Excessive Iodine Intake Does Not Increase the Recurrence Rate of Graves' Disease after Withdrawal of the Antithyroid Drug in an Iodine-Replete Area

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Key Words

Hyperthyroidism · Graves' disease · Antithyroid drug · Iodine · Korea

Abstract

Background and Objectives: The relationship between iodine intake and effects of antithyroid drugs (ATD) for Graves' disease, especially in iodine-deficient areas, has been demonstrated in many studies. However, it was not clear how chronic high iodine intake influenced the effectiveness of ATD in an iodine-replete area. This study aimed to clarify the effect of iodine intake on clinical outcomes of Graves' disease after discontinuation of ATD in Korea, an iodine-replete area. **Methods:** A total of 142 patients with Graves' disease who visited the outpatient clinic regularly and stopped their ATD between October 2011 and April 2013 were enrolled in our study. Urinary iodine concentration (UIC) was measured just before and after the discontinuation of ATD. **Results:** Median UIC was not significantly different between the remission and relapse groups, as well as among the four treatment groups (group 1, remission after initial treatment; group 2, remission after repeated treatment; group 3, early relapse within a year; group 4, late relapse after a year). Re-

mission rates did not show a significant difference between the excessive iodine intake (UIC ≥ 300 $\mu\text{g/l}$) and average iodine intake groups (UIC < 300 $\mu\text{g/l}$). **Conclusions:** The present study suggests that excessive iodine intake does not have an effect on the clinical outcomes of Graves' disease in an iodine-replete area, and therefore diet control with iodine restriction might not be necessary in the management of Graves' disease.

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Introduction

As antithyroid drugs (ATD) still remain the preferred modality of treatment for Graves' disease [1, 2], clinical competence and appropriate management taking into account an array of clinical and laboratory features related to the subsequent risk of relapse have been emphasized [3]. Many studies have suggested that variation in iodine intake affects the efficacy of ATD in patients with Graves' disease. Taurog [4] demonstrated that intrathyroidal degradation of ATD was influenced by intrathyroid iodide content, and that chronic exposure to excessive iodine

resulted in a decrease in ATD uptake in thyrocytes. Other studies have reported that the remission rate is parallel to the estimates of declining iodine intake, and a high iodine intake adversely influences the effectiveness of ATD [5, 6]. However, a recent study in Japan, a country with an excessive iodine intake, showed that iodine restriction did not ameliorate the effect of ATD [7]. Korea is also one of the countries with excessive iodine intake, but the remission rate is not too low compared to that in other countries reported previously [8, 9]. Therefore, clarifying the effects of iodine intake on the relapse rate, especially in an iodine-replete area, is warranted for appropriate management after ATD discontinuation in patients with Graves' disease.

Measurement of urinary iodine concentration (UIC) in 24-hour urine samples is considered the best method to evaluate the status of iodine intake [10, 11]. Urinary iodine/creatinine ratio (I/Cr) from a random, spot-urine sample could serve as a useful and reliable alternative to 24-hour urine collection [12, 13].

In the present study, we evaluated urinary iodine excretion and the clinical course of patients with Graves' disease after discontinuation of ATD; with the aim of identifying the effect of iodine intake on clinical outcomes, especially in an iodine-replete country.

Methods

Patients and Study Design

A total of 253 patients with Graves' disease who visited the Thyroid Center at Samsung Medical Center regularly between October 2011 and April 2013 were initially screened in the study. All the patients were diagnosed based on clinical assessment, elevated serum T3 and free T4 levels, suppressed serum TSH levels, and/or increased ^{99m}Tc uptake on thyroid scan. We included the patients who had taken ATD for at least 12 months and then stopped their ATD based on the following criteria: normalization of increased T3 and free T4, restoration of suppressed TSH, and increased anti-TSH receptor antibody (TRAb). Patients who were followed-up more than 12 months after therapy cessation were finally included. Urine iodine was measured just before and after the discontinuation of ATD without offering any information about the test to the patients. Patients who were pregnant, underwent regular computer tomography, and underwent radioiodine therapy or surgery were also excluded. After exclusion, 142 patients were finally enrolled in our study. One hundred and twenty-two patients were treated with methimazole/carbimazole, and the remaining 20 patients were treated with propylthiouracil. The size of the thyroid gland was recorded by a single observer (J.H.C.), and pretreatment large goiter was confirmed as being visible and large (>40 g) on inspection and palpation during the examination. The goiter size was considered to be decreased if it was reduced by more than 30% of the pretreatment size at the end of ATD. Ophthalmopathy was

classified according to the Werner's criteria [14, 15] as absent (class 0–1) or present (class 2–6). Remission was defined as a euthyroid state maintained for at least more than a year; relapse was defined as apparent recurrence of hyperthyroidism with laboratory findings such as suppressed TSH and elevated free T4 during the follow-up period after discontinuation of ATD. Patients were divided into remission ($n = 104$) and relapse ($n = 38$) groups. They were also subdivided into four subgroups: remission after initial treatment (group 1, $n = 76$), remission after repeated treatment (group 2, $n = 28$), early relapse within a year (group 3, $n = 26$), and late relapse after a year (group 4, $n = 12$). This study was approved by the institutional review board of Samsung Medical Center.

Measurements

Urinary Iodine and Creatinine

UIC was measured by inductively coupled plasma-mass spectrometry (ICP-MS) using the Agilent 7500 series instrument (Agilent Technologies, Inc., Tokyo, Japan), which has been demonstrated to be extremely accurate in measuring UIC [16–19]. The intraday coefficient of variation for UIC ranged from 0.3 to 1.2% and the interday coefficient of variation ranged from 1.4 to 3.3%. Urinary creatinine was measured using the Cobas Integra 800 instrument (Roche Diagnostics, Basel, Switzerland). UIC was expressed as simple UIC ($\mu\text{g/l}$) and I/Cr ratio ($\mu\text{g/g Cr}$) from spot-urine samples. During the follow-up period, spot-urine samples were checked more than 2 times for UIC.

Thyroid Function Tests and Thyroid Antibodies

Serum T3, free T4, and TSH concentrations were measured using commercialized radioimmunoassay kits (Immunotech, Marseille, France). All samples were run in duplicate. The reference ranges of T3, free T4, and TSH were 1.1–2.9 nmol/l, 10–23 pmol/l, and 0.40–4.20 mU/l, respectively. TRAb titer was measured by a radioreceptor assay using TRAK human kit (Brahms GmbH, Hennigsdorf, Germany) [20]. TRAb values <1.0 mU/l were regarded as negative.

Statistical Analysis

Statistical analysis was performed using the SPSS statistics 21.0 (SPSS Inc., Chicago, Ill., USA). A Mann-Whitney test and t test were used for comparing clinical characteristics between the remission and relapse groups. A Kruskal-Wallis test and ANOVA were used for comparisons among the four groups. An exact χ^2 test was performed to compare remission and relapse rates between excessive and average iodine intake group. Subgroup analysis for the age groups was performed by the Kruskal-Wallis test. Bonferroni's correction was applied to the post hoc analysis of the between-age group comparisons to allow for the number of comparisons performed. $p < 0.05$ was considered statistically significant.

Results

Comparisons of Clinical and Laboratory Features between the Remission and Relapse Groups (Table 1)

The remission group included 104 patients and the relapse group included 38 patients. Mean duration of fol-

Table 1. Comparisons of clinical and laboratory features between the remission and relapse groups

	Remission (n = 104)	Relapse (n = 38)	p
Age, years	47±12	45±13	n.s.
Women	69 (66.3)	26 (68.4)	n.s.
Treatment duration, months	27±22	26±23	n.s.
Follow-up duration, months	49±26	57±24	n.s.
Follow-up duration since withdrawal of ATD, months	20±8	29±12	<0.001
Pretreatment large goiter (>40 g)	19 (18.3)	5 (13.2)	n.s.
Posttreatment goiter decrease (>30%)	46 (44.2)	11 (28.9)	n.s.
Ophthalmopathy	11 (10.6)	5 (13.2)	n.s.
Pretreatment serum T3, nmol/l	3.6 (2.7–4.6)	3.7 (2.9–4.9)	n.s.
Pretreatment serum free T4, pmol/l	37 (30–45)	35 (28–50)	n.s.
Pretreatment serum TSH, mU/l	0.01 (0.01–0.03)	0.01 (0.01–0.04)	n.s.
Pretreatment serum TRAb, IU/l	39.3 (10.6–74.4)	28.4 (6.0–58.0)	n.s.
Pretreatment high TRAb (>30 IU/l)	60 (57.7)	21 (55.3)	n.s.
Posttreatment serum TRAb, IU/l	0.6 (0.2–1.6)	0.8 (0.3–3.7)	n.s.
History of retreatment after relapse	28 (26.9)	18 (47.4)	0.02
UIC, µg/l	412 (187–1,438)	408 (272–1,274)	n.s.
Urine I/Cr, µg/g Cr	309 (146–948)	320 (145–1,079)	n.s.

Data expressed as n (%), means ± SD, or medians (interquartile range). n.s. = Not significant.

low-up after withdrawal of the ATD was 23 months. Clinical and laboratory features including median UIC and urinary I/Cr were not different between the two groups.

Comparisons of Clinical and Laboratory Features among the Four Treatment Groups (Table 2)

Early relapse of hyperthyroidism within a year after ATD withdrawal was observed in 26 (68%) of 38 patients and the mean time to relapse was 7 months. However, 12 patients (32%) had a late relapse after a year and the mean time to relapse was 18 months. Pretreatment serum TRAb levels in group 1 were higher than those in group 2 ($p = 0.006$). Median UIC and urinary I/Cr levels were higher in group 4 than in group 3 in tendency, but the difference was not significant ($p = 0.9$). Early relapse within a year after ATD withdrawal was not dependent on whether it had been a retreatment or not ($p = 0.20$).

Comparisons of Remission Rates between the Average and Excessive Iodine Intake Groups

Based on the average value of UIC (358 µg/l) from previous data in Koreans (data not published), patients with UIC less than 300 µg/l were stratified into the average io-

dine intake group and UIC more than 300 µg/l into the excessive iodine intake group. The remission rate was similar in the two groups (table 3). Subgroup analysis for the age groups (<40, 40–49, 50–59, and ≥60 years of age) was performed considering the discrepancy of iodine intake amount. Median urinary I/Cr was significantly lower in the group under 40 than in the group above 60 years of age (233.4 µg/g Cr, 870.4 µg/g Cr; $p = 0.003$); however, the remission rate showed no difference ($p = 0.8$, data not shown).

Discussion

The long-term remission rate after ATD treatment in patients with Graves' disease has been reported to be approximately 50%, ranging from 30 to 70% [8, 9]. In agreement with the majority of data reported in the literature, relapse of hyperthyroidism was more frequent in the first year after drug withdrawal [21–24]. Thus, if serum T3, free T4, and TSH levels are maintained within the normal range for at least 1 year after withdrawal of ATD, remission can be considered [2]. Because a large proportion of patients with Graves' disease in Korea prefer ATD

Table 2. Comparisons of clinical and laboratory features among the four treatment groups

	Remission (n = 104)		Relapse (n = 38)	
	group 1 (n = 76)	group 2 (n = 28)	group 3 (n = 26)	group 4 (n = 12)
Age, years	46±12	49±12	48±13	39±12
Women	51 (67.1)	18 (64.2)	16 (61.5)	10 (83.3)
Treatment duration, months	29±22	22±20	24±21	30±28
Follow-up duration, months	49±26	51±26	51±21	67±26
Follow-up duration since withdrawal of ATD, months	19±8 ^a	21±8 ^a	26±14	35±5 ^a
History of relapse	0	28 (100)	10 (38.4)	8 (66.6)
Pretreatment large goiter (>40 g)	15 (19.7)	4 (14.3)	4 (16%)	1 (7.7)
Posttreatment goiter decrease (>30%)	36 (47.4)	10 (35.7)	8 (30.8)	3 (25)
Ophthalmopathy	7 (9.2)	4 (14.3)	4 (16)	1 (7.7)
Pretreatment serum T3, nmol/l	3.8 (3.3–4.6)	3.2 (2.2–4.6)	3.6 (2.6–5.0)	3.7 (2.6–5.0)
Pretreatment serum free T4, pmol/l	40 (31–45)	36 (26–45)	35 (26–53)	36 (31–50)
Pretreatment serum TSH, mU/l	0.01 (0.01–0.03)	0.01 (0.01–0.04)	0.01 (0.01–0.02)	0.02 (0.01–0.04)
Pretreatment serum TRAb, IU/l	53.3 (24.5–78.2) ^b	19.1 (3.3–54.5) ^b	21.4 (4.5–57.4)	37.2 (10.3–58.2)
Pretreatment high TRAb (>30 IU/l)	50 (65.8) ^c	10 (35.7) ^c	12 (46.2)	9 (75)
Posttreatment serum TRAb, IU/l	0.7 (0.2–1.7)	0.5 (0.2–1.6)	0.7 (0.4–3.7)	1.6 (0.1–4.4)
UIC, µg/l	453 (176–1,535)	402 (246–699)	364 (240–1,070)	790 (338–925)
Urine I/Cr, µg/g Cr	307 (120–1,029)	320 (240–627)	285 (145–1,003)	315 (151–1,060)

Data expressed as n (%), means ± SD, or medians (interquartile range). ^a p < 0.001 (group 1 vs. group 4, group 2 vs. group 4). ^b p = 0.009 (group 1 vs. group 2). ^c p = 0.006 (group 1 vs. group 2).

Table 3. Comparisons of remission and relapse rates between the average iodine intake group (UIC <300 µg/l) and the excessive iodine intake group (UIC ≥300 µg/l)

	UIC <300 µg/l	UIC ≥300 µg/l	p
Remission	41 (78.8)	63 (70)	0.20
Relapse	11 (21.2)	27 (30)	

Data expressed as n (%).

for retreatment as well as initial treatment compared to alternative modalities [2], predicting the clinical outcome following ATD treatment is important for most physicians.

A meta-analysis showed that maintenance of ATD longer than 18 months did not improve the remission rate in adults [25], most of the patients in our study were treated for 12–36 months (mean: 27). Under consistent treatment conditions, whether the dietary iodine intake actually affects the remission rate after discontinuing ATD is an important issue facing physicians in Korea.

Hence, we conducted this study to investigate the effects of iodine intake on clinical outcomes following withdrawal of ATD. There are not an adequate number of studies analyzing the direct correlation between iodine intake and remission or relapse rate after withdrawal of ATD. There are studies showing that iodine supplementation increases the recurrence rate [26] and administration of pharmacological doses of iodine in patients with previous ATD treatment for Graves' disease reportedly led to development of hyperthyroidism [27]. However, considering the discrepancy in iodine intake across the

countries, clinical outcomes according to the amount of iodine intake especially in iodine-replete area are warranted. According to a recent study, median UIC and urinary I/Cr levels in 1,072 Korean euthyroid patients were 358 µg/l (24–9,224) and 341 µg/g Cr, respectively (data not published), which were higher than those reported in other countries. In our study group, median UIC and urinary I/Cr levels were 410 µg/l and 314 µg/g Cr, respectively.

Median UIC and urinary I/Cr levels were not significantly different between the remission and relapse groups; as well as among the four treatment groups. Remission and relapse rates were similar between the excessive (≥ 300 µg/l) and average iodine intake (< 300 µg/l) groups. In young patients less than 40 years of age who had a relatively lower iodine intake, median urinary I/Cr levels tended to be higher in patients who experienced a relapse than in those who were in remission; however, it was not statistically significant.

There are several studies describing the significance of the relationship between iodine intake and the efficacy of ATD treatment. Some reports proposed that increases in iodine intake might be responsible for the decreased effectiveness of the ATD, thereby resulting in a reduced remission rate. They reported that relative resistance to ATD was seen in patients from an iodine-sufficient area in contrast to more successful outcome seen in comparable patients from an iodine-deficient area [6]. Another study also reported that the remission rate was parallel to the estimates of declining iodine intake, and high iodine intake adversely influenced the effectiveness of ATD [5]. Taurog [4] demonstrated that intrathyroidal degradation of ATD in vitro was influenced by intrathyroidal iodide content, and that chronic exposure to excessive iodine intake resulted in a decrease in uptake into thyrocytes and rapid excretion of ATD. In addition, it has already been documented that excessive iodine ingestion may precipitate or aggravate thyrotoxicosis [28]. This effect can be attributed to the fact that iodine is a substrate for excessive hormone biosynthesis in autonomously functioning thyroid glands. However, a high relapse rate of up to 67.5% has been found in Copenhagen, in which the iodine intake is relatively low compared to other countries following long-term treatment with ATD [29].

In contrast with the inconsistent results from iodine-deficient areas, the relationship between iodine intake and clinical outcome of Graves' disease in iodine-replete areas has not been evaluated in an adequate number of studies. In a recent interventional study from Japan, a

country with an excessive iodine intake, Hiraiwa et al. [7] demonstrated that restriction of dietary iodine did not ameliorate the effect of ATD on Graves' disease. They interpreted that the negative result could be attributable to unique dietary factors in their population or previous exposure to an iodine-rich diet, and that the thyroid probably had a large reservoir of preformed thyroid hormones. Actually, iodine-induced hyperthyroidism is more common in iodine-deficient areas than in iodine-sufficient areas [30]. Therefore, after discontinuation of treatment for Graves' disease, the amount of iodine intake might not alter the intrinsic regulatory mechanism of thyroid hormone synthesis, especially in the environment of chronic exposure to sufficient dietary iodine.

Initial and posttreatment clinical and laboratory features (table 1), which are known as the subsequent risk factors of relapse [3], did not show a significant difference in the remission and relapse groups. High TRAb levels were more frequent in group 1 compared to group 2 (table 2). This finding can be interpreted as follows: hyperthyroid patients with low TRAb levels could easily achieve remission even after retreatment, or patients who had a history of relapse were followed regularly so that relapse could be detected earlier with low TRAb levels. Patients with retreatment were also included in the groups for analysis, so those clinical and laboratory features were assessed at different time points compared to the previous study [3]. Therefore, the factors, which are known to predict risk of relapse, obtained in this study should be interpreted with caution. Additionally, our study was not designed for assessing these factors as the primary endpoint. Meanwhile, under similar conditions of these clinical features distributed evenly among the treatment groups, comparison of the UIC and urinary I/Cr levels among the groups became more significant.

There are some limitations to our study. First, remission in our study was defined as a euthyroid state maintained for more than a year after discontinuation of ATD. There could be certain cases that relapsed after the period of follow-up, after a year of remission. We could not exclude this possibility, and relapse may have occurred. However, most of the data reported in the literature suggest that the relapse rate is higher in the first year after ATD withdrawal [21–24]. Furthermore, only 1.9% (2/104) of the patients in the remission group was followed for less than 20 months (17 and 19 months, respectively). Second, the estimated UIC might vary depending on the recent diet. Therefore, we calculated the average value of UIC in their repeated spot-urine samples, while almost all of our patients showed an analogical tendency

in UIC (data not shown). Median UIC and urinary I/Cr levels indicate the usual dietary habits before or after the discontinuation of ATD. Third, this study was not an intervention study that directly confirms the causality between iodine intake and clinical outcome of Graves' disease. We already know that many studies have described the physiologic relationship between iodine intake and hyperthyroidism. Therefore, intervention studies with iodine restriction will be more helpful in the future to see the clinical outcome of Graves' disease in iodine-replete area.

In conclusion, our study confirms that excessive iodine intake does not have an effect on the clinical outcomes of Graves' disease in an iodine-replete area. Thus, dietary iodine restriction might not be necessary during the course of ATD for Graves' disease and after discontinuation, in an iodine-replete area. Further clarification with a large-scaled intervention study would be helpful in management of patients with Graves' disease in an iodine-replete area.

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Disclosure Statement

The authors declare that there is no conflict of interest.

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