containing no iodine. Both investigators and subjects were masked to group assignment, and tablets were coded as "A" and "B"; during the study, a data safety monitoring board held the codes and the codes were broken only after the completion of statistical analyses.

The women returned to the health center monthly at which time we distributed 36 new tablets; the women returned leftover tablets from the previous month, which were counted and recorded to register compliance. After 3 mo, 9 additional women who met the inclusion criteria and wished to join the study but who were absent at the baseline visit were randomly assigned to the 2 groups (Figure 1). At each monthly visit, we collected a second-morning-void spot urine sample into iodine-free plastic cups. Urine aliquots were stored at −20°C until analysis.

At baseline and after 3 and 6 mo, we asked the women to present after an overnight fast at the health clinic between 0800 and 1200 h. We measured weight to the nearest 100 g by using a mechanical scale (Seca) and height to the nearest 0.5 cm by using a roll-up measuring tape fixed to the wall. We measured waist circumference to the nearest 0.1 cm by using a nonstretchable measuring tape; the measurement was taken midway between the lowest palpable rib and the top of the iliac crest while subjects were standing, with their abdomen relaxed and exhaling. We collected 4 evacuated tubes of blood through a forearm venipuncture [1 serum tube (5 mL), 1 heparin-containing tube (5 mL), 1 EDTA-containing tube (2 mL), and 1 fluoride tube (2 mL)] and transported them to the laboratory for processing on the afternoon of the sampling day. We measured glycated hemoglobin (HbA1c) and then centrifuged the remaining blood at room temperature for 10 min at 3000 *g* to separate plasma and serum. Plasma and serum were placed into aliquots and stored at −20°C until analysis in Zurich.

Co-primary outcomes were TSH, total cholesterol, and LDL cholesterol and secondary outcomes were free T3 (fT3) and free T4 (fT4), thyroglobulin, leptin, fasting glucose and insulin, HbA1c, C-peptide, TGs, HDL cholesterol,

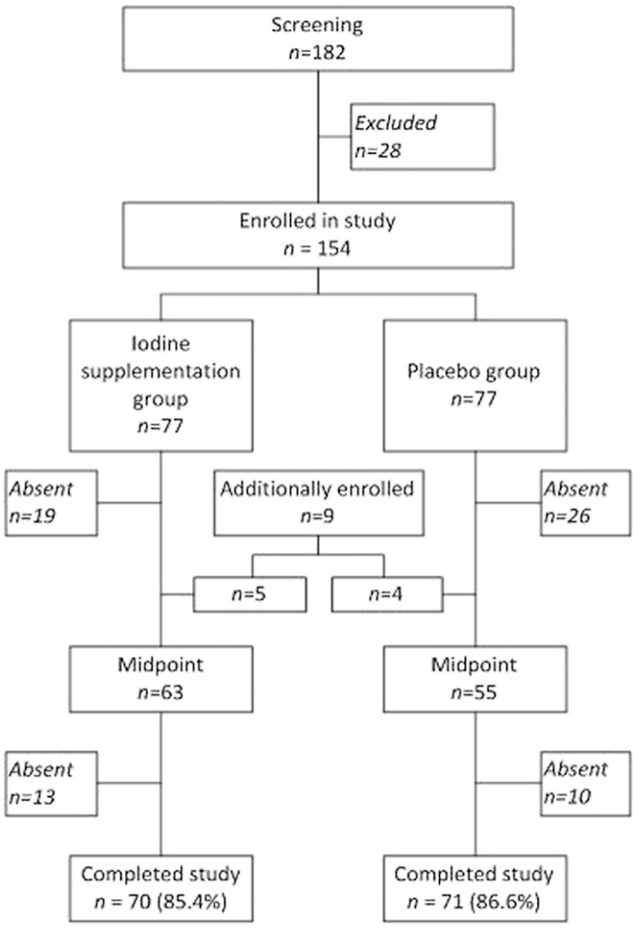

FIGURE 1 Study overview.

C-reactive protein (CRP), and UIC. At the end of the study, after the 6-mo measurements, all of the women in the placebo group received a single dose of oral iodized poppyseed oil (~190 mg iodine; Guerbet).

Laboratory analyses. HbA1c was analyzed by using the fully automated system Cobas Integra (Roche Diagnostics). TGs, total cholesterol, HDL cholesterol, and glucose were determined at the Clinical Chemistry Laboratory at University Hospital Zurich from heparinized plasma or, for glucose, fluoride plasma by using enzymatic assays on the Cobas System (Roche Diagnostics). LDL-cholesterol concentrations were calculated by the Friedewald formula, and non–HDL cholesterol was calculated as follows: non–HDL cholesterol = total cholesterol – HDL cholesterol. Insulin and C-peptide were also determined from serum at the Clinical Chemistry Laboratory at University Hospital Zurich by using a fully automated chemiluminescence immunoassay (Immulite 2000; Siemens Healthcare Diagnostics). The same system (Immulite 2000) was used at the Human Nutrition Laboratory at ETH Zurich to determine fT3, fT4, TSH, thyroglobulin, and CRP from serum. Leptin was measured from heparinized plasma by using an ELISA kit (Human Leptin ELISA, clinical range; Bio Vendor). Urinary iodine was measured by using the Pino

TABLE 1 Anthropometric measurements, inflammation, and serum thyroid function tests among overweight Moroccan women participating in an iodine supplementation study, by group[1]

			P^3		
	Control[2]	Treatment	Group	Time	Group × time
Weight, kg			0.57	0.85	0.19
0 mo	78 (75, 80)	75 (72, 80)			
3 mo	78 (76, 80)	78 (75, 84)			
6 mo	78 (76, 83)	75 (75, 78)			
BMI, kg/m^2			0.91	0.84	0.20
0 mo	31.7 (31.1, 32.9)	31.2 (30.3, 32.8)			
3 mo	32.0 (30.9, 33.2)	32.2 (30.8, 33.3)			
6 mo	32.1 (31.1, 33.2)	31.4 (30.5, 32.6)			
WC, cm			0.35	<0.001	0.76
0 mo	97 (96, 100)	95 (92, 99)			
3 mo	100 (96, 103)	100 (96, 103)			
6 mo	99 (98, 102)	99 (95, 103)			
UIC, μg/L			<0.001	0.001	<0.001
0 mo	45.5 (38.3, 56.5)	38.2 (33.7, 45.2)			
3 mo	38.0 (33.1, 43.3)	54.4 (42.9, 84.9)			
6 mo	39.5 (31.7, 47.6)	77.0 (59.9, 88.6)			
Free T3, pg/mL			0.32	<0.001	0.19
0 mo	3.9 (3.7, 4.1)	3.9 (3.8, 4.0)			
3 mo	3.8 (3.7, 4.1)	4.2 (3.9, 4.4)			
6 mo	3.2 (3.0, 3.3)	3.1 (2.9, 3.2)			
Free T4, ng/dL			0.91	<0.001	<0.001
0 mo	1.03 (0.98, 1.04)	0.97 (0.94, 0.99)			
3 mo	0.98 (0.96, 1.02)	1.03 (1.01, 1.07)			
6 mo	0.90 (0.89, 0.93)	0.94 (0.92, 0.99)			
Free T3:T4 ratio			0.69	<0.001	0.002
0 mo	3.79 (3.58, 4.05)	3.96 (3.77, 4.26)			
3 mo	3.90 (3.50, 4.33)	4.20 (3.75, 4.33)			
6 mo	3.40 (3.20, 3.65)	3.35 (2.97, 3.47)			
TSH, mIU/L			0.02	<0.001	0.02
0 mo	1.30 (1.05, 1.40)	1.10 (0.90, 1.40)			
3 mo	1.00 (0.80, 1.20)	0.80 (0.70, 1.05)			
6 mo	1.20 (1.00, 1.40)	0.80 (0.60, 1.00)			
Thyroglobulin, μg/L			0.003	0.001	< 0.001
0 mo	41.9 (32.8, 56.6)	34.5 (26.2, 44.6)			
3 mo	40.8 (35.1, 56.7)	16.1 (12.0, 27.7)			
6 mo	49.9 (40.0, 68.3)	23.4 (16.6, 41.1)			
CRP, mg/L			0.49	0.040	0.11
0 mo	5.9 (4.3, 8.5)	4.9 (3.5, 6.3)			
3 mo	5.4 (3.5, 8.2)	5.7 (3.1, 7.2)			
6 mo	5.4 (4.0, 8.2)	4.1 (3.1, 5.6)			

[1] Values are medians (95% CIs); n = 77, 63, and 70 in the treatment group and 77, 55, and 71 in the control group at baseline and at 3 and 6 mo, respectively. Specimens used for the analysis were as follows: urine for UIC; serum for T3, T4, TSH, thyroglobulin, and CRP. CRP, C-reactive protein; T3, triiodothyronine; T4, thyroxine; TSH, thyrotropin; UIC, urinary iodine concentration; WC, waist circumference.
[2] The control group received 1 placebo tablet daily and the treatment group received 1 iodine tablet containing 200 μg potassium iodide daily.
[3] Linear mixed-model analysis on the entire study population; P values are for the individual effects of group and time as well as their interaction. Covariates used in the models by dependent variable: UIC (compliance, insulin, TSH, thyroglobulin), free T4 (TSH), TSH (compliance, UIC), thyroglobulin (compliance), CRP (insulin).

modification of the Sandell-Kolthoff reaction (22). External controls were provided by the EQUIP program (US CDC).

Reference ranges given by the manufacturers of the respective kits were as follows: glucose, 3.9–5.6 mmol/L; insulin, ≤29 mIU/L; C-peptide, 0.9–7.1 μg/L; HbA1c, <6.5% for diabetes; total cholesterol, ≤5 mmol/L; HDL cholesterol, >1.0 mmol/L; LDL cholesterol, ≤3.0 mmol/L; non–HDL cholesterol, <4.0 mmol/L; TGs, ≤1.7 mmol/L; fT3, 1.8–4.2 pg/mL; fT4, 0.89–1.76 ng/dL; TSH, 0.4–4.0 mIU/L; thyroglobulin, ≤55 μg/L; and CRP, <3 mg/L. Overt hypothyroidism was defined as TSH >4.0 mIU/L + fT4 <0.89 ng/dL. Subclinical hypothyroidism was defined as TSH >4.0 mIU/L + normal fT4. Overt hyperthyroidism was defined as TSH < 0.4 mIU/L + fT4 >1.76 ng/dL. Subclinical hyperthyroidism was defined as TSH <0.4 mIU/L and normal fT4. Isolated hypothyroxinemia was defined as fT4 <0.89 ng/dL + normal TSH.

Statistical analyses. Statistical analysis was conducted by using IBM SPSS Statistics 20 (IBM) and RStudio_0 (RStudio). Data were checked for normality by using the Kolmogorov-Smirnov test. Data are presented as medians (95% CIs). Baseline group comparisons were performed by using independent-samples *t* test for normally distributed data (waist circumference and total cholesterol) and Kruskal-Wallis test for nonnormally distributed data (all other variables). Time by treatment effects on continuous variables were investigated with SPSS by using linear mixed models with time and group as well as their interaction as fixed factors and subject identification as a random factor. All dependent variables were log-transformed for the analysis to ensure normal distribution of the residuals. Baseline variables significantly correlated with the dependent variable and improving the model fit were included as covariates.

Pearson's chi-square test was used to investigate differences in the prevalence of abnormal values for the biochemical variables between groups at baseline. Mixed models with logistic regression (generalized mixed model) in RStudio were further used to investigate time by treatment effects in the prevalence of abnormal values of the different variables. Again, time and group as well as their interaction were used as fixed factors, whereas subject identification was a random factor in the models. A *P* value <0.05 was considered to be significant for all analyses.

Subgroups to investigate time by treatment effects on continuous variables were defined as follows: subjects with elevated total cholesterol (>5 mmol/L) and subjects with elevated LDL cholesterol (>3 mmol/L). The same mixed-model analysis as described above for continuous variables was used.

Results

At screening, 182 women presented to the study site, and 28 were excluded because they did not meet the inclusion criteria (Figure 1). The remaining 154 women were included and randomly assigned to 2 equal groups. At midpoint, an additional 9 women were enrolled in the study and randomly assigned to the 2 groups. Fourteen percent of women dropped out during the 6-mo study (Figure 1). On the basis of tablets returned at the monthly visits, median (95% CI) compliance was 82% (77%, 88%). There were no serious adverse events during the study. Salt samples (n = 4) collected from retail outlets in the area contained between 0.19 and 0.54 mg I/kg.

Anthropometric variables, inflammation, UIC, and thyroid function tests for all 3 study time points by group, with time by treatment analysis using linear mixed models, are shown in **Table 1**. Baseline characteristics did not significantly differ between the 2 groups, except for serum fT4, which was lower in the intervention group at baseline (P = 0.034). On the basis of their median UIC of 42 μg/L at baseline (both groups combined), the women in this study were moderately iodine deficient (23). There was no significant increase in the median UIC in the control group during the study. With the use of mixed-model analysis in the total study population including the 3 main time points (baseline, 3 mo, and 6 mo), there was a significant time by treatment effect for UIC (higher with treatment, P < 0.001; covariates: compliance, insulin, TSH, thyroglobulin). The monthly measurements of UIC are shown by group in **Figure 2**. A similar analysis including the 7 monthly time points confirmed a significant time by treatment effect on UIC (P = 0.014; covariate: compliance).

As shown in Table 1, there was a significant time by treatment effect with the use of mixed models on the entire study population for the following: *1*) serum fT4 (higher with treatment, P < 0.001; covariate: TSH), *2*) serum TSH (lower with treatment, P = 0.024; covariate: compliance), *3*) fT3:fT4 ratio (lower with treatment, P = 0.002), and *4*) serum thyroglobulin (lower with treatment, P < 0.001; covariate: compliance). The difference in serum TSH between groups at 6 mo was 0.4 (95% CI: 0.1, 0.7) mIU/L or 33%.

At baseline and at 3 and 6 mo, when comparing the treatment to the placebo groups, we found the following: *1*) the prevalences of subclinical hyperthyroidism were 4%, 15%, and 15% vs. 4%, 4%, and 4% (time by treatment interaction, P = 0.013); *2*) the prevalences of overt hypothyroidism were 1%, 2%, and 2% vs. 1%, 2%, and 0 (no significant effects); *3*) there were no cases of

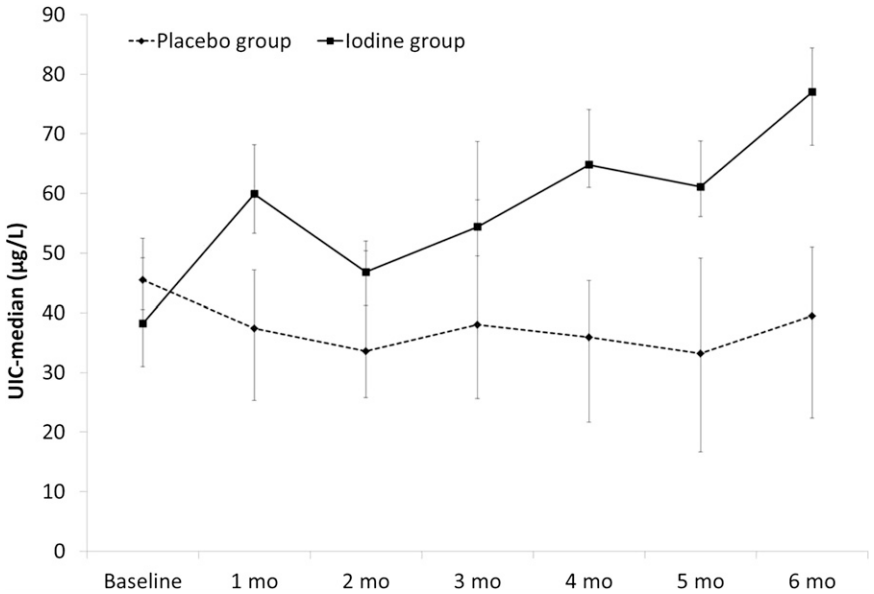

FIGURE 2 UICs among overweight Moroccan women who received 200 μg iodine or placebo daily for 6 mo, by group. Values are medians (95% CIs). There was a significant group (P < 0.001), time (P = 0.001), and time by treatment (P < 0.001) effect on UIC (covariate: compliance). n = 77 at baseline in each group; n = 70 in the treatment and n = 71 in the control group at 6 mo. UIC, urinary iodine concentration.

subclinical hypothyroidism, with the exception of a single case at baseline in the control group; *4*) there were no cases of overt hyperthyroidism; *5*) the prevalences of isolated hypothyroxinemia was 15.6%, 5.1%, and 25.0% vs. 13.3%, 10.9%, and 38.2% (significant time effect, $P < 0.001$, but no significant treatment effect or interaction); and *6*) the prevalences of elevated serum thyroglobulin were 28.6%, 22.0%, and 23.4% vs. 41.3%, 37.3%, and 49.2% (significant time by treatment effect, with a reduction in the treatment group; $P = 0.004$). The percentage change in UIC from baseline to 6 mo was significantly

TABLE 2 Plasma glucose and lipid variables and plasma leptin among overweight Moroccan women participating in an iodine supplementation study, by group[1]

			P[3]		
	Control[2]	Treatment	Group	Time	Group × time
HbA1C, %			0.63	<0.001	0.93
0 mo	6.2 (6.0, 6.3)	6.1 (6.0, 6.3)			
3 mo	6.1 (5.9, 6.1)	6.1 (6.0, 6.1)			
6 mo	5.8 (5.8, 5.9)	5.9 (5.8, 6.0)			
Glucose, mmol/L			0.48	<0.001	0.32
0 mo	5.0 (4.9, 5.2)	5.3 (5.1, 5.4)			
3 mo	5.0 (4.9, 5.2)	5.2 (5.0, 5.3)			
6 mo	5.2 (5.0, 5.4)	5.2 (5.0, 5.5)			
Insulin, mIU/L			0.11	0.13	0.76
0 mo	7.8 (6.9, 9.6)	6.6 (6.1, 7.5)			
3 mo	7.0 (5.8, 10.0)	6.5 (5.9, 7.4)			
6 mo	8.1 (6.3, 9.1)	6.0 (5.2, 7.6)			
HOMA-IR			0.22	0.21	0.31
0 mo	2.0 (1.7, 2.3)	1.6 (1.5, 1.7)			
3 mo	2.1 (1.5, 2.7)	1.7 (1.3, 2.1)			
6 mo	1.9 (1.5, 2.1)	1.6 (1.2, 1.8)			
C-peptide, μg/L			0.03	<0.001	0.88
0 mo	1.4 (1.3, 1.7)	1.2 (1.1, 1.4)			
3 mo	1.5 (1.2, 1.7)	1.3 (0.9, 1.6)			
6 mo	2.0 (1.7, 2.1)	1.7 (1.6, 2.0)			
Total cholesterol, mmol/L			0.54	<0.001	0.10
0 mo	4.9 (4.7, 5.0)	4.8 (4.4, 5.3)			
3 mo	4.6 (4.3, 5.0)	4.5 (4.2, 5.1)			
6 mo	4.6 (4.3, 4.8)	4.3 (4.1, 4.8)			
HDL cholesterol, mmol/L			0.38	<0.001	0.24
0 mo	1.2 (1.2, 1.3)	1.2 (1.1, 1.3)			
3 mo	1.2 (1.1, 1.3)	1.1 (1.0, 1.2)			
6 mo	1.2 (1.1, 1.3)	1.1 (1.1, 1.2)			
LDL cholesterol, mmol/L			0.74	<0.001	0.17
0 mo	3.0 (2.9, 3.2)	3.2 (2.7, 3.4)			
3 mo	2.8 (2.7, 3.0)	2.8 (2.5, 3.2)			
6 mo	2.9 (2.7, 3.2)	2.6 (2.5, 3.0)			
Non–HDL cholesterol, mmol/L			0.82	<0.001	0.50
0 mo	3.5 (3.4, 3.8)	3.7 (3.2, 3.9)			
3 mo	3.5 (3.2, 3.6)	3.4 (3.0, 3.8)			
6 mo	3.3 (3.2, 3.7)	3.2 (3.0, 3.5)			
TGs, mmol/L			0.42	0.040	0.45
0 mo	1.2 (1.1, 1.3)	1.2 (1.0, 1.3)			
3 mo	1.3 (1.1, 1.4)	1.3 (1.0, 1.4)			
6 mo	1.1 (1.0, 1.3)	1.1 (1.0, 1.2)			
Leptin, μg/L			0.02	0.004	0.06
0 mo	28.9 (25.4, 32.6)	24.4 (21.0, 28.4)			
3 mo	27.5 (21.8, 34.7)	26.4 (20.9, 28.8)			
6 mo	28.6 (25.6, 31.8)	23.3 (20.4, 25.6)			

[1] Values are medians (95% CIs); $n = 77$, 63, and 70 in the treatment group and 77, 55, and 71 in the control group at baseline and at 3 and 6 mo, respectively. Specimens used were as follows: EDTA-treated blood for HbA1c; fluoride plasma for glucose; serum for insulin and C-peptide; heparinized plasma for all lipid variables and leptin. HbA1c, glycated hemoglobin; non–HDL cholesterol, total cholesterol minus HDL cholesterol.

[2] The control group received 1 placebo tablet daily and the treatment group received 1 iodine tablet containing 200 μg potassium iodide daily.

[3] Linear mixed-model analysis on the entire study population; P values are for the individual effects of group and time as well as their interaction. Covariates used in the models by dependent variable are as follows: HOMA-IR (BMI, leptin, HDL cholesterol, TSH), C-peptide (insulin); total cholesterol (free T4); TGs (free T4).

and negatively correlated with the percentage change in serum TSH ($r = -0.37$, $P < 0.001$) and thyroglobulin ($r = -0.43$, $P < 0.001$) in the entire group of subjects.

Variables of glucose and lipid metabolism and plasma leptin concentrations during the study by group are shown in **Table 2**. Baseline characteristics did not differ between the 2 groups except for serum insulin, which was significantly lower in the supplementation group at baseline ($P = 0.033$). At 6 mo, the difference between the 2 groups in plasma total and LDL cholesterol was 0.3 (95% CI: −0.1, 0.7) mmol/L (7%) and 0.3 (95% CI: −0.1, 0.7) mmol/L (10%), respectively. In the entire group analyzed by using mixed models, there were no time by treatment effects on any of the glucose and lipid variables, with the exception of borderline significant trends toward an effect on leptin (lower in the treatment group; $P = 0.06$) and total cholesterol (lower in the treatment group; $P = 0.10$) (Table 2). In the subgroup analysis, dividing subjects by baseline total cholesterol into those with elevated plasma total cholesterol (>5 mmol/L) and those with normal plasma total cholesterol, there was a significant time by treatment interaction on total cholesterol in subjects with elevated baseline total cholesterol ($P = 0.034$) but not in those with normal total cholesterol ($P = 0.72$). However, a similar subgroup analysis dividing subjects by baseline LDL cholesterol showed no significant time by treatment interaction in either the high plasma LDL-cholesterol or the normal plasma LDL-cholesterol groups ($P = 0.12$ and $P = 0.37$, respectively). In the entire study population, percentage changes in total, LDL, and HDL cholesterol from baseline to 6 mo were not correlated with percentage changes in UIC, TSH, or thyroglobulin ($P > 0.05$).

Table 3 shows the prevalence of abnormal metabolic variables during the study by group. None of the distributions were significantly different between the 2 groups at baseline (chi-square test, $P > 0.05$). The prevalence of hyperlipidemia at baseline was high: nearly half of the women had elevated LDL cholesterol and more than one-third had elevated total cholesterol. There was a significant reduction in the prevalence of elevated total cholesterol in the intervention group (time by treatment effect, $P = 0.015$) (**Figure 3**A). Furthermore, there was a nonsignificant trend toward a reduction in the prevalence of elevated non–HDL cholesterol in the intervention group (time by treatment effect, $P = 0.09$). Although the values seemed to indicate a reduction in the prevalence of elevated LDL cholesterol [from 50.6% to 35.4% in the treatment group, with minimal change in the control group (47.4% to 44.9%)], this difference was not significant (P-interaction = 0.23) (Figure 3B).

TABLE 3 Prevalence of abnormal metabolic variables among overweight Moroccan women participating in an iodine intervention study, by group[1]

			P[3]		
	Control[2]	Treatment	Group	Time	Group × time
Elevated HbA1c (≥6.5%)			0.85	<0.001	0.39
0 mo	26.0 (19)	24.0 (18)			
3 mo	18.9 (10)	16.1 (10)			
6 mo	10.4 (7)	10.6 (7)			
Diabetes (fasting blood glucose ≥7.0 mmol/L)			0.97	0.99	0.55
0 mo	4.0 (3)	5.2 (4)			
3 mo	1.9 (1)	6.5 (4)			
6 mo	4.5 (3)	7.7 (5)			
Elevated total cholesterol (>5 mmol/L)			0.15	0.65	0.015
0 mo	36.8 (28)	44.2 (34)			
3 mo	31.6 (18)	37.3 (22)			
6 mo	34.8 (24)	21.5 (14)			
Elevated LDL cholesterol (>3.0 mmol/L)			0.41	0.44	0.23
0 mo	47.4 (36)	50.6 (39)			
3 mo	36.8 (21)	40.7 (24)			
6 mo	44.9 (31)	35.4 (23)			
Low HDL cholesterol (≤1.0 mmol/L)			0.93	0.86	0.25
0 mo	28.9 (22)	27.3 (21)			
3 mo	33.3 (19)	42.2 (25)			
6 mo	31.9 (22)	36.9 (24)			
Elevated non–HDL cholesterol (≥4.0 mmol/L)			0.41	0.12	0.09
0 mo	21.1 (26)	39.0 (30)			
3 mo	24.6 (14)	30.5 (18)			
6 mo	29.0 (20)	21.5 (14)			
Elevated TGs (>1.7 mmol/L)			0.12	0.017	0.011
0 mo	18.4 (14)	9.1 (7)			
3 mo	15.8 (9)	13.6 (8)			
6 mo	10.1 (7)	12.3 (8)			

[1] Values are percentages (n); n = 77, 63, and 70 in the treatment group and 77, 55, and 71 in the control group at baseline and at 3 and 6 mo, respectively. HbA1c, glycated hemoglobin; non–HDL cholesterol, total cholesterol minus HDL cholesterol.
[2] The control group received 1 placebo tablet daily and the treatment group received 1 iodine tablet containing 200 μg potassium iodide daily.
[3] Generalized mixed-model analysis of the entire study population; P values are for the individual effects of group and time as well as their interaction.

There was a significant decrease in the prevalence of elevated TGs in the placebo group (time by treatment effect, $P = 0.011$). Adding age or compliance as covariates did not significantly improve any of the models. There were no significant time by treatment effects on measures of glucose or insulin metabolism or subclinical inflammation (Table 3).

Discussion

Iodine supplementation was well accepted by the study population and compliance was high (median consumption of the tablets was 82%). Only 5 of the women in the treated group had a UIC >300 μg/L (the WHO cutoff that suggests iodine excess) during the study (23). Although there were no cases of overt hyperthyroidism in the treated group, the prevalence of subclinical hyperthyroidism significantly increased, from 4% to 15%. We excluded subjects at baseline with clinical thyroid nodularity, because this group is at a high risk of developing hyperthyroidism when iodine intakes are rapidly increased (6). However, in this chronically iodine-deficient population, it is likely that many of the women had small thyroid nodules not detected by palpation and, in some, iodine supplementation triggered thyroid nodular autonomy (24). However, we did not measure anti-thyroid antibodies, which may be triggered by increases in iodine intake (25), so we cannot be certain of the etiology of the subclinical hyperthyroidism in the treated women.

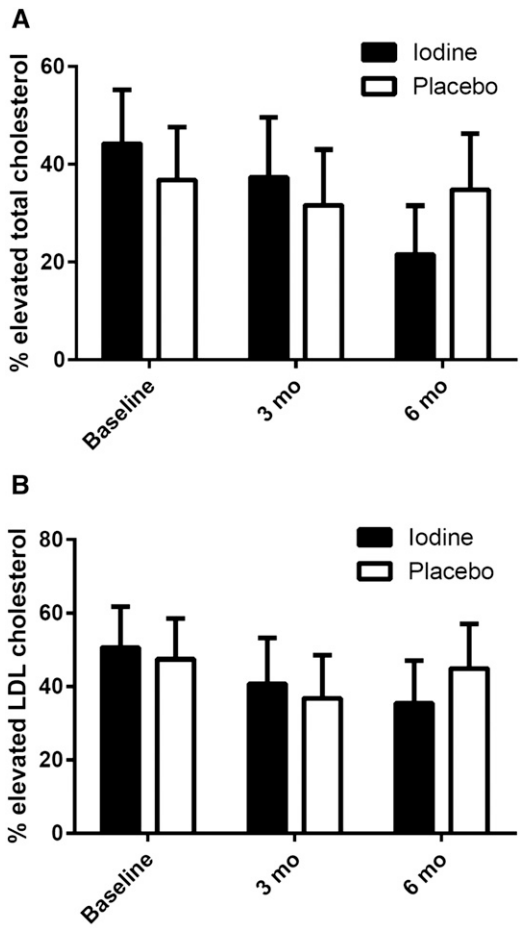

FIGURE 3 Prevalence of elevated plasma total cholesterol (>5 mmol/L) (A) and plasma LDL cholesterol (>3 mmol/L) (B) in overweight Moroccan women who received 200 μg iodine or a placebo daily for 6 mo, by group. Time by treatment interaction using generalized mixed-model analysis: $P = 0.015$ (total cholesterol), $P = 0.23$ (LDL cholesterol). Error bars indicate 95% CIs. $n = 77$, 63, and 70 in the treatment group and $n = 77$, 55, and 71 in the control group at baseline and at 3 and 6 mo, respectively.

In this study, iodine supplementation modestly improved thyroid function; there was a small but significant increase in fT4 and a decrease of ~30% in median TSH and thyroglobulin, suggesting reduced thyroid stimulation; but most changes resulted in concentrations that still were within the reference ranges. Nevertheless, iodine supplementation clearly reduced hypercholesterolemia. Cross-sectional studies suggest that TSH is correlated with serum lipids even within the normal TSH range (9). In the Nort-Trondelag Health Study in >30,000 euthyroid individuals, serum TSH was significantly positively correlated with total cholesterol, LDL cholesterol, and TGs and negatively associated with HDL cholesterol (9). Among euthyroid Hispanic individuals ($n = 2771$), after adjustment for age, sex, and BMI, serum TSH was positively associated with total cholesterol and TGs (26). However, among euthyroid Korean subjects ($n = 1240$), there was no correlation between serum TSH and serum lipids (27).

Thyroid hormone has multiple effects on the regulation of lipid synthesis, absorption, and metabolism (7). In overt hypothyroidism, reduced clearance of LDL cholesterol from the serum (28) combined with an increase in intestinal cholesterol absorption (29) leads to an increase in serum total and LDL cholesterol. Overt hypothyroidism appears to have little effect on serum HDL cholesterol (7), but it may reduce lipoprotein lipase activity and thereby increase serum TGs (30). In mild or subclinical hypothyroidism, it is likely that similar but more subtle lipid alterations occur (7). Systematic reviews of the effects of T4 therapy on lipid concentrations in mild thyroid failure reported reductions in total cholesterol (31, 32) and lower LDL cholesterol (31). In our study, iodine repletion reduced elevated total cholesterol but had no effect on HDL cholesterol or TGs, results that are generally consistent with the above findings. Also, hypothyroid individuals with higher baseline lipids generally have greater reductions in serum lipid concentrations after T4 treatment (7); similarly, in our study, women with higher baseline total cholesterol concentrations (>5 mmol/L) showed greater reductions with iodine repletion.

In a previous secondary analysis of iodine intervention studies in 5- to 14-y-old iodine-deficient children with subclinical hypothyroidism (16), iodine treatment significantly decreased total and LDL cholesterol and improved the LDL- to HDL-cholesterol ratio. In an uncontrolled study in German adolescents with goiter presumably due to iodine deficiency, iodine treatment also decreased total cholesterol (15). Our study design, a randomized controlled trial, and our study population, young to middle-aged women, confirm and extend these previous findings and suggest that the correction of iodine deficiency may improve the lipid profile in pediatric, adolescent, and adult populations.

We included overweight and obese women in this study because, compared with normal-weight women, they are at higher risk of subclinical hypothyroidism, hyperlipidemia, insulin resistance, and subclinical inflammation (17, 18). The cause of the higher TSH concentration in obese subjects and whether it is an independent risk factor for cardiovascular disease remain unclear (33). One potential link is leptin, the adipocyte-derived hormone that is increased with increasing body fat, and that has been linked to subclinical inflammation (34). In humans, direct correlations between TSH and leptin were reported in cross-sectional and longitudinal studies (33).

Leptin stimulates TSH production by the hypothalamic-pituitary axis in rats (35). At the same time, TSH may stimulate leptin production by adipocytes (36), suggesting cross-talk between these 2 hormones (17). This latter effect may be visible in our study, because there was a nonsignificant trend (P = 0.062) toward a reduction in leptin as TSH decreased with iodine treatment.

Iodine supplementation in our study did not reduce fasting plasma glucose, insulin, or C-peptide concentrations. This suggests that improving iodine intakes does not affect insulin sensitivity in overweight women. Previous studies that explored associations between mild hypothyroidism and insulin metabolism are equivocal (37, 38). In our study, iodine treatment did not significantly change serum CRP, which is consistent with previous trials of T4 replacement in subclinical hypothyroidism that generally did not find reductions in CRP (8).

From a baseline median UIC of 42 μg/L, iodine supplementation steadily increased the median UIC over the trial (Figure 2); and although the median doubled in the treated group, at 6 mo it remained below the WHO cutoff, indicating iodine sufficiency (≥100 μg/L) (1). There was no leveling off of the median UIC in the treated group in the later months of the study, so it is likely that depleted thyroidal iodine stores, which can be as high as 15–20 mg in iodine-sufficient adults (6), were not yet replete after 6 mo. Thus, a limitation of the study is the relatively short intervention period; because there were progressive reductions in total cholesterol and LDL cholesterol at 3 and 6 mo, a longer intervention period might have led to even greater improvements in the lipid profile. However, we felt that a study period longer than 6 mo for the placebo group was unacceptable for ethical reasons. A further limitation of our study is that we did not measure changes in thyroid autoimmunity during the intervention; this might have provided insights into the underlying etiology of TSH elevation and posttreatment hyperthyroidism; and because anti-thyroglobulin antibodies can confound serum thyroglobulin assays, this would have strengthened interpretation of the changes in serum thyroglobulin.

In summary, our findings suggest that iodine deficiency in overweight women produces a more atherogenic lipid profile. Further research is needed in different populations with varying severity of iodine deficiency and metabolic risk factors to determine whether these findings are generalizable. If confirmed, this effect may also be important in higher-income countries, such as Russia, the United Kingdom, Finland, and Italy, where iodine deficiency remains common (39) and where there is a high prevalence of obesity and cardiovascular disease. In iodine-deficient countries such as these and others, strengthening iodine prophylaxis may not only reduce thyroid disorders in adults and improve cognition in children (23) but also help reduce cardiovascular disease risk.

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