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Inhibitory effect of low-dose inorganic iodine on thyroidal radioactive iodine uptake in healthy Japanese adults

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Abstract. In the event of a nuclear power plant accident, prophylactic administration of potassium iodide (KI) is recommended to prevent thyroid damage due to uptake of radioiodine. To assess the inhibitory effect of low-dose inorganic iodine on thyroidal radioactive iodine uptake (RAIU) in healthy adults without dietary iodine restriction, single or repeated doses of 10 mg inorganic iodine solution were given to 22 Japanese volunteers, 18 men and 4 women with the mean age of 35.7 years, between 2011 and 2013. Changes in urinary iodine excretion, thyroid function and 24-hour RAIU were also evaluated. The median 24-hour RAIU without iodine restriction was 13 % (range, 5-26 %). A single-dose of 10 mg inorganic iodine suppressed the median 24-hour RAIU measured one hour after iodine administration to 3 % (range, 1-7 %) and, in 90.9% of 22 participants their 24-hour RAIU was < 5 %. For seven participants given 10 mg of inorganic iodine daily for 14 days, the median 24-hour RAIU measured at 24 hours after the last administration of iodine was 6 % (range, 2-12 %), although the inhibitory effect was diminished in two participants. Serum thyroid stimulating hormone concentration was slightly elevated in three participants without decreased serum FT3 and FT4 levels. We conclude that a single-dose of 10 mg inorganic iodine is sufficient to inhibit RAIU in adults, although the inhibitory effect of repeated-dose on RAIU is diminished when KI is given once daily. The dose, duration or interval of iodine administration should be evaluated in iodine-sufficient regions in a future.

Key words: Inorganic iodine, Potassium iodide, Thyroidal uptake, Radioiodine

WHEN a nuclear power plant accident occurs, prophylactic administration of stable iodine, that is, potassium iodide (KI) is recommended to prevent health damage due to radioiodine [1, 2]. Stable iodine given shortly before, during, or immediately after exposure to radioiodine reduces the uptake of radioactive iodine by the thyroid as well as the radiation dose to the thyroid. Iodine prophylaxis must be carried out promptly, ideally several hours before and no later than a few hours following exposure [3]. Some health and governmental agencies have issued KI prophylaxis based on the International Atomic Energy Agency (IAEA) recommendation and there are some differences among guidelines. For instance, the World Health Organization (WHO) guidelines adopt 1 cGy as a threshold of exposure for pregnant or lactating women and children (≤ 18 years of age), while the Food and Drug Administration (FDA) guidelines recommend a threshold of 5 cGy [2, 4]. Both guidelines recommend a relatively high dose of KI prophylaxis (*i.e.*, 130 mg), although the threshold value differs according to age, that is, age ≥ 12 years by WHO; age of 18-40 years by FDA. The guideline in Japan regarding KI prophylaxis [5] does not refer to a threshold of radioiodine exposure; however, the recommended dosages of inorganic iodine as KI are similar to those of FDA and WHO, which are 12.5 mg of inorganic iodine (16.3 mg of KI) for newborn infants less than one month, 25 mg (32.6 mg of KI) for individuals from one month to 3 years, 38 mg (50 mg of KI) for 3 to 13 years and 76 mg (100 mg of KI) for 13 to 40 years of age. KI tablets are given orally once a day [5]. Because inorganic iodine has a variety of adverse effects including skin rash, gastrointestinal complaints or silent thy-

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roiditis, and since repeated iodine administration can induce hypothyroidism, it is preferable to minimize the dose and length of administration of KI.

Iodine nutritional status at the time of exposure to radioactive iodine strongly affects the thyroid radiation dose [6], and it is also reported that iodine deficiency increases the risk of ^{131}I-related thyroid cancer [7].

Japan is regarded as an iodine sufficient country [8], and there are still controversies on the timing, dose, and length of administration of KI to block the uptake of radioiodine by the thyroid. We hypothesize that Japanese population can attain enough radioactive iodine uptake (RAIU) suppression by relatively smaller amounts of KI because the most residents in Japan traditionally ingested sufficient amount of iodine from their daily meal. The purpose of this study is to evaluate the effect of low-dose inorganic iodine on thyroidal RAIU and thyroid function without dietary iodine restriction.

Materials and Methods

Subjects

This study was conducted between March 28, 2011, and March 26, 2013. Twenty- two participants, 18 men and 4 women were recruited from the healthy volunteers. Their mean age ± standard deviation (SD) and range were 35.7 ± 9.9 and 22 - 57 years old, respectively. Seven of the 9 authors of this manuscript were included in the study. Their initials, gender and ages are as follows; YK, female, 38 years, TU, male, 40, KM, male, 41, KS, male, 41, KI, male, 36, AS, male, 39 and HY, male, 57.

All participants had normal thyroid function, as indicated by a serum free tri-iodothyronine (FT3), free thyroxine (FT4) and thyroid-stimulating hormone (TSH) levels were within the normal range for Japanese of our hospital. Serum thyroglobulin antibody (TgAb) and thyroperoxidase antibody (TPOAb) were also negative. Pregnant and nursing women or subjects with kidney disease were excluded. This study was approved by the ethics committee of Ito Hospital, and informed consent was obtained from all participants.

Study design

Base-line uptake study

In all, 22 participants without dietary iodine restriction RAIU of the thyroid gland was measured at 24 hours after administration of radioactive iodine (^{123}I) (24-hour RAIU), urinary iodine (UI), serum FT3, FT4 and TSH concentrations were measured just before administration of ^{123}I (Fig. 1A).

24-hour RAIU at one hour after single-dose administration of 10 mg iodine solution and changes in thyroid function and UI excretion

After more than one week washout period for previous ^{123}I ingestion, ^{123}I was given again to all 22 par-

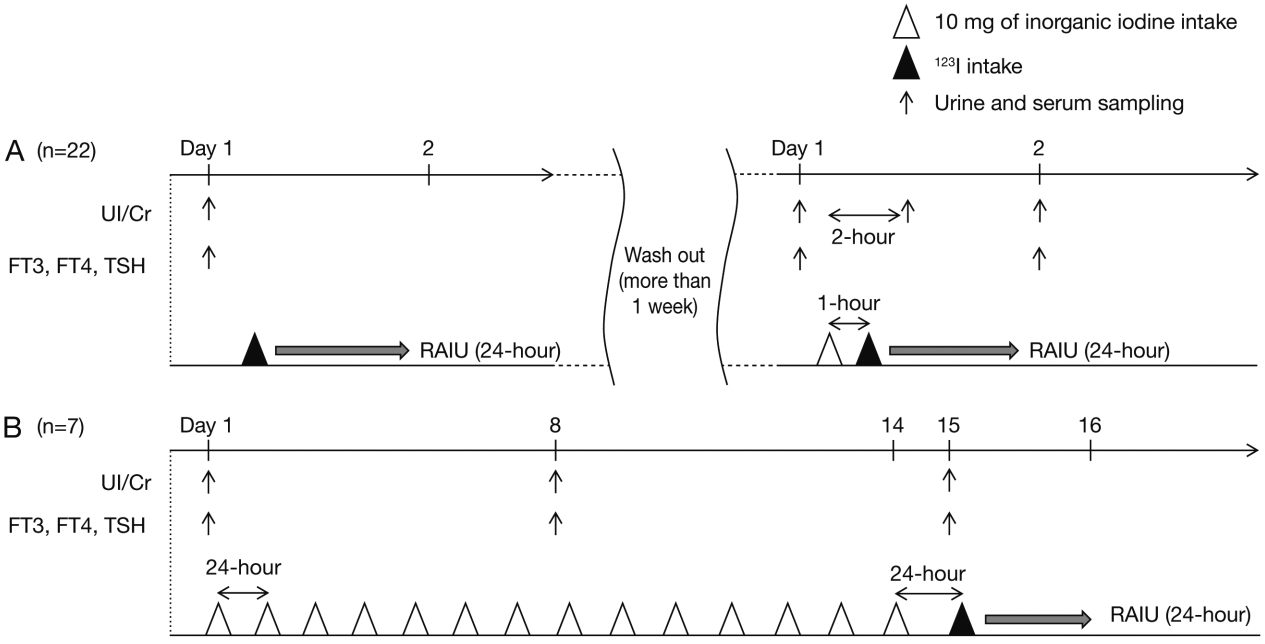

Fig. 1 Study design

ticipants at 1-hour intervals after administration of single-dose of 10 mg inorganic iodine. Then 24-hour RAIU was assessed. Serum FT3, FT4, TSH and UI concentrations were measured just before administration of iodine and at the 24-hour RAIU measurement. One more spot urine sample for UI measurement was obtained at 2 hours after iodine administration because it is reported that UI excretion reaches a maximum level at 2 hours [9] (Fig. 1A).

Changes of thyroid function, UI excretion and 24-hour RAIU after daily administration of 10 mg iodine solution for 2 weeks

Of 22 study participants, six men and one woman with a mean ± SD age of 43.4 ± 6.9 year, were selected and given 10 mg of iodine solution daily in the morning for 14 days. On day 15 their 24-hour RAIU was measured at 24 hours after the last administration of inorganic iodine. Serum FT3, FT4, TSH and UI concentrations were determined on day 1 before administration of inorganic iodine and as well as on days 8 and 15 (Fig. 1B).

Measurement of 24-hour RAIU

At 24 hours after administration of 7.4 MBq of ^{123}I (iodine-capsule 123, Nihon Medi-Physics Co., Ltd., Tokyo, Japan), the participants underwent measurement of thyroidal RAIU *via* a γ-ray scintillation counter (ND-451F; Hitachi Aloka Medical, Tokyo, Japan). Participants were seated facing the detector, which was positioned 70 cm from the anterior surface of the neck at the level of the cricoid cartilage. Counts were obtained from the neck for 1 min with and without a neck filter (15 × 15 × 3 cm lead sheet). In order to correct background activity, a ^{123}I capsule was placed 70 cm from the detector, and the radiation count was measured for 1 min with a phantom just before administration of ^{123}I capsule. Radiation counts were recorded and transformed to counts per minute (cpm) for RAIU calculation. RAIU was calculated as a percentage of the administered dose of ^{123}I, as corrected for physical decay and background activity using the following formula: RAIU (%) = [(neck count [cpm] without filter)-(neck count [cpm] with filter)] / [(background count [cpm]) × k] ×100 (%), where *k* represents the attenuation coefficient.

Preparation of iodine solution

We used Japanese Pharmacopoeia "potassium iodide" (Nichi-Iko Pharmaceutical Co., Ltd., Toyama, Japan), which contains 1 g of potassium iodide in 1 g. Potassium iodide (140 g) was completely dissolved in sterile purified water, and sodium thiosulfate (0.1 g) was added to maintain the iodide in the reduced state. After 24-hour, sterile purified water was added to make the total volume as 250 mL. This solution was formulated so that one drop from a 5-mL eye dropper (Nice Sterile Eye Drop Bottle, Yamayu, Umano Chemical Container Co., Osaka, Japan) (approximately 0.025 mL/drop) contained 10 mg of inorganic iodine. In this study, the dosage regimen of stable iodine is expressed either in total KI or in iodine alone: 100 mg of inorganic iodine is equivalent to 130 mg of KI.

Laboratory methods

Serum FT3, FT4 and TSH were measured by an electrochemiluminescence immunoassay (ECLusys FT3, FT4 and TSH; Roche Diagnostics, Mannheim, Germany) and their reference ranges for adults in our hospital are 0.2-4.5 μIU/mL, 2.2-4.8 pg/mL and 0.8-1.6 ng/dL, respectively. TgAb and TPOAb were determined by solid-phase radioimmunoassays (Roche Diagnostics), and the normal ranges are less than 28 IU/mL and less than 40 IU/mL, respectively.

Spot urine samples were obtained between 0900 h and 1100 h before taking KI solution. UI concentration (μg/L) was measured by inductively coupled plasma mass spectrometry (detection limit; 5 μg/L, intraassay coefficient of variation; 1.7-1.9 %). To estimate the 24-hour renal UI excretion using spot urine sample UI concentration to creatinine ratio (UI/Cr; μg/g·cre) was calculated from the urinary creatinine concentration (mg/dL).

Statistical analysis

All statistical analyses were performed using JMP version 8.0.2 software (SAS Institute, Cary, NC). For parametric data, results are expressed as mean ± SD if the data are continuous variables. Continuous variables with a non-parametric distribution are expressed as median values and range. A Mann-Whitney U test was used to compare thyroidal RAIU by age. The paired *t*-test was used for the comparisons of the data taken between before and after iodine administration. ANOVA was used for the comparisons of repeated measurements for FT3, FT4 and TSH. The Kruskal-Wallis test was used to compare UI/Cr measurements taken on three different days in repeated-dose study. *P* values < 0.05 were considered to indicate statistical significance.

Results

24-hour RAIU without dietary iodine restriction

The median 24-hour thyroidal RAIU in all 22 participants without dietary iodine restrictions was 13 % (range, 5-26 %). In 14 subjects younger than 40 years median 24-hour RAIU was 15 % (range, 10-26 %), significantly higher than that in eight subjects older than 40 years (12.75 %, range, 5-17 %), (Mann-Whitney U test, $p = 0.0399$).

The median UI/Cr value was 201.3 μg/g·cre (range, 101.7- 746.1 μg/g·cre) and the mean ± SD values of serum FT3, FT4 and TSH concentrations were 3.18 ± 0.38 pg/mL, 1.29 ± 0.16 ng/dL and 1.66 ± 0.73 μIU/mL, respectively, indicating euthyroid status.

24-hour RAIU at one hour after single-dose administration of 10 mg iodine solution and changes in thyroid function and UI excretion

The median 24-hour RAIU after a single-dose administration of 10 mg of iodine solution was significantly suppressed from 13 % (range, 5-26 %) to 3 % (range, 1-7 %) (paired *t*-test, $p < 0.0001$). The median inhibitory rate of 24-hour RAIU was 81.0 % (range, 0-92.3 %). In 20 of 22 participants (90.9 %) their 24-hour RAIUs were suppressed to less than 5 % (Fig. 2).

The mean serum FT3, FT4 and TSH values remained within the physiological normal range without a significant change at 25 hours after inorganic iodine ingestion (3.15 *vs*. 3.05 pg/mL, 1.28 *vs*. 1.22 ng/dL, respectively); however, that of TSH increased significantly from 1.67 μIU/mL to 2.0 μIU/mL (paired *t*-test, $p < 0.01$).

The median UI/Cr value enormously increased from 189.1 μg/g·cre (range, 54.5-1,008.1 μg/g·cre) to 11,400 μg/g·cre (range, 4,470-25,400 μg/g·cre) at 2 hours after taking 10 mg of KI (paired *t*-test, $p < 0.0001$) and then decreased but still high in level of 1,989 μg/g·cre (range, 765.2-5,373 μg/g·cre) at 25 hours.

Changes of 24-hour RAIU, UI excretion and thyroid function after daily administration of 10 mg iodine solution for 2 weeks

For 7 participants that received daily iodine solution for 14 days the median RAIU measured at 24 hours after last administration of 10 mg iodine was 6 % (range, 2-12 %), significantly higher than that of RAIU measured one hour after single-dose of iodine (3 %) although it was still lower than that of the control status (12 %) (Fig. 3). In 6 of 7 participants, the 24-hour

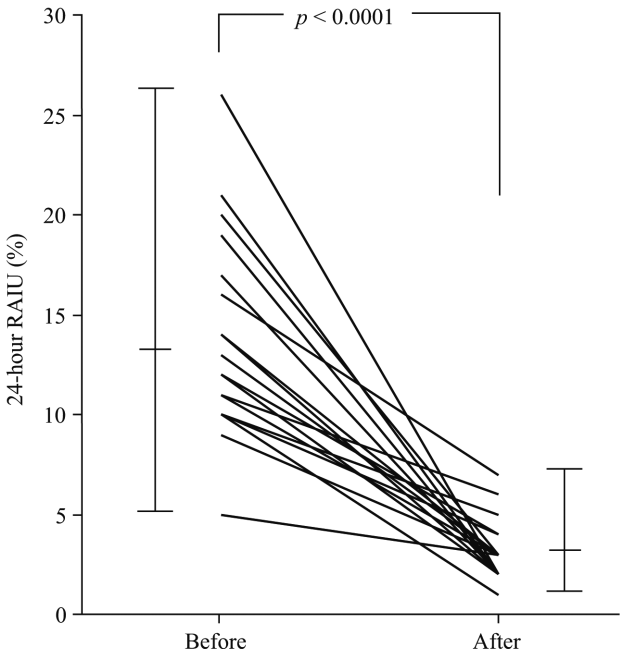

Fig. 2 Changes of 24-hour RAIU before and after 10 mg iodine administration (n=22). The horizontal line in the middle of the bar represents median RAIU value. Whiskers denote the highest and lowest RAIU values.

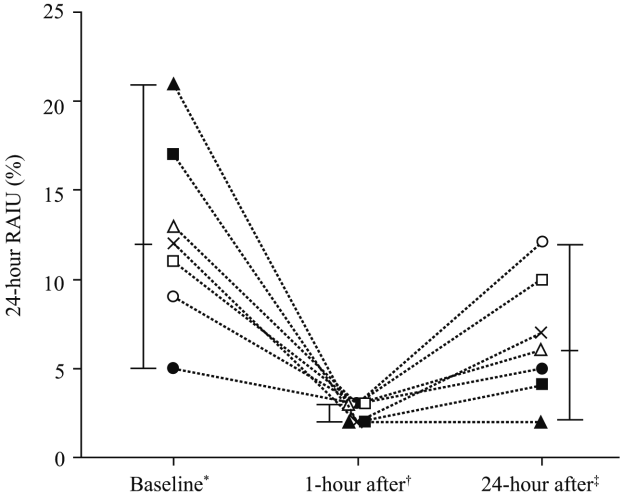

Fig. 3 Comparison of inhibitory effect of 10 mg iodine on 24-hour RAIU of 7 participants among three different conditions. The horizontal line in the middle of the bar represents median RAIU value. Whiskers denote the highest and lowest RAIU values. *Baseline: 24-hour RAIU without iodine administration. Urine was sampled just before ^{123}I administration. †1-hour after: ^{123}I was administrated 1-hour after iodine administration. Urine was sampled 2 hour after iodine administration. ‡24-hour after: ^{123}I was administrated 24-hour after iodine administration. Urine was sampled just before ^{123}I administration.

RAIU measured on day 15 was higher compared to those at one hour after single-dose iodine administration. The RAIU values for two participants on day 15 were more than 10 % that was comparable to their baseline values and their UI/Cr values were relatively low (1,051.7 and 2,300 μg/g·cre, respectively).

The median UI/Cr concentrations markedly increased from 205.9 μg/g·cre to 3,528.7 μg/g·cre on day 8 and remained through day 15 (3,768.9 μg/g·cre).

The mean serum TSH concentration significantly increased on day 15 although it was within the normal range while there were no significant changes in the mean serum FT3 and FT4 values during study period (Table 1). In 3 of 7 participants, serum TSH value increased above the upper limit of reference range (4.5 μIU/mL) without decreasing serum FT3 or FT4. Their TSH values were 5.09 μIU/mL on day 8, 4.77 μIU/mL or 5.03 μIU/mL on day 15, respectively. Elevated TSH value on day 8 returned to 3.29 μIU/mL on day 15 in one participant.

Relationship between 24-hour RAIU and urinary iodine excretion

Fig. 4 depicts the relationship between 24-hour RAIU and UI excretion in the three different iodine statuses, that is, baseline, single- and repeated-dose of 10 mg inorganic iodine. Linear-regression model of repeated measures yielded a significant negative correlation ($Y=-0.0007156*X + 11.04$; $R^2=0.5218$, $p=0.0002$). In the participants with UI excretion of more than 5,000 μg/g·cre their RAIUs were suppressed below 5 %.

Discussion

Previous studies on stable iodine prophylaxis were conducted under dietary iodine restriction. Because nuclear power plant accidents are unpredictable, our study design without dietary iodine restriction is suitable for applying after actual events. To protect the thyroid gland, a computer simulation found that thyroid blockade by oral KI is most effective when given between 24-hour prior to and 2-hour after exposure to radioiodine [10]. Our data suggests that a single low-dose of inorganic iodine (10 mg) given one hour before exposure of radioactive iodine effectively suppressed 24-hour RAIU from 13 % to 3 % in euthyroid Japanese adults and might be useful in decreasing radiation exposure of the thyroid gland to radioiodine. Our results are consistent with previous low-dose iodine studies [11, 12]. Blum and Eisenbud in the US reported that 5 mg of KI reduced 24-hour RAIU from 33 % to 7.3

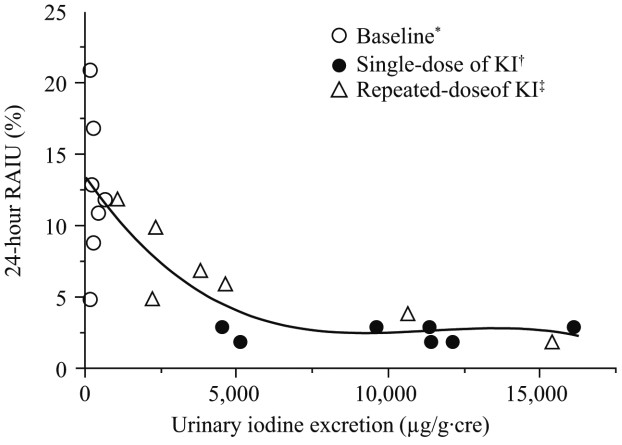

Fig. 4 Correlation between 24-hour RAIU and urinary iodine excretion measured in 7 participants in three different iodine statuses. The regression line is drawn by polynomial model ($R^2=0.672$). *Baseline: 24-hour RAIU without iodine administration. Urine was sampled just before ^{123}I administration. †Single-dose : ^{123}I was administrated 1-hour after iodine administration. Urine was sampled 2-hour after iodine administration. ‡Repeated-dose : ^{123}I was administrated 24-hour after iodine administration. Urine was sampled just before ^{123}I administration.

Table 1 Changes in thyroid function and urinary iodine excretion before, during and after daily administration of 10 mg iodine for 2 weeks

	Day 1	Day 8	Day 15	*p* value
FT3 (pg/mL)	3.26 ± 0.44	2.93 ± 0.27	3.07 ± 0.30	0.2305
FT4 (ng/dL)	1.35 ± 0.23	1.24 ± 0.19	1.31 ± 0.14	0.5485
TSH (μIU/mL)	2.12 ± 0.83*	3.11 ± 1.28	3.59 ± 1.20*	0.0246*
UI/Cr (μg/g·cre)	205.9†‡ (120.7-578.5)	3,528.7† (1,274.61-11,569.8)	3,768.9‡ (1,051.75-15,380.4)	0.0061†‡

FT3, FT4 and TSH are expressed as mean ± SD, UI/Cr is expressed as median (range), Urine samples on days 8 and 15 were obtained just before the next iodine administration and at 24 hours after the last iodine ingestion, respectively.

% although this dose was given in only one of 62 volunteers [12]. Koutras and Livadas in Greece showed that 5 mg of KI reduced RAIU from 32.0 % to 11.6 % in 10 adults while 10 mg of KI reduced RAIU to 4.5 % [11]. In contrast, a similar study conducted in the US by Sternthal *et al*. reported that a single dose of 10 mg of KI failed to suppress 24-hour RAIU (19.4 % *vs*. 12.5 %), whereas 30, 50, or 100 mg of KI suppressed RAIU to 0.7-1.5 % [13]. Although the exact reason for the difference among these studies is not clear, the possible reasons might be the differences of the time of RAIU measurement, age and habitual dietary iodine intake in study populations. For example, the Japanese routinely consume iodine-rich seaweed products and, in a recent study, the median UI concentration was reported to be 213 μg/L in adults [14] that is above the daily requirements of iodine intake according to the WHO criteria [15].

When there are difficulties with immediate evacuation and sheltering in cases of nuclear accidents, an extended duration of protection from radioactive iodine might be necessary. The effect of long-term repeated KI administration on RAIU has been investigated. Cuddihy *et al*. reported a significant RAIU reduction in 4 euthyroid subjects (two children of 8.6 years old and 2 young adults of 22.7 years old) in response to 1.8-4.2 mg iodine (2.3-5.5 mg KI) given daily for more than 14 days [16]. Sternthal *et al*. also reported that in five subjects the different daily doses of KI (10, 15, 30, 50 and 100 mg) given for 11 days markedly suppressed 24-hour RAIU from 17.2-22.6 % to 0.6-4.0 % [13]. In Japan, Nagataki *et al*. reported that 24-hour RAIU was maintained at 3.5 % when 7 euthyroid males were given 10 mg of iodine as KI three times a day for 4 weeks under dietary seaweed restriction [17]. In our study, continued suppression of thyroidal RAIU can be achieved by repeated use of low-dose inorganic iodine without any thyroid dysfunction; however, the median value of 24-hour RAIU measured at 24 hours after last KI administration was higher than that at one hour after single-dose of inorganic iodine (6 % *vs*. 3 %). The inhibitory effect of inorganic iodine on RAIU was diminished in some participants with low UI excretion. This observation clearly suggests that there is relationship between UI excretion and thyroidal RAIU levels. Ingested iodine is almost completely absorbed in the digestive tract within a 30-60 min [18], and more than 90 % of iodine is excreted in the urine. Takamura *et al*. reported the changes of UI concentrations after intake of 100 mg KI in 9 euthyroid males residing in Nagasaki, Japan or Gomel, Republic of Belarus. UI excretion peaked at 2 hours after intake of KI and then decreased to near the level before KI intake at 24 hours [9]. Provided that urinary iodine excretion simultaneously reflects plasma iodide levels, it might be much better to ingest KI three times a day than once daily in order to maintain plasma iodide concentration within an effective range for prolonged thyroid protection by administrating low-dose iodine.

One of the possible adverse effects of KI on thyroid gland is iodine-induced hypothyroidism in newborn infants and adults with preexisting thyroid diseases. In our study slight elevation of serum TSH concentration with stable serum thyroid hormone levels was observed in heathy adults after the administration of 10 mg iodine for 2 weeks. This observation consists with previous reports [13, 19]. Ikeda *et al*. reported that under seaweed restricted diet, 10 mg KI daily for one week in 8 Japanese adults increased slightly serum TSH level without significant changes in serum T4 and T3 levels [19]. However, in the present study, subclinical hypothyroidism occurred in three participants, suggesting the risk of iodine side effects might be present if administered repeatedly even in a small dose. Further studies are needed to clarify the efficacy and safety of repeated administration of low-dose KI to minimize side effects.

The effect of iodine-rich foods on thyroid blockade in radiation emergencies has not been fully investigated. *Kombu* is an edible kelp from the *Laminariaceae* family with high iodine content and consumed widely in East Asia. Takamura *et al*. observed that the ratio of iodine excretion with iodine-rich food containing 76 mg iodine was significantly lower than that of KI tablet (containing 38 mg inorganic iodine) until 6-hour after the intake, and concluded that thyroid blockade by iodine-rich food was not sufficient or adequate [9]. However, in 1958 Iino *et al*. reported that single-dose ingestion of 10 g of *kombu* containing approximately 23 mg of inorganic iodine reduced thyroidal RAIU from 14-39 % to 2.0-4.2 % in 10 healthy Japanese. In addition, when subjects ingested 7-16 g of *kombu* daily for 14 days, their RAIU decreased from 15-21 % to less than 5 % [20]. More research on iodine kinetics in foodstuff and thyroid blockade effect by iodine-rich food is necessary.

The strength of our research is that, without iodine restriction, the effect of low-dose KI, by single or repeated

administration on RAIU, was evaluated from the viewpoint of urinary iodine excretion; while the weakness is the limited size of participants including some of the authors that might give a possible bias on results.

In summary, 10 mg inorganic iodine given one hour before the exposure of radioiodine sufficiently inhibits thyroidal RAIU in Japanese healthy adults; however, the inhibitory effect by repeated low-dose inorganic iodine attenuates at 24 hours after the last administration when it is given once a day. Although the effect of KI on thyroid blockade in radiation emergencies is established, optimal dosage, duration or interval of KI administration should be evaluated in iodine-sufficient regions.

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Disclosure

The authors declare that they had no conflicts of interest in regard to this study.

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