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Effect of iodine restriction on short-term changes in thyroid function in patients with subclinical hypothyroidism

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ABSTRACT

Purpose: Elevated iodine intake is related to a higher prevalence of subclinical hypothyroidism (SCH). We investigated the short-term effect of dietary iodine restriction on thyroid function in patients with SCH with high iodine intakes.
Methods: The iodine levels in 64 SCH patients with serum TSH levels from 4.0 to 10.0 mIU/L and normal serum fT4 levels (n = 64) were assessed using 24-hour urine iodine test results and iodine intake levels calculated using a semi-quantitative food frequency questionnaire. Dietary iodine restriction was not recommended for patients with an iodine intake in the normal range (group A, n = 13), but seaweed restriction was recommended for patients with high iodine intakes (group B, n = 33). Thyroid functions and iodine levels were rechecked after three months. Another eighteen patients were prescribed thyroid hormone replacement therapy according to clinical criteria.
Results: Median baseline iodine intake for the 64 patients was 290.61 μg/day, and median 24-hour urine iodine was 33.65 μmol/g of creatinine. The major source of dietary iodine was seaweed, which accounted for 72.2% of median baseline intake. Urine iodine and calculated iodine intake levels were positively correlated with serum TSH levels ($p < 0.001$ and $p = 0.027$, respectively), and calculated iodine intakes were significantly correlated with urine iodine levels ($p = 0.001$). In group B, iodine restriction significantly decreased urine iodine ($p = 0.042$) and TSH levels ($p = 0.004$), and conversion to euthyroid status was achieved in 16 of the 33 patients (48.5%).
Conclusion: Iodine intake and urine iodine levels are correlated with thyroid function in SCH patients, and dietary iodine restriction can aid functional thyroid recovery in patients with elevated iodine intakes.

Keywords: subclinical hypothyroidism; iodine; thyroid gland

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Other
This paper contains some contents of the first author's master dissertation.

INTRODUCTION

Subclinical hypothyroidism (SCH) is diagnosed when the serum thyroid-stimulating hormone (TSH) levels are above the normal range, and the serum free T4 (fT4) levels are within the normal range [1]. SCH is frequently diagnosed by primary care physicians and has relatively high prevalence when compared with overt hypothyroidism [1-3]. It is important to note that SCH can develop into overt hypothyroidism, requiring long term treatment [4], and SCH itself may be a risk factor for other diseases such as cardiovascular disease and cognitive impairment [1].

Previously, a large prospective survey for five years ignited interest in the relationship between high iodine intake and a higher prevalence for hypothyroidism, including SCH or autoimmune thyroiditis [2]. High urine iodine excretion in patients with untreated SCH predicted subsequent thyroid failure [5]. Significant association between SCH and higher iodine intake was also suggested from preterm infants (through breast milk) to children and adolescents [6,7].

Iodine intake and urine iodine excretion were reported relatively higher in South Korean (hereafter, Korean) patients, which depends primarily on the consumption levels of seaweed such as sea tangle and sea mustard [8]. By a semi-quantitative food frequency questionnaire (FFQ), the habitual ingestion of seaweed-containing dietary supplements with excessive iodine concentration in South Korea (hereafter, Korea) was suggested to have an adverse effect on thyroid function [9].

We speculate that lowering iodine intake can improve thyroid function and reduce the risk of progression to overt hypothyroidism in SCH patients with higher iodine intake. The aim of this study is to evaluate the effect of iodine intake on the short-term clinical course of SCH with higher iodine intake.

METHODS

Subjects

Patients diagnosed with SCH were referred to the outpatient clinic of the Severance Hospital in Seoul, Korea, between 2008 and 2009. SCH was defined by elevated serum TSH (4.0–10.0 mIU/L) with a normal serum fT4. **Fig. 1** depicts the flow of selections, tests, and follow-ups of participants for each visit. At the first visit (screening period), patients with the following criteria were excluded from the study: requiring any thyroid hormone replacement at the first visit or taking any other medication affecting thyroid function, aged less than 10 or more than 80 years, having any disease with the potential influence on thyroid function, past history of thyroid disease, or pregnancy within the last 12 months. Otherwise, patients (n = 77) were asked to revisit after three months without any medication or dietary education, after which four patients failed to follow-up.

At their second visit, patients were tested for thyroid function and autoimmune antibodies (serum fT4, TSH, thyroid peroxidase antibody [TPO-Ab], thyroglobulin antibody [Tg-Ab], and thyroglobulin levels), complete blood counts, serum chemical profiles including lipid profile, and 24-hour urine iodine excretion levels. Nine patients were not classified as SCH in the second visit, and only patients reconfirmed for SCH (n = 64) were finally analyzed for the relationship between iodine levels and thyroid function. Among these SCH patients, anyone who needed thyroid hormone replacement (n = 18) was excluded from 3-month

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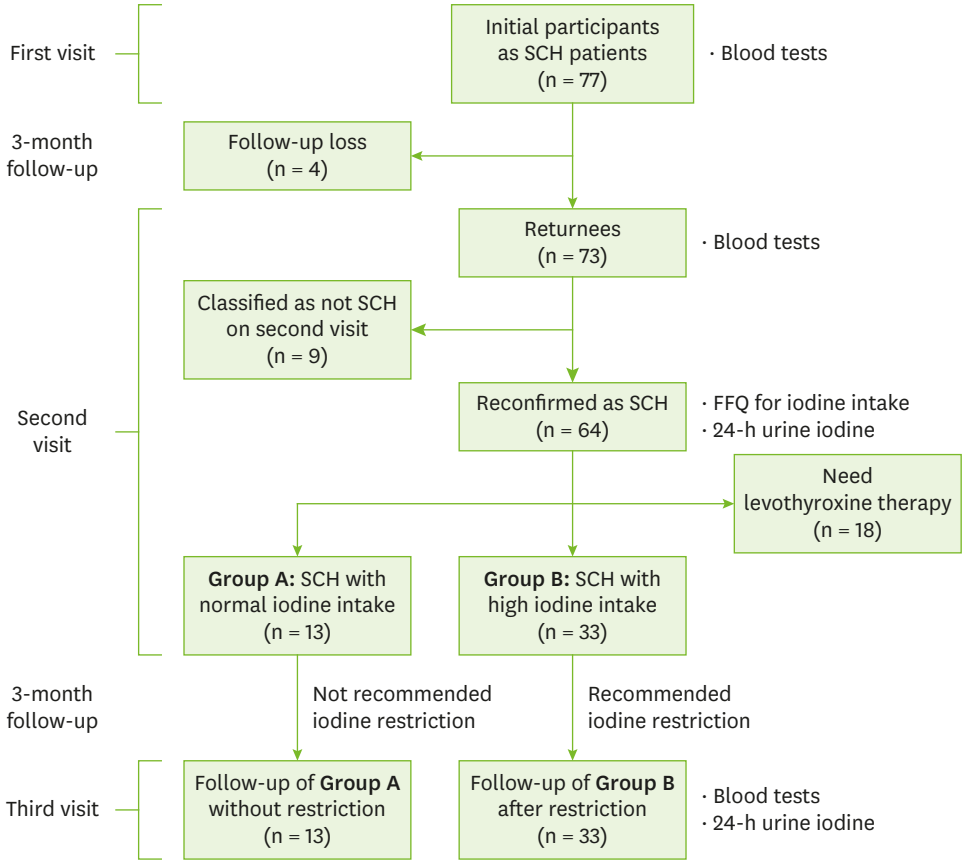

Fig. 1. Selection, assessment, grouping, and follow-up of participants with subclinical hypothyroidism.
SCH, subclinical hypothyroidism; FFQ, food frequency questionnaire.

follow-up study, and levothyroxine at 0.05 to 0.075 mg was prescribed for controlling hypercholesterolemia and symptoms suggestive of hypothyroidism, and preventing disease progression to overt hypothyroidism and development of goiters, according to the clinical guideline [10]. Other patients were classified into 2 groups according to their laboratory results and calculated iodine intake using a semi-quantitative FFQ: a patient who was in the reference range of 24-hour urine iodine (8.6–41.3 μmol/g of creatinine) with calculated iodine intake under 1,000 μg/day did not receive dietary iodine intake restriction (group A, n = 13); a patient who was over the reference range of 24-hour urine iodine and/or calculated iodine intake over 1,000 μg/day was subjected to dietary iodine intake restriction (group B, n = 33). For individuals in group B, a trained physician educated patients not to eat seaweed [sea tangle or kelp, sea tangle-containing dietary supplements, kelp broth, brown seaweed or sea mustard, laver, and green laver] or iodized salt.

Three months later, patients of groups A and B returned for follow-up tests including thyroid function, autoimmune antibodies, and 24-hour urine iodine. This study was reviewed and approved by the Institutional Review Board of Severance Hospital in Korea (4-2009-0415).

Measurement of dietary iodine intake

A semi-quantitative FFQ was designed to estimate the usual daily iodine intake for each subject over the last year (**Supplementary Table 1**) at the second visit. This questionnaire

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contained questions regarding average food intake frequency and intake amount. The food items included those with relatively high iodine contents, such as seaweed, that are generally consumed by Koreans. Every patient filled out the questionnaire, which was then reviewed by a single physician. The iodine content table for Korean foods by Moon et al. [11] was used for analysis. The dietary iodine intake level was calculated as follows:

$$I = \sum_{i=1}^{n} Fi \times Qi \times Ci$$

where I is the dietary iodine intake, F is the frequency of eating the food per day, Q is the portion size, C is the iodine content in the food, *i* is the food item, and *n* is the number of food items. To ensure the questionnaire's validity, calculated iodine intake levels were compared to 24-hour urine iodine excretion.

In addition, FFQ included questions about habitation location, age, height, weight, histories of alcohol intake and smoking (packs/year), disease history, and symptoms related to hypothyroidism, including generalized weakness, fatigue, cold intolerance, constipation, and weight gain.

Assays

Thyroid-stimulating hormone was measured by immunoradiometric assay using TSH-CTK-3 (DiaSorin, Saluggia, Italy), and fT4 was measured by radioimmunoassay using an AMEREX-MAB FT4 kit (Trinity Biotech plc, Wicklow, Ireland). Antibodies for thyroid peroxidase and thyroglobulin were measured by anti-TPO_n and anti-Tg_n KRYPTOR (BRAHMS, Henningsdorf, Germany). Normal ranges given by the manufacturer were as follows: TSH, 0.3–4.0 mIU/L; fT4, 0.73–1.95 ng/dL; TPO-Ab, 0–60 U/mL; and Tg-Ab, 0–60 U/mL. Thyroglobulin was measured by immunoradiometric assay with reference range of 0–39.2 ng/mL. Urine iodine level was determined using an ion selective electrode method [12] and expressed as measured 24-hour urine iodine excretion (μmol/g of creatinine) [13]. The normal urine iodine range given was 8.6–41.3 μmol/g of creatinine.

Statistical evaluation

Data were expressed as the mean ± SD when those showed a normal distribution or as medians with interquartile ranges (IQR) when those showed a skewed distribution. For comparison of the baseline characteristics between groups, Fisher's exact test and analysis of covariance (ANCOVA) with a post hoc Scheffe's procedure were used as appropriate. Pearson's correlation coefficient was used to test the correlation between any two variables. Linear regressions were used to examine the effect of calculated iodine intake from each food category on 24-hour urine iodine excretion. The Wilcoxon signed-rank test was used to analyze the changes according to iodine restriction in each group. The mixed-effect model was used to compare the changes according to iodine restriction between the groups. A $p < 0.05$ was considered significant. Statistical analyses were performed using SPSS for Windows (version 25.0; SPSS, Chicago, IL, USA). Serum levels of TSH, TPO-Ab, Tg-Ab, thyroglobulin, calculated iodine intake from the questionnaire, and 24-hour urine iodine excretion showed skewed distributions. Hence, those variables were transformed to logarithmic values prior to analysis.

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RESULTS

Basal characteristics of the SCH patients

A total of 77 patients were referred, and 13 patients were ineligible (four loss to follow-up; nine not classified as SCH by the blood test in the second visit). The basal characteristics of the other 64 SCH patients are shown in **Table 1**: 79.7% were female and the mean age at diagnosis was 49.8 ± 12.5 years. Twenty-nine patients (45.3%) showed high urine iodine excretion over the reference range. The median calculated iodine intake was 290.61 μg/day (IQR, 163.87–3,493.76), which is almost two-fold higher than the recommended daily allowance (150 μg/day) by the World Health Organization (WHO) or the Dietary Reference Intakes for Koreans [14,15]. Twenty-three patients (35.9%) showed calculated iodine intakes over 1,000 μg/day, and 16 patients (25.0%) showed calculated iodine intakes over 3,000 μg/day. Median 24-h urine iodine excretion was 33.65 (IQR, 19.68–88.30) μmol/g of creatinine. The urine iodine excretion and iodine intake calculated from the FFQ of group B were significantly higher than those of group A.

Correlation between urine iodine excretion and iodine intake calculated from the questionnaire

To check excessive iodine intake as an independent risk factor of SCH, correlations between each thyroid function test and urine iodine excretion or calculated iodine intake were analyzed (**Table 2**). A higher 24-h urine iodine level was significantly correlated with a higher

Table 1. Basal characteristics of included subclinical hypothyroidism patients and comparisons of the three groups

Variables	Group A: normal iodine intake (n = 13)	Group B: high iodine intake (n = 33)	Need levothyroxine therapy (n = 18)	Total (n = 64)	p-value
Age at diagnosis (yrs)	49.2 ± 18.1	51.7 ± 11.4	46.8 ± 9.2	49.8 ± 12.5	0.408
Male/female (n/n)	6/7	5/28	2/16	13/51	0.049
Body mass index (kg/m^2)	24.2 ± 3.5	23.3 ± 2.9	22.9 ± 2.6	23.3 ± 2.9	0.611
Family history of thyroid disease (no/yes)	9/2	25/5	13/5	47/12	0.632
Symptom of SCH (no/yes)	3/8	8/22	3/15	14/45	0.713
Free T4 (ng/dL)	1.02 ± 0.15	0.90 ± 0.18	0.87 ± 0.18	0.91 ± 0.18	0.074
TSH (mIU/L)	4.83 (4.49–5.64)	6.12 (4.38–7.39)	7.24 (6.38–8.89)	6.23 (4.49–7.46)	0.013[1)]
Tg-Ab (U/mL)	10.70 (5.50–16.60)	14.70 (7.67–35.15)	25.15 (10.88–63.30)	14.08 (7.56–41.82)	0.321
TPO-Ab (U/mL)	25.60 (15.10–819.49)	22.60 (11.17–35.90)	212.90 (17.50–1,004.33)	27.00 (13.78–237.28)	0.012[2)]
Thyroglobulin (ng/mL)	6.35 (1.50–15.57)	15.77 (6.20–25.50)	14.52 (6.23–34.54)	13.40 (4.93–24.49)	0.052
24-hrs urine iodine (μmol/g of creatinine)	23.40 (19.85–34.30)	55.10 (32.85–142.20)	21.70 (10.63–37.73)	33.65 (19.68–88.30)	0.037[3)]
Calculated iodine intake (μg/day)	194.73 (120.00–271.14)	1,042.93 (230.48–6,008.97)	249.85 (93.08–2,553.21)	290.61 (163.87–3,493.76)	0.017[4)]

Data are expressed as mean ± SD or median (interquartile range) (all such values). Group A includes patients within the reference range of 24-hour urine iodine with calculated iodine intake under 1,000 μg/day. Group B includes patients over the reference range of 24-hour urine iodine and/or calculated iodine intake over 1,000 μg/day. Patients who needed thyroid hormone replacement were classified in another group. Fisher's exact test was used for qualitative variables. Analysis of covariance with a post hoc Scheffe's procedure were used for quantitative variables, and sex was adjusted in the comparisons of all variables listed below body mass index.
SCH, subclinical hypothyroidism; TSH, thyroid-stimulating hormone; Tg-Ab, thyroglobulin antibody; TPO-Ab, thyroid peroxidase antibody
[1)]Post-hoc tests: Group A was different from the group needed levothyroxine therapy (p = 0.003). [2)]Post-hoc tests: Group B was different from the group needed levothyroxine therapy (p = 0.003). [3)]Post-hoc tests: Group B was different from groups A and the group needed levothyroxine therapy (p = 0.034 and 0.008, respectively). [4)]Post-hoc tests: Group B was different from group A (p = 0.005).

Table 2. Correlation between 24-hrs urine iodine excretion/calculated iodine intake from the FFQ and thyroid function test/thyroid antibodies (age- and sex-adjusted, n = 64)

Variables	Free T4	TSH	Tg-Ab	TPO-Ab	Thyroglobulin
24-hrs urine iodine					
Correlation coefficient	−0.062	0.434	0.052	−0.083	0.143
p-value	0.633	< 0.001	0.688	0.523	0.273
Calculated iodine from FFQ					
Correlation coefficient	−0.173	0.281	0.027	−0.078	0.059
p-value	0.183	0.027	0.832	0.549	0.653

The p-value was obtained by Pearson's correlation coefficient.
TSH, thyroid-stimulating hormone; Tg-Ab, thyroglobulin antibody; TPO-Ab, thyroid peroxidase antibody; FFQ, food frequency questionnaire.

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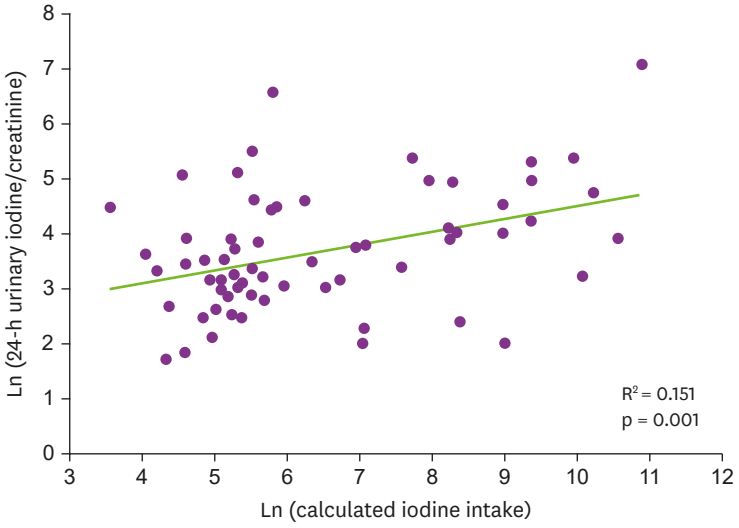

Fig. 2. Regression analysis between total iodine intake calculated from the food frequency questionnaire and 24-h urinary iodine excretion.
Variables were transformed into natural logarithmic values (Ln). Units before logarithmic transformation are μg/day for iodine intake and μmol/g of creatinine for 24-hour urine iodine. The p-value was obtained by Pearson's correlation coefficient (R).

serum TSH level ($p < 0.001$). A higher iodine intake level calculated from the FFQ was also closely related with a higher serum TSH level ($p = 0.027$). However, serum fT4 had no significant correlation with urine iodine excretion or calculated iodine intake level. None of serum Tg-Ab, TPO-Ab or thyroglobulin levels was correlated with any iodine profile.

The total amount of iodine intake was significantly correlated with 24-hour urine iodine excretion (**Fig. 2**). The contribution of each food to iodine intake is shown in **Table 3**. The major source of dietary iodine was seaweed (72.2% by median values), which is abundant in Korea and Korean diets [9]. Among the various types of seaweed, the most important source of dietary iodine was sea tangle with median 177.26 μg/day (0–2,178.26 μg/day), followed by sea mustard with median 35.09 μg/day (17.29–74.38 μg/day), and laver with median 28.06 μg/day (5.07–45.95 μg/day). Iodine intake from fish was also correlated with 24-hour urine iodine excretion.

Changes in thyroid function following different iodine restriction strategies

To check the compliance of patients who were recommended iodine-restricted diets, the differences in 24-hour urine iodine excretion between the second and third visits were compared (**Table 4**). The median 24-hour urine iodine excretion was significantly decreased

Table 3. Calculated amount of iodine intake from food and its contribution to 24-hour urine iodine excretion (n = 64)

Food group	Median (IQR) (μg/day)	Regression coefficient β	p-value	95% CI
Seaweed	209.91 (66.77–3,406.29)	0.187	0.002	0.071 to 0.303
Fish	24.93 (12.91–49.33)	0.308	0.018	0.054 to 0.562
Milk/dairy products	18.51 (1.55–48.29)	0.123	0.352	−0.385 to 0.139
Meat	10.07 (5.54–21.96)	0.025	0.877	−0.294 to 0.343
Vegetables	1.69 (0.80–3.64)	0.290	0.223	−0.034 to 0.245
All foods	290.61 (163.87–3,493.76)	0.207	0.001	0.092 to 0.370

Statistics were carried out using linear regression. The amount of iodine intake was calculated by the food frequency questionnaire.
IQR, interquartile range; CI, confidence interval.

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Table 4. Changes in urine iodine excretion and thyroid function/antibody titer according to iodine intake strategy

Variables	Group A: no iodine intake restriction (n = 13)			Group B: iodine intake restriction (n = 33)			Mixed effect model
	Second visit	Third visit	p-value	Second visit	Third visit	p-value	p-value
24-hrs urine iodine (μmol/g of creatinine)	23.40 (19.85–34.30)	40.80 (29.10–75.13)	0.012	55.10 (32.85–142.20)	37.10 (17.38–90.88)	0.042	0.017
Free T4 (ng/dL)	1.02 ± 0.15	0.99 ± 0.18	0.889	0.90 ± 0.18	1.00 ± 0.21	0.022	0.228
TSH (mIU/L)	4.83 (4.49–5.64)	5.12 (3.45–8.40)	0.093	6.12 (4.38–7.39)	3.86 (2.79–5.52)	0.004	0.013
Tg-Ab (U/mL)	10.70 (5.50–16.60)	6.10 (5.50–22.94)	0.735	14.70 (7.67–35.15)	9.51 (5.50–31.40)	0.276	0.645
TPO-Ab (U/mL)	25.60 (15.10–819.49)	25.09 (12.9–1,931.78)	0.499	22.60 (11.17–35.90)	9.60 (5.50–33.30)	0.014	0.067
Thyroglobulin (ng/mL)	6.35 (1.50–15.57)	9.09 (3.97–23.65)	0.093	15.77 (6.20–25.50)	9.61 (5.07–24.79)	0.003	0.004

Data are expressed as median (interquartile range) or mean ± SD. The p-value was obtained by Wilcoxon signed-rank test for comparison of second and third visits in each group or by mixed effect model adjusted for age and sex for comparison of inter-visit changes between groups.
TSH, thyroid-stimulating hormone; Tg-Ab, thyroglobulin antibody; TPO-Ab, thyroid peroxidase antibody.

in group B while increased in group A. Changes in the 24-h urine iodine excretion level in three months was significantly different between groups A and B (p = 0.017) according to the mixed-effect model, after adjustment for age and sex.

To verify whether thyroid function was improved after restriction of excessive iodine intake, thyroid hormone levels of patients between the second and third visits were compared (**Table 4**). In group B, after iodine restriction, the serum TSH level was significantly decreased and the serum fT4 level was significantly increased. The level of TPO-Ab was also decreased. Conversion from SCH to euthyroid status was observed in 16 patients (48.5%). In group A, however, there was no significant change in thyroid function or antibody titer between visits. There were no significant changes in complete blood count or serum chemical profile including lipid profile in either group (data not shown). Using a mixed-effect model, groups A and B were compared with respect to the changes between the two visits after adjustments for age and sex. Iodine restriction had a significant effect on the levels of serum TSH (p = 0.013) and thyroglobulin (p = 0.004) after adjustments. The TPO-Ab level showed a decreasing trend after iodine restriction (p = 0.067), although there was no difference in the fT4 level after adjustments (p = 0.228).

DISCUSSION

This study showed relatively higher iodine intake in SCH patients in Korea. Calculated iodine intake by FFQ was correlated significantly with the levels of 24-hour urine iodine excretion. In patients with higher iodine intake, recommendation of iodine intake restriction was compliant, and their thyroid function was ameliorated after restriction. These results emphasize the importance of checking and controlling iodine intake in clinical settings and imply possible improvement of thyroid function at least in this population.

In this study, higher iodine intake/excretion was significantly correlated with more severe impairment of thyroid function, consistent with previous studies of patients with SCH [16-18]. Iodine intake/excretion was correlated with TSH but not fT4 levels probably because all SCH patients were within normal fT4 ranges. To maintain normal thyroid function, thyroid hormone synthesis transiently reduces in the presence of excess iodine (acute Wolff-Chaikoff effect) [19]. When failing to escape from this phenomenon in susceptible individuals, persistent excess iodine may trigger thyroid dysfunction, which is one of the major explanations of the mechanism of iodine-induced thyroid dysfunction [20]. However, given that iodine levels in the group that required thyroid hormone replacement in our

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study were not higher than the overall mean, it cannot be interpreted that excessive iodine is the sole cause of thyroid dysfunction. This group showed higher TPO-Ab levels, implying more patients with autoimmune thyroiditis. Other suggested immune mechanisms by iodine include the immune reaction against the thyroid gland triggered by highly iodinated thyroglobulin [21] and increased expression of an adhesion molecule on thyrocytes causing immune cell infiltration [22].

Among the many dietary assessment methods available, semi-quantitative FFQ is one of the mostly commonly used methods to quantify dietary intake [23]. This type of FFQ for iodine has shown a significant correlation with 24-hour urine iodine excretion and 4-day weighed dietary record [24]. The iodine intake calculated by the FFQ that we developed in this study was also significantly correlated with urine iodine levels, validating the usefulness of the FFQ as a measurement tool. Even though our FFQ did not cover all the foods in the real world, the calculated iodine intake in SCH patients was relatively high, considering the recommendation of iodine intake of 150 μg/day for adults with a safe upper limit at 1,000 μg/day by WHO or tolerable upper limit of 1,100 μg/day by the American Thyroid Association [14,25,26]. In an analysis of data from the 2013–2015 Korea National Health and Nutrition Examination Survey (KNHANES) by Choi et al. [27], median iodine intake calculated in the Korean population was 352.1 μg/day, which is even relatively higher than our study. This difference might be from a different methodology because KNHANES used a 24-hour dietary recall method based on 855 food items. Lee et al. [28] conducted the Total Diet Study to estimate the dietary iodine intake of Koreans, whose median iodine intake was 129.0 μg/day. This estimation is relatively lower than our study, which might be derived from a different database of iodine concentration. However, the similarity of major iodine contribution by seaweed (55.7%, Choi et al. [27]; 77.4% Lee et al. [28]; and 72.2% in our study) implies validity of the FFQ that we developed. In another dietary evaluation for Korean thyroid cancer patients preparing for radioactive iodine therapy, seaweed was the largest contributor to iodine intake during the usual diet period and to iodine restriction during low-iodine diet period [29].

We confirmed the viability of using FFQ as a supplement to iodine assessment in clinical practice in this study. For example, a few patients had unexpectedly high 24-hour urine iodine excretion levels despite restrictions of high iodine containing food and low iodine intakes estimated by FFQ. In these patients, after a careful review of FFQ and interview, we found that they may have eaten processed foods with high levels of iodine-containing seasonings around the day of urine collection. The validity of the 24-hour urine excretion for iodine status can be diminished on these occasions. While widely accepted for population-based studies, 24-hour urine iodine excretion has wide intra-individual fluctuations. This is evidenced by the wide fluctuation of urinary iodine in group A between the second and third visits. Given that this group did not change their diet, this might imply day to day fluctuations. In another study to evaluate iodine status among patients with papillary thyroid cancer, spot urine iodine levels were correlated with calculated iodine intake by 24-hour recall methods but not by FFQ [30]. To determine the iodine levels in an individual, in addition to urine iodine levels, it will be necessary to combine an interview or a questionnaire for dietary intake as shown in the group assignment in our study. Moreover, Koreans may eat many other foods, such as iodide-rich salt, that possess high iodine contents. Considering these specific conditions, careful review is necessary when performing FFQ evaluations to confirm the main determinants of excess iodine intake prior to food restriction.

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Iodine restriction was related with improved thyroid function in SCH patients with high iodine intakes in this study. Furthermore, the trend of decreased TPO-Ab after iodine restriction suggests alleviation of thyroidal damage and inflammation in autoimmune thyroiditis, demonstrating the importance of adequate screening of iodine intake and proper management for SCH patients. Correction of reversible factors, including iodine intake regulation, should be considered in SCH patients as the benefit of thyroid hormone replacement can outweigh the risk only in specific candidates [1]. Studies of the relationship between iodine and SCH had been initially focused more on prevalent SCH in the iodine-depleted area [31,32] and supplement of iodine through dairy products [33,34], iodized salt [35,36], and iodized oil [36]. Recently, the iodine excess and its effect on thyroid dysfunction has attracted more attention [37], especially studies in coastal areas and countries rich in seaweed and fish [7,17,38]. Improvement in thyroid function after iodine restriction in overt hypothyroidism patients with excessive iodine intake has been previously demonstrated [39,40]. Recovery from growth retardation as well as improvement in thyroid function was demonstrated in juvenile hypothyroidism patients [41]. Future longitudinal studies may be necessary to check the long-term effects of iodine restriction in SCH patients with higher iodine intake.

The three-month interval between visits in group B was probably sufficient to detect the effects of iodine restriction. Urine iodine excretion was reported to be positively correlated with the serum TSH level of even one month later in SCH patients [5]. Previous studies have documented that a suitable duration of iodine restriction was 12 weeks for overt hypothyroidism patients [39,40], which implies that our three-month interval can be a good reference range for follow-up after iodine restriction in SCH patients. Considering the recommendation to repeat thyroid function test after 2-3 months in new SCH patients [42], it will be a practical strategy for a physician or a clinical nutritionist to assess iodine intake for SCH patients at their first visit and to recommend iodine restriction if necessary. Moreover, conversion from SCH to euthyroid status in half of the restriction group implies importance of iodine assessment in these subjects.

There are several limitations in this study. First, as aforementioned, the FFQ we designed for this study does not contain all items ingested, but rather a subset of them. Instead, the section for dietary seaweed was investigated in detail because seaweed has the highest iodine content, and its ingestion occupies the largest source of iodine intake in Korea. The iodine contents of foods vary according to region [8,43], and it is necessary to modulate the questionnaire by main sources of excess iodine intake in each region. Recently, the iodine database for Korean foods has been periodically revised [27], and applying these updated database may lead to a more accurate analysis. Second, for usual outpatient clinics with a single physician, this FFQ is rather long to be checked by patients and reviewed by the physician. A more shortened version of a validated questionnaire and a computing program for calculation will be necessary to apply in a real-world setting. Third, to measure urine iodine level, the ion selective electrode method was used, for which inductively coupled plasma-mass spectrometry has recently become the gold standard with high specificity and sensitivity [27,44]. Fourth, participants did not receive thyroid ultrasonography, which could have provided useful information on the disease's progression if done [45]. Fifth, this study was conducted in a single tertiary care institution, with a small number of participants (n = 33) in the iodine-restricted group. In addition, this is a short-term observational study and not a controlled randomized trial. groups A and B were divided according to iodine intake levels. When compared to the second visit, iodine intake in the third visit of group A

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increased while that of group B decreased. In general, if one has a group and divides it in two groups according to a parameter, the low group is expected to increase, and the high group is expected to decrease, called 'regression toward the mean'. A well-designed randomized controlled trial will be needed to confirm the key findings of this study.

SUMMARY

In our study, enrolled SCH patients showed relatively high baseline iodine intake and 24-hour urine iodine levels. Calculated iodine intake by the questionnaire was significantly correlated with urine iodine levels. The major source of dietary iodine was seaweed. The higher urine iodine content and calculated iodine intake were related with the higher serum TSH levels. Recommendation of iodine restriction in SCH patients with high iodine intake was confirmed by decreased urine iodine levels, and their serum TSH levels were significantly reduced. These results imply that iodine restriction could reverse hampered thyroid function in the SCH patient with high iodine intake and may increase the possibility of returning to euthyroid status without thyroid hormone replacement. More longitudinal studies need to be conducted to determine other possible effects of iodine restrictions on thyroid function and outcomes of SCH.

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SUPPLEMENTARY MATERIAL

Supplementary Table 1

The semi-quantitative FFQ designed to estimate the usual daily iodine intake in this study

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REFERENCES

1. Biondi B, Cappola AR, Cooper DS. Subclinical hypothyroidism: a review. JAMA 2019; 322(2): 153-160.
PUBMED | CROSSREF
2. Teng W, Shan Z, Teng X, Guan H, Li Y, Teng D, et al. Effect of iodine intake on thyroid diseases in China. N Engl J Med 2006; 354(26): 2783-2793.
PUBMED | CROSSREF
3. Hoogendoorn EH, Hermus AR, de Vegt F, Ross HA, Verbeek AL, Kiemeney LA, et al. Thyroid function and prevalence of anti-thyroperoxidase antibodies in a population with borderline sufficient iodine intake: influences of age and sex. Clin Chem 2006; 52(1): 104-111.
PUBMED | CROSSREF
4. Arrigo T, Wasniewska M, Crisafulli G, Lombardo F, Messina MF, Rulli I, et al. Subclinical hypothyroidism: the state of the art. J Endocrinol Invest 2008; 31(1): 79-84.
PUBMED | CROSSREF
5. Karmisholt J, Laurberg P. Serum TSH and serum thyroid peroxidase antibody fluctuate in parallel and high urinary iodine excretion predicts subsequent thyroid failure in a 1-year study of patients with untreated subclinical hypothyroidism. Eur J Endocrinol 2008; 158(2): 209-215.
PUBMED | CROSSREF

6. Chung HR, Shin CH, Yang SW, Choi CW, Kim BI. Subclinical hypothyroidism in Korean preterm infants associated with high levels of iodine in breast milk. J Clin Endocrinol Metab 2009; 94(11): 4444-4447.
PUBMED | CROSSREF
7. Kang MJ, Hwang IT, Chung HR. Excessive iodine intake and subclinical hypothyroidism in children and adolescents aged 6-19 years: results of the sixth Korean National Health and Nutrition Examination Survey, 2013-2015. Thyroid 2018; 28(6): 773-779.
PUBMED | CROSSREF
8. Kim JY, Moon SJ, Kim KR, Sohn CY, Oh JJ. Dietary iodine intake and urinary iodine excretion in normal Korean adults. Yonsei Med J 1998; 39(4): 355-362.
PUBMED | CROSSREF
9. Kim JY, Kim KR. Dietary iodine intake and urinary iodine excretion in patients with thyroid diseases. Yonsei Med J 2000; 41(1): 22-28.
PUBMED | CROSSREF
10. Garber JR, Cobin RH, Gharib H, Hennessey JV, Klein I, Mechanick JI, et al. Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. Endocr Pract 2012; 18(6): 988-1028.
PUBMED | CROSSREF
11. Moon SJ, Kim JY, Chung YJ, Chung YS. The iodine content in common Korean foods. Korean J Nutr 1998; 31(2): 206-212.
12. Zhang W, Mnatsakanov A, Hower R, Cantor H, Wang Y. Urinary iodine assays and ionophore based potentiometric iodide sensors. Front Biosci 2005; 10(1-3): 88-93.
PUBMED | CROSSREF
13. Konno N, Yuri K, Miura K, Kumagai M, Murakami S. Clinical evaluation of the iodide/creatinine ratio of casual urine samples as an index of daily iodide excretion in a population study. Endocr J 1993; 40(1): 163-169.
PUBMED | CROSSREF
14. World Health Organization; United Nations Children's Fund; International Council for the Control of Iodine Deficiency Disorders. Recommended iodine levels in salt and guidelines for monitoring their adequacy and effectiveness. Geneva: World Health Organization; 1996.
15. Ministry of Health and Welfare; The Korean Nutrition Society. Dietary reference intakes for Koreans 2020. Sejong: Ministry of Health and Welfare; 2020.
16. Chong W, Shan ZY, Sun W, Teng WP. Multivariate analysis of relationships between iodine biological exposure and subclinical thyroid dysfunctions. Chin Med Sci J 2005; 20(3): 202-205.
PUBMED
17. Konno N, Makita H, Yuri K, Iizuka N, Kawasaki K. Association between dietary iodine intake and prevalence of subclinical hypothyroidism in the coastal regions of Japan. J Clin Endocrinol Metab 1994; 78(2): 393-397.
PUBMED
18. Alsayed A, Gad AM, Abdel-Baset H, Abdel-Fattah A, Ahmed A, Azab A. Excess urinary iodine is associated with autoimmune subclinical hypothyroidism among Egyptian women. Endocr J 2008; 55(3): 601-605.
PUBMED | CROSSREF
19. Wolff J, Chaikoff IL. Plasma inorganic iodide as a homeostatic regulator of thyroid function. J Biol Chem 1948; 174(2): 555-564.
PUBMED | CROSSREF
20. Markou K, Georgopoulos N, Kyriazopoulou V, Vagenakis AG. Iodine-Induced hypothyroidism. Thyroid 2001; 11(5): 501-510.
PUBMED | CROSSREF
21. Luo Y, Kawashima A, Ishido Y, Yoshihara A, Oda K, Hiroi N, et al. Iodine excess as an environmental risk factor for autoimmune thyroid disease. Int J Mol Sci 2014; 15(7): 12895-12912.
PUBMED | CROSSREF
22. Sharma RB, Alegria JD, Talor MV, Rose NR, Caturegli P, Burek CL. Iodine and IFN-γ synergistically enhance intercellular adhesion molecule 1 expression on NOD.H2^{h4} mouse thyrocytes. J Immunol 2005; 174(12): 7740-7745.
PUBMED | CROSSREF
23. Thompson FE, Byers T. Dietary assessment resource manual. J Nutr 1994; 124(11 Suppl): 2245S-2317S.
PUBMED | CROSSREF
24. Rasmussen LB, Ovesen L, Bülow I, Jørgensen T, Knudsen N, Laurberg P, et al. Evaluation of a semi-quantitative food frequency questionnaire to estimate iodine intake. Eur J Clin Nutr 2001; 55(4): 287-292.
PUBMED | CROSSREF

25. World Health Organization. Iodine and health: eliminating iodine deficiency disorders safely through salt iodization. Geneva: World Health Organization; 1994.
26. Leung AM, Avram AM, Brenner AV, Duntas LH, Ehrenkranz J, Hennessey JV, et al. Potential risks of excess iodine ingestion and exposure: statement by the American Thyroid Association Public Health Committee. Thyroid 2015; 25(2): 145-146.
PUBMED | CROSSREF
27. Choi JY, Ju DL, Song Y. Revision of an iodine database for Korean foods and evaluation of dietary iodine and urinary iodine in Korean adults using 2013-2015 Korea National Health and Nutrition Examination Survey. J Nutr Health 2020; 53(3): 271-287.
CROSSREF
28. Lee J, Yeoh Y, Seo MJ, Lee GH, Kim C. Estimation of dietary iodine intake of Koreans through a Total Diet Study (TDS). Korean J Community Nutr 2021; 26(1): 48-55.
CROSSREF
29. Ju DL, Park YJ, Paik HY, Kim MJ, Park S, Jung KY, et al. Dietary evaluation of a low-iodine diet in Korean thyroid cancer patients preparing for radioactive iodine therapy in an iodine-rich region. Nutr Res Pract 2016; 10(2): 167-174.
PUBMED | CROSSREF
30. Choi JY, Lee JH, Song Y. Evaluation of iodine status among Korean patients with papillary thyroid cancer using dietary and urinary iodine. Endocrinol Metab (Seoul) 2021; 36(3): 607-618.
PUBMED | CROSSREF
31. Skeaff SA, Thomson CD, Gibson RS. Mild iodine deficiency in a sample of New Zealand schoolchildren. Eur J Clin Nutr 2002; 56(12): 1169-1175.
PUBMED | CROSSREF
32. Hiéronimus S, Bec-Roche M, Ferrari P, Chevalier N, Fénichel P, Brucker-Davis F. Iodine status and thyroid function of 330 pregnant women from Nice area assessed during the second part of pregnancy. Ann Endocrinol (Paris) 2009; 70(4): 218-224.
PUBMED | CROSSREF
33. Girelli ME, Coin P, Mian C, Nacamulli D, Zambonin L, Piccolo M, et al. Milk represents an important source of iodine in schoolchildren of the Veneto region, Italy. J Endocrinol Invest 2004; 27(8): 709-713.
PUBMED | CROSSREF
34. Brantsaeter AL, Haugen M, Julshamn K, Alexander J, Meltzer HM. Evaluation of urinary iodine excretion as a biomarker for intake of milk and dairy products in pregnant women in the Norwegian Mother and Child Cohort Study (MoBa). Eur J Clin Nutr 2009; 63(3): 347-354.
PUBMED | CROSSREF
35. Mousavi SM, Tavakoli N, Mardan F. Risk factors for goiter in primary school girls in Qom city of Iran. Eur J Clin Nutr 2006; 60(3): 426-433.
PUBMED | CROSSREF
36. Zimmermann MB, Aeberli I, Melse-Boonstra A, Grimci L, Bridson J, Chaouki N, et al. Iodine treatment in children with subclinical hypothyroidism due to chronic iodine deficiency decreases thyrotropin and C-peptide concentrations and improves the lipid profile. Thyroid 2009; 19(10): 1099-1104.
PUBMED | CROSSREF
37. Sun X, Shan Z, Teng W. Effects of increased iodine intake on thyroid disorders. Endocrinol Metab (Seoul) 2014; 29(3): 240-247.
PUBMED | CROSSREF
38. Han MR, Park YJ, Paik HY, Song Y. An iodine database for common Korean foods and the association between iodine intake and thyroid disease in Korean adults. Int J Thyroidol 2015; 8(2): 170-182.
CROSSREF
39. Kasagi K, Iwata M, Misaki T, Konishi J. Effect of iodine restriction on thyroid function in patients with primary hypothyroidism. Thyroid 2003; 13(6): 561-567.
PUBMED | CROSSREF
40. Yoon SJ, Choi SR, Kim DM, Kim JU, Kim KW, Ahn CW, et al. The effect of iodine restriction on thyroid function in patients with hypothyroidism due to Hashimoto's thyroiditis. Yonsei Med J 2003; 44(2): 227-235.
PUBMED | CROSSREF
41. Okamura K, Sato K, Ikenoue H, Nakagawa M, Kuroda T, Yoshinari M, et al. Primary hypothyroidism manifested in childhood with special reference to various types of reversible hypothyroidism. Eur J Endocrinol 1994; 131(2): 131-137.
PUBMED | CROSSREF
42. Peeters RP. Subclinical hypothyroidism. N Engl J Med 2017; 376(26): 2556-2565.
PUBMED | CROSSREF

43. Haldimann M, Alt A, Blanc A, Blondeau K. Iodine content of food groups. J Food Compos Anal 2005; 18(6): 461-471.
CROSSREF

44. Zywicki RS, Sullivan DM, Bao L, Bolong W, Boyd M Jr, Chen SY, et al. Determination of total iodine in infant formula and adult/pediatric nutritional formula by inductively coupled plasma-mass spectrometry (ICP-MS): collaborative study, final action 2012.15. J AOAC Int 2015; 98(5): 1407-1416.
PUBMED | CROSSREF

45. Shin DY, Kim EK, Lee EJ. Role of ultrasonography in outcome prediction in subclinical hypothyroid patients treated with levothyroxine. Endocr J 2010; 57(1): 15-22.
PUBMED | CROSSREF