Iodide-sensitive Graves’ hyperthyroidism and the strategy for resistant or escaped patients during potassium iodide treatment

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Abstract. The effectiveness of potassium iodide (KI) (100 mg/day) was evaluated in 504 untreated patients with Graves’ hyperthyroidism (GD). Initial response to KI within 180 days, the effect of additional methylmercaptoimidazole (MMI) or radioactive iodine (RI) in resistant or escaped patients, and long-term prognosis were evaluated. Serum fT₄ levels became low or normal in 422 patients (83.7%, KI-sensitive group) without serious side effects. Among these patients, serum TSH levels became high (n = 92, hypothyroid) or normal (n = 78) in 170 patients (33.7%) (KI-sensitive with a recovered TSH response, Group A), but remained suppressed in 252 patients (50.0%) (KI-sensitive with TSH suppression, Group B). Serum fT₄ levels decreased but remained high in 82 patients (16.3%) (KI-resistant, Group C). Older patients, or those with small goiter and mild GD were more KI-sensitive with a recovered TSH response than others. Escape from KI effect occurred in 0%, 36% and 82% in Group A, B and C, respectively. Patients in Group B and C were successfully treated with additional low-dosage MMI or RI. After 2–23 years’ treatment (n = 429), remission (including possible remission) and spontaneous hypothyroidism were significantly more frequent in Group A (74.3% and 11.1%, respectively,) than in Groups B (46.3% and 2.8%, respectively) or C (53.6% and 1.5%, respectively) (p < 0.0001). In conclusion, a high KI sensitivity with a recovered TSH response was observed in about a third of the patients in GD associated with a better prognosis. Additional MMI or RI therapy was effective in escaped or KI-resistant patients with suppressed TSH level.

Key words: Hyperthyroidism, Antithyroid drug, Potassium iodide, Graves’ disease

IODIDE SENSITIVITY in cases of chronic thyroiditis is well-known [1-6]. Iodide sensitivity of patients with Graves’ hyperthyroidism (GD) has been unclear, although iodide in higher doses is an established and time-honored treatment of GD [7-9]. Following the development of modern assays for serum thyroid hormone, Emerson et al. reported a decrease in serum thyroid hormone levels after 4 to 11 days of iodide therapy in GD [10], but escape was observed in two-thirds of the patients. This high incidence of escape suggested that iodide alone is not adequate therapy for controlling GD and encouraged switching GD therapy from iodide to thionamide antithyroid drugs (ATDs) [11]. However, later clinical studies suggested the usefulness of potassium iodide (KI) [12-20].

Regarding thionamide, adverse side effects were shown to be serious problem from the outset [11]. Propylthiouracil (PTU) and methylmercaptoimidazole (MMI) were found to be the most active ATDs [21]. However, both MMI and PTU were still associated with severe notorious [22-26] or unfamiliar [27-29] side effects. In Japan, one GD patient on average dies due to thionamide-induced agranulocytosis every year [30].

Previous studies have shown that KI is effective for treating patients with GD who show side effects to thionamide [17] or untreated GD patients complicated with malignancy who require chemotherapy, thereby avoiding the risk of thionamide-induced granulocytopenia during anti-cancer treatment [20]. The possibility of KI therapy was therefore suggested in general untreated GD from the beginning. Compared with the era of Plummer [7] and Thompson [8], recent advances in thyroid function tests and medical screening have revealed many patients to have mild or even asymptomatic GD that may be sensitive to excess iodide [20].

Given the above, in the present study, we evaluated the efficacy of KI in untreated patients with GD in order
to avoid or minimize the risk of notorious thionamide-induced side effects.

**Materials and Methods**

Between 1996 and 2004, a total of 504 patients with untreated GD who visited our hospital without impending serious symptoms were treated with KI (100 mg once daily after breakfast). Serum free T4 (fT$_4$) and free T3 (fT$_3$) levels were measured monthly. Patients with notably poor adherence to the drug were excluded from the study. After both serum fT$_4$ and fT$_3$ levels normalized, the serum fT$_4$ and thyroid-stimulating hormone (TSH) levels were monitored. If the serum fT$_4$ and/or fT$_3$ levels remained high after 2–3 months, the KI dosage was gradually increased to 200–500 mg mainly in KI-resistant or escaped patients. Patients with serious symptoms, such as those with arrhythmia, heart failure or psychic symptoms, were treated with MMI and KI from the beginning and excluded from this study. GD was diagnosed in patients with elevated serum fT$_4$ and/or fT$_3$ levels, suppressed serum TSH levels and positive TSH-binding inhibitor immunoglobulin (TBII) and/or thyroid-stimulating antibody (TSAb) [17, 20, 31-34]. A high thyroidal radioactive iodine uptake (RAIU) was confirmed in all the patients in order to strictly exclude those with painless thyroiditis and autonomous functioning thyroid nodules [4].

The classification of the response of the patients to KI administration during the first 180 days is shown in Table 1 [34]. If the serum fT$_4$ levels normalized even temporarily, the patients were classified as KI-sensitive patients, which was further divided into Group A when serum TSH level became detectable, or Group B when serum TSH level remained suppressed. Group A was further divided into Group A1 when the serum fT$_4$ level became low and/or the serum TSH level became abnormally high (hypothyroid or KI-too sensitive) or Group A2 when the serum fT$_4$ level became normal and abnormal TSH elevation was not observed. Group B was further divided into B1 (low fT$_4$ and normal or low normal fT$_3$ levels with inappropriately suppressed TSH), B2 (normal fT$_4$ and normal fT$_3$ levels even temporarily with suppressed TSH) and B3 (normal or low fT$_4$ and high fT$_3$ level with suppressed TSH—T$_3$ toxicosis type). If the decrease in serum fT$_4$ was poor and fT$_3$ remained higher than normal, patients were classified into the KI-resistant group (Group C). When the serum fT$_4$ and/or fT$_3$ levels became elevated after temporary reduction in serum fT$_4$ levels while taking 100 mg KI within 180 days, they were diagnosed as showing escape from acute KI effects [10]. For patients in Group C and escaped or symptomatic patients in Group B, the KI dosage was reduced to 100 mg, and low-dose (5–15 mg) MMI (depending on the severity of thyrotoxicosis) was added to KI (combined KI and MMI therapy). In the patients who were resistant to these treatments, high-dose (20–30 mg) MMI was added to KI, or ablative therapy, such as radioactive iodine (RI) or surgery, was recommended. If MMI was added to KI before the fT$_4$ level normalized within 180 days, they were classified as Group C.

After 180 days, KI therapy with or without MMI was continued. When patients achieved and maintained a euthyroid status, the thionamide drug was carefully discontinued, and the patient was treated with KI until remission. Following the disappearance of thyroid stimulating indices, including positive TBII or TSAb and an enlarged goiter [32], the patient was asked whether they wished to stop the drug or continue the KI therapy.

If patients maintained a euthyroid status with normal serum TSH levels and negative TBII for >1 year after the cessation of the drug, they were considered to have entered remission. If the patient seemed to be in remission with normal fT$_4$ and TSH levels and negative TBII but wanted to continue KI therapy (50 mg KI), or when patients dropped out within one year after the withdrawal of the drug, they were classified into the possible remission group. Otherwise, they were classified into the non-remission (NR) group. Patients who spontaneously achieved a hypothyroid status were classified as the hypothyroid group and treated with L-thyroxine (LT$_4$) [33, 34].

Commercially available 50 mg KI pills containing 38.25 mg or 76.5% iodide (Nichi-Iko Pharmaceutical Co., Ltd., Toyama, Japan) were prescribed [17, 20]. In this study, the dose is expressed as the dose of KI for convenience.

Serum fT$_4$ and fT$_3$ levels were measured in duplicate by RIA using a radiolabelled analogue of T$_4$ (Amerlex fT$_4$ and fT$_4$ MAB kit, Kodak Japan, Ltd. Tokyo, Japan) [5] and TSH level was measured by immunoradiometric assay (SPAC TSH, Daiichi Radioisotope Labs, Tokyo, Japan) [6]. After 2004, serum fT$_4$, fT$_3$ and TSH levels were measured by electrochemiluminescence immunoassays (Roche Diagnostics GmbH, Mannheim, Germany) [20]. The correlation between the assays was $r = 0.986$ for TSH ($n = 128$), $r = 0.987$ for fT$_4$ ($n = 130$) and $r = 0.977$ for fT$_3$ ($n = 117$). When the serum fT$_4$ level was above the upper limit of the assay, the serum samples were measured using diluted sample after the equilibrium dialysis method (Nihon Medi-Physics Co. Ltd., Tokyo, Japan) [33]. Autoantibodies to thyroglobulin (Tg) (TGHA) and thyroid microsomal antigen (MCHA) were measured by hemagglutination using commercial kits (Fujirebio Pharmaceutical Co. Ltd., Tokyo, Japan) [4-6, 32].
The serum TBII level was mostly measured using a first-generation radioreceptor assay kits (Baxter Health Care Co. Ltd., Tokyo, Japan) [4, 5, 32, 33]. Starting in 2004 during long-term follow up, TBII was measured using a second-generation TBII assay with the human recombinant TSH receptor (normal <1 IU/L, DYNOtest TRAb human kit, Yamasa Corporation, Chiba, Japan), and the results were expressed as the percent inhibitory activity. The correlation coefficient between these two method expressed as the percent inhibitory activity was 0.8566 according a Spearman’s analysis (n = 1,987) [33].

| Group | A1 | A2 | B1 | B2 | B3 | C | p value |
|-------|----|----|----|----|----|---|--------|
| Serum free T4 | low | normal | low | normal | normal (high fT4) | remained high |
| KI sensitivity | too sensitive | sensitive | sensitive | sensitive | | |
| Serum TSH | high | normal | suppressed | suppressed | suppressed | suppressed |
| n (%/Total) | 92 (18.3%) | 78 (15.5%) | 27 (5.4%) | 142 (28.2%) | 83 (16.5%) | 82 (16.3%) |

(A) A comparison of the clinical data before the treatment

Age (years)

| Sex (Male:Female) | 45.3 ± 15.7 | 41.3 ± 15.2 |
|-------------------|------------|------------|
| TBII (%)          | 4.23       | 26.0       |
| TSAb (%)          | 49.0       | 256        |
| TGHA+             | 25.27      | 86.14      |
| MCHA+             | 70.82      | 89.54      |

(B) Clinical escape (%/n)

| RAU (%/s h) | 45.0      | 34.4 |
| free T3 (ng/dL) | 4.0 ± 2.8 | 3.6 ± 1.3 |
| free T4 (pg/mL) | 10.1 ± 5.1 | 9.3 ± 4.5 |

(C) Abnormal data observed during treatment

| TBII (days) | 539 | 173 |
| Struma (days) | 418 | 112 |
| Follow-up period (years) | 7.3 | 7.1 |

KI sensitivity was evaluated depending on the changes in serum fT3 and TSH levels during first 180 days. Values are shown as the mean ± standard deviation or median (interquartile range). Group A: KI sensitive with recovered TSH response, hypothyroid (A1) or euthyroid (A2). Group B: KI sensitive but suppressed TSH, low fT3, and inappropriately suppressed serum TSH (B1), normal fT3 and fT4, even temporarily (B2), normal fT3 and high fT4 (B3 - T3 toxicity). Group C: KI resistant and suppressed TSH. Clinical escape was defined by the re-elevation of serum fT3 and/or fT4 level observed within 180 days during KI treatment. KI: Potassium iodide, TBII: TSH binding inhibitor immunoglobulin. TSAb: Thyroid-stimulating antibody, TGHA and MCHA: Antithyroglobulin or antithyroid microsomal antibody measured by hemagglutination, respectively. RAU: Thyroid radioactive iodine uptake.

The data of TSAb were not available in two patients in Group A1 and A2 and in one patient in Groups B2 and B3.
formula: 0.7 \times \text{the maximum width (cm)} \times \text{the maximum thickness (cm)} \times \text{the maximum length (cm)} \text{for each lobe (r = 0.8825, n = 1,105)} [33].

The serum and urinary total iodine levels and urinary creatinine levels were measured as previously reported [5, 17] in randomly selected patients. The serum non-hormonal iodine (NHI) levels were calculated by subtracting the amount of iodine contained in serum total T\(_3\) and T\(_4\) from the total iodine level and 5-h RAIU were measured as previously reported [4, 17, 32, 33]. The reference values in our laboratory were as follows: serum fT\(_4\) 0.8–1.7 ng/dL, fT\(_3\) 2.2–3.8 pg/mL, TSH 0.42–3.81 mU/L, TBII <15%, TSAb <180%, RAIU 4%–20%/5 h, thyroid volume 5–20 mL, TGHA or MCHA <100.

**Statistical analyses**

Normal continuous variables were expressed as the mean ± standard deviation, while median and interquartile ranges were reported for skewed variables. Comparisons were performed using Pearson’s χ\(^2\) test between categories and Student’s t-test, Wilcoxon’s rank sum test or a multivariate logistic regression analysis between continuous variables. The regression was calculated with forced entry method. Correlations between continuous numerical variables were assessed using Spearman’s rank correlation coefficient. The analyses were performed using the JMP 15 software program (SAS Institute, Inc., Cary, NC, USA). A p value below 0.05 was considered to be statistically significant.

The study was approved by the Ethics Committee of Kyushu University. The clinical study was registered to the official Clinical Trials Registry (Clinical Trials.gov Identifier: NCT04686006). We did not obtain informed consent from the participants involved in our study because the study was restricted to existing data with all personal identifiers removed.

**Results**

**Initial response to KI treatment and high prevalence of KI-sensitive GD**

Following KI therapy, the serum fT\(_4\) levels declined in all patients (Figs. 1 and 2), and became low or normal in 422 patients (83.7%) suggesting KI-sensitive GD (Table 1).

**KI-sensitive GD with elevated or normal TSH (Group A)**

The serum TSH levels became higher than normal, or normal with low fT\(_4\) levels in 92 (18.3%) patients, suggesting iodide-induced hypothyroidism (KI-too sensitive hypothyroid Group A1) (Fig. 1). The serum fT\(_4\) level became low after 74 (48–105) days, and the TSH level increased after 131 (77–167) days. At the initial stage of this study, the KI dosage was reduced to avoid hypothyroidism (tapering therapy), as is usually performed when patients are treated with MMI. However, it soon became apparent that re-elevation of the serum fT\(_4\) level frequently occurred with this tapering therapy (Fig. 1). Therefore, in the latter half of this study, the patients were treated with the combination of 100 mg KI and LT\(_4\) when the serum fT\(_4\) level became low and the TSH level became detectable (combined fixed dose KI and LT\(_4\) therapy). In this combined therapy (n = 39), compared with tapering therapy (n = 41), a relapse of hyperthyroidism was not observed (0% vs. 71%, p < 0.0001) and the degree of TSH elevation was reduced (e.g. 10.7 [6.6–23.3] μU/mL vs. 27.3 [8.6–68.3] μU/mL), although the difference was not significant (p = 0.0561).

Both the serum fT\(_4\) and TSH levels normalized, suggesting inclusion in the KI-sensitive euthyroid Group A2 with recovered hypothalamus-pituitary system (Table 1, Fig. 2-A2), in 78 (15.5%) patients. The serum fT\(_4\) level normalized after 21 (14–34) days, and the TSH level normalized after 112 (71–150) days. As in Group A1, the tapering of the KI dosage induced elevation of the serum fT\(_4\) level in some patients, and 100 mg KI was maintained in most patients while TBII remained positive.

Since serum fT\(_4\) level became normal within 60 days in 157 (92.4%) of 170 patients in Group A, KI dosage was increased to 200 mg only in 6 (3.5%) patients in Group A, 54 (44–56) days after initiation of the treatment.

**KI-sensitive GD with suppressed TSH (Group B)**

The serum fT\(_4\) levels became low or normal, but the TSH levels remained suppressed in 252 (50.0%) patients, suggesting a KI-sensitive status with TSH suppression (Group B); these patients were further divided into three groups. As shown in Table 1 and Fig. 2, the serum TSH level remained suppressed even when the serum fT\(_4\) level became low in 27 (5.4%) patients (Group B1) or when both the fT\(_4\) and fT\(_3\) levels normalized in 142 (28.2%) patients (Group B2). The serum fT\(_4\) level normalized but the fT\(_3\) level remained high in 83 patients (16.5%) (Group B3, T\(_3\) toxicosis). In Group B1 with inappropriately suppressed serum TSH levels, the prevalence of patients with positive TGHA or MCHA was elevated (Table 1).

**KI-resistant GD (Group C)**

In 82 (16.3%) patients, the serum fT\(_4\) level remained high despite an apparent decrease during the first 1–2 months (Group C; Table 1, Fig. 2-C).
Escape from acute KI effect in Groups B & C

Re-elevation of the serum fT4 and/or fT3 levels while taking 100 mg KI (escape) was observed in 33–37% or 82% of the patients in Group B and Group C, respectively, as shown in Table 1-(B) and Fig. 2, at 48 (35–74) days after the initiation of KI treatment. Most instances of escape were accompanied by re-elevation of the serum fT4 but only fT3 re-elevation was observed in 12 (7.6%) patients (T3 escape). Escape was observed in none of the patients in Group A. The re-elevation of hormones after 180 days or later or when the drug was reduced was not considered “escape” in this study.

Results of a multivariate logistic analysis of factors influencing the clinical course (Table 2)

In a multivariate logistic analysis of the clinical data before treatment, as shown in Table 2, an age, TGHA, MCHA, thyroid volume and the serum fT3 level at baseline were significantly associated with the KI sensitivity and recovered TSH (Group A), compared with Groups B & C. Since there was a strong correlation between the serum fT4 and fT3 level (r = 0.6718, p < 0.0001), the serum fT4 level was also considered to be significantly associated with the difference. Positive TGHA was more frequent (72.9% vs. 67.6%) and positive MCHA less frequent (66.0% vs. 80.0%) in Group A than in Groups B & C. The percentages of patients in Groups A, B or C and escaped patients, stratified by the difference in these factors, are shown in Table 3-I. In total, 170 (33.7%) of the patients were KI sensitive with a recovered hypothalamus-pituitary system (Group A). KI sensitivity was frequent among older patients (>65 years old) and mild GD cases (thyroid volume <20 mL, fT4 <4 ng/dL, fT3 <10 pg/mL), with escape suggested in only 10%–30% of these cases. KI sensitivity was less frequent and escape more frequent among young patients (<40 years old) and severe GD cases (thyroid volume ≥40 mL, fT4 >7 ng/dL, fT3 >10 pg/mL). In older patients (>65 years old), the serum fT4 level before treatment was 37% lower (3.6 ± 0.7 vs. 5.7 ± 0.2 ng/dL, p = 0.0031) and the serum NHI level during 100 mg KI treatment 38% higher (335 [298–369] vs. 243 [176–325] μg/L, p = 0.0045) than in younger patients (<40 years old).

Compared with Groups A & B, as shown in Table 2,
Fig. 2 Changes in the serum fT$_4$ level in patients with untreated Graves’ hyperthyroidism who were initially treated with 100 mg potassium iodide (KI). A2: KI-sensitive patients in whom both the serum fT$_4$ and TSH levels normalized. B: KI-sensitive patients with suppressed TSH. B1: The serum fT$_4$ level became lower than normal even temporarily. B2: The serum fT$_4$ and fT$_3$ levels normalized, even temporarily. B3: The serum fT$_4$ level normalized even temporarily but the fT$_3$ level remained high (T$_3$ toxicosis). C: Iodide-resistant patients in whom serum fT$_4$ level decreased but remained above the normal range. The re-elevation of the fT$_4$ level (escape) was observed in 33%–37% of Group B and in 82% of Group C. The patients were then treated with combined KI and methylmercaptoimidazole (MMI) therapy, as shown with red marks and lines. To clarify the effect of MMI on the escaped patients, 53 patients in Group B2 and 15 in Group B3 in whom the fT$_4$ level became normal and remained within the normal range for 180 days were not drawn in the figure. In Group C, 1 patient was treated with $^{131}$I at day 98 as shown by RI.

Table 2 A multivariate logistic analysis of the difference before treatment between the KI-sensitive and KI-resistant groups with or without TSH suppression or escape in patients with Graves’ hyperthyroidism treated with 100 mg KI therapy ($n$ = 504)

| Comparison                      | Group A vs. Groups B & C | Groups A & B vs. Group C | Escape vs. non-escape |
|---------------------------------|--------------------------|--------------------------|-----------------------|
| Age (years)                     | 0.0261                   | 0.0831                   | 0.0091                |
| Sex (Male:Female)               | 0.5093                   | 0.0088                   | 0.0267                |
| TBII (%)                        | 1.4273                   | 0.7806                   | 0.04801               |
| TSAb ($\times$10%)             | 0.3852                   | 0.0088                   | 0.0523               |
| TGHA+                           | 0.0010                   | 0.5162                   | 0.2324               |
| MCHA+                           | 0.0193                   | 0.1870                   | 0.0531               |
| Thyroid volume (mL)             | 0.0319                   | 0.0056                   | 0.3260               |
| RAIU (%/5 h)                    | 0.2657                   | 0.0056                   | 0.1847               |
| free T$_4$ (ng/dL)              | 0.5377                   | 0.0142                   | 0.0681               |
| free T$_3$ (pg/mL)              | 0.0001                   | 0.0023                   | 0.0295               |

Group A: KI-sensitive patients with recovered serum TSH. Group B: KI-sensitive patients with suppressed serum TSH. Group C: KI-resistant patients. Escape: Re-elevation of the serum fT$_4$ and/or fT$_3$ levels after temporary reduction in serum fT$_4$ levels while taking 100 mg KI within 180 days. See legends for Table 1. Odds ratio and 95% confidence interval are shown. * $p < 0.05$ The comparison between Group A vs. Groups B & C suggests the factors responsible for KI sensitivity and recovered TSH response. The comparison between Groups A & B vs. Group C suggests the factors responsible for the refractory response to KI.
the significant factors found in Group C (KI-resistant) were sex, TSAb, thyroid volume, fT4 and fT3 at baseline. In escaped patients compared with non-escaped patients, the significant factors were age, sex, TBII and fT3.

**Strategy for KI-resistant and/or escaped patients (1)**

Addition of low-dose thionamide

In 202 patients in Group C and escaped or symptomatic patients in Group B, low-dose MMI (5–15 mg)
was added within 180 days (Figs. 2 and 3). The MMI dosage was 5 mg in 45 patients (22.3%) mainly in Group B1–3, 10 mg in 25 patients (12.4%) mainly in Group B2–3 and 15 mg in 132 patients (65.3%) mainly in Group C. The MMI dosage was increased to 20–30 mg in 6 patients in Group C. The time required for the normalization of the serum $\text{fT}_4$ level was 49 (28–70) days after the addition of MMI (Fig. 3) but iatrogenic hypothyroidism during combined KI and MMI therapy was observed in 36.5% of the patients (Fig. 2).

Even in non-escaped patients, elevation of the serum $\text{fT}_4$ level beyond 180 days was observed in 18 (10.6%) of 170 patients after 637 (404–927) days in Group A and in 86 (53.1%) of 162 patients after 350 (265–660) days in Group B, when the drug dosage was reduced or under stressful conditions (late exacerbation). These patients were also treated with combined KI and MMI therapy.

Once patients achieved a euthyroid status, MMI was able to be gradually withdrawn after 2.0 (0.8–3.6) years, and the patients maintained a euthyroid status by taking only KI, suggesting that they had overcome their KI-insensitivity or escape when they became less thyrotoxic. Twenty-four patients maintained a euthyroid status requiring continuous combined KI and MMI therapy for two to eight years.

**Strategy for KI-resistant and/or escaped patients (2) RI or surgery**

During this study, 126 (25.0%) patients were treated by ablative therapy (RI 104 patients and surgery 22 patients), which was performed after 1,981 (906–2,687) days in Group A ($n = 13$), 1,324 (1,010–1,883) days in Group B1 ($n = 13$), 1,339 (551–3,080) days in Group B2 ($n = 41$), 819 (399–1,372) days in Group B3 ($n = 33$) and 938 (301–1,659) days in Group C ($n = 26$). Even in Group A, some patients wished to undergo ablative therapy before marriage or for other reasons. Of note, the RAIU before RI, after refraining from taking KI and excess iodide just for 4–7 days, was 60.0% (38.0%–73.6%)/5 h, which was almost the same as the values of 55.8% (40.0%–67.9%)/5 h before KI treatment (Table 4-I). Among the 93 patients who were followed for more than 1 year after RI, 46 (49.5%) patients achieved a hypothyroid status at 888 (152–1,755) days after RI, 34 (36.6%) achieved a euthyroid status, and 13 (14.0%) remained thyrotoxic, requiring a second round of RI therapy or control with KI and LT$_4$ [35]. The estimated thyroid volume decreased from 45 (32–72) to 7(4–10) mL after RI.

**Urinary excretion of iodide and serum non-hormonal iodine (NHI) levels**

As shown in Table 4-I, a marked increase in the serum NHI level was observed during 100 mg or 200 mg KI treatment, with approximately 100 or 200 mg/g creatinine iodine, respectively, excreted into the urine. The serum NHI level and urinary iodide excretion before RI after the withdrawal of KI for 4–7 days were almost the same as before the treatment of GD. Regarding the serum NHI level during treatment with 100 mg KI, (Table 4-II), there was considerable overlap of the NHI level, but the NHI level was significantly higher in Group A1 or B1, wherein the serum $\text{fT}_4$ level decreased to a lower value than normal, than in the other groups. The serum NHI level was 10–50 μM in about 90.0% of the patients in Groups A & B and 77.4% in KI-resistant Group C, in which the level was <10 μM in 22.6%, suggesting a high prevalence of patients with an insufficiently high NHI level ($p = 0.0112$).

We further compared the KI sensitivity depending on the serum NHI level during 100 mg KI treatment. When the NHI level was <10 μM ($n = 44$), 14 (31.8%) patients were included in Group C. When the NHI was ≥10 μM ($n = 299$), only 48 (16.1%) patients were included in Group C. The difference between these values was significant ($p = 0.0112$) and the odds ratio was 0.41 (95%
confident interval [CI], 0.20–0.83), suggesting KI resistance when the NHI level was <10 μM. The serum NHI level was >50 μM in only 1 patient in Group A2 in this study.

**The long-term prognosis of the patients (Fig. 4)**

The long-term prognosis was evaluated in the 429 patients who were followed for 2–23 years. The estimated thyroid volume after drug treatment (at the last visit or at the time of ablation in the ablated patients) was <40 mL in 350 (81.6%), 40–79 mL in 56 (13.1%), 80–159 mL in 20 (4.7%) and ≥160 mL in 3 (0.7%). Among these patients, 86 (59.7%) of the 144 patients in Group A, 78 (36.1%) of the 216 patients in Group B and 23 (33.3%) of the 69 patients in Group C eventually went into remission after 7.4 (1.9–23.0) years, with a disappearance of TBII activity and decrease in the estimated thyroid volume. These patients remained euthyroid for 10.6 (3.6–21.2) years without drugs. Complete remission was not confirmed in about 10%–20% of the patients in each group because they wished to continue taking 50 mg KI even when TBII remained negative in order to avoid late relapse [32]. These patients were defined as the possible remission group. Sixteen (11.1%) patients in Group A, 6 (2.8%) patients in Group B and 1 (1.4%) patient in Group C spontaneously achieved a hypothyroid status. The prognosis was significantly better in Group A than in Groups B & C (p < 0.0001) by the χ² test.

In non-ablated patients, TBII remained positive in 8 (5.6%) patients in Group A, 32 (14.8%) patients in Group B and 5 (7.2%) patients in Group C, requiring KI monotherapy in 21 patients or combined KI and MMI therapy in 24 patients (non-ablated NR).

A multivariate logistic analysis including the clinical

**Table 4** The urinary excretion of iodine, serum non-hormonal iodine level and thyroidal radioactive iodine uptake before or during KI treatment and before RI therapy in the patients with Graves’ hyperthyroidism

| KI dosage | Urinary Iodine (mg/g creatinine) | Serum NHI (μg/L) | Thyroidal radioactive iodine uptake (%/5 h) |
|-----------|---------------------------------|-----------------|------------------------------------------|
|           | n | median (range) | n | median (range) | n | median (range) |
| none⁰     | 420 | 0.16 (0.1–0.3) | 432 | 133 (109–162) | 504 | 55.8 (40.0–67.9) |
| 100 mg⁰   | 312 | 101 (72–149) | 343 | 2,465 (1,790–3,263) |
| 200 mg⁰   | 13 | 196 (128–268) | 80 | 4,090 (3,252–5,190) |
| before RI⁰ | 37 | 0.18 (0.1–0.3) | 37 | 156 (92–200) | 104 | 60.0 (38.0–73.6) |
| p value⁰ | 0.8081 | 0.1375 | 0.5871 |

The values shown are the median and interquartile range or number and percentage in the group.

NHI: serum non-hormonal iodine. KI: potassium iodide. RI: ¹³¹I therapy. a) Before treatment; b) During the treatment with 100 mg or 200 mg KI; c) Before RI therapy after KI withdrawal for 4–7 days; d) A comparison of the values before KI treatment and before RI. e) See classification for Table 1. The serum NHI, urinary total iodine and urinary creatinine levels were measured as previously reported [⁵, ⁶]. The serum NHI level was calculated by subtracting the amount of iodine contained in serum total T₃ and T₄ from the total iodine level.

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data at baseline and initial response to KI during 180 days also suggested that the prognosis was better in Group A than in Groups B & C (p < 0.0001), although there was no significant difference between Groups A & B and Group C (p = 0.6995) or between Group B and Group C (p = 0.3879). A multivariate logistic analysis including the clinical data at baseline and the time required for normalization of serum fT₄, fT₃, TSH and TBII levels, suggested that the significant factors for better prognosis (remission or spontaneous hypothyroidism vs. non-remission) were age (p = 0.0366) and years required for normalization of serum TSH (p < 0.0001) or TBII (p < 0.0001), with odds ratios of 0.982 (95% CI, 0.965–0.999), 1.001 (95% CI, 1.001–1.002) and 1.001 (95% CI 1.001–1.002), respectively, while the earlier normalization of serum fT₄ (p = 0.5627) or fT₃ (p = 0.5840) had no significant influence, with odds ratios of 1.001 (95% CI 0.998–1.004) and 0.9995 (95% CI 0.998–1.001), respectively. The age was significantly younger in the non-remission group than in the other groups (37.0 ± 15.0 vs. 41.0 ± 15.1 years old). Regarding the occurrence of spontaneous hypothyroidism, the only significant factor before treatment was the presence of MCHA (p = 0.0007), which was positive in all patients who became spontaneously hypothyroid but in only 74.0% of other patients. The difference was also confirmed by a χ² test (p = 0.0048).

**Side effects and complications**

None of the patients showed any signs of sialadenitis, hematological abnormalities, liver dysfunction or serious complications, such as thyroid crisis or severe eye changes, during KI treatment. One patient complained of skin eruption four days after beginning KI. The drug was changed to MMI, which also induced drug eruption. The patient was treated with PTU and excluded from the study.

Side effects of 5–15 mg MMI, which was administered with KI, were observed in 29 (9.3%) of 311 patients, including skin eruption (23; 7.4%), leukocytopenia (2; 0.6%), liver dysfunction (2; 0.6%), arthralgia (1; 0.3%) and vomiting (1; 0.3%).

**Discussion**

The inhibitory action of excess iodide is complicated and probably related to the physiological autoregulatory action of iodine on the thyroid gland [36-43], including the inhibitory effect on the organification of iodide, known as the acute Wolff-Chaikoff (WC) effect [36]. These changes may be associated with the doubled mRNA expression of the immunity-associated genes [44] or morphological changes in the thyroid gland including necrosis or mononuclear cell infiltration [2, 45, 46]. Electron microscopic studies revealed an altered follicle shape and diminished numbers of microvilli [47] or apical blebbing, cytoplasmic fragments desquamation, endoplasmic reticulum vesiculation and accumulation of lipofuscin in secondary lysosomes [48] in the presence of 10⁻⁵ M or 10⁻⁴ M NaI.

The inhibitory effect of iodide has been believed to be transient, so escape from the acute WC effect can occur, likely inhibiting the active iodide transport mechanism via the sodium-iodide symporter (NIS) [49, 50]. The thyroid/serum (T/S) ratio of iodide or concentration activity of iodide in thyrocytes has been extensively studied [51] and was reported to be 25–40 in normal thyroid and more than 100 in the stimulated thyroid under conditions of the overproduction of TSH due to

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**Fig. 4** The prognosis of the patients with Graves’ hyperthyroidism initially treated with 100 mg potassium iodide (KI) and followed for 2–23 years (n = 429), depending on the early response during 180 days (Table 1). If patients wished to continue a small maintenance dose of KI (50 mg/day) even when TBII was negative with a small goiter, they were defined as the possible remission group. See the legends for Figs. 1 and 2. The number in parenthesis is the number of patients in each group. Remission (including possible remission) and spontaneous hypothyroidism were significantly more frequent in Group A (74.3% and 11.1%, respectively), than in Group B (46.3% and 2.8%) or Group C (53.6% and 1.5%) (p < 0.0001). The prognosis was not markedly different between Groups B and C (p = 0.5117). The time required for remission was 1,025 (676–1,532) days in Group A (n = 84) and 1,847 (1,276–3,147) days in Groups B & C (n = 99). The difference was significant (p < 0.0001).
goitrogens or a low-iodine diet (LID). If the iodide content within the thyrocyte is the main factor underlying the inhibitory effect, a suppressed NIS function might be overcome if a large amount of iodide is administered to induce passive entrance into thyrocytes.

The dosage required for the WC effect was 50–500 μg in rats on a stock diet [39] and 5–20 μg in rats on LID [40]. Since the iodine content in the rat thyroid gland was approximately 10 μg on a stock diet and 0.5 μg on LID [52], excess iodide ingestion far exceeding that in the native thyroid gland may be required to induce the WC effect. The iodine content of the human thyroid gland was estimated to be about 10 mg [53]. Considering our previous clinical experiences [2, 17, 20], the initial dosage of KI for the treatment of GD was determined to be 100 mg in this study.

Regarding the iodine concentration necessary for the WC effect, in vivo and in vitro studies using normal rat thyroid suggested that the threshold of the WC effect seemed to be around 10–50 μM [36, 42], and almost complete inhibition of organification was observed in the presence of >50 μM iodide. Of note, this concentration was almost the same as that inducing minute morphological changes in the thyrocyte [47, 48].

In the present study, the serum fT4 level decreased in all patients with GD after taking 100 mg KI (Figs. 1 and 2), and became low or normal in 83.7% of the patients suggesting high prevalence of KI-sensitive GD. The prevalence of KI-induced hypothyroidism was 18.3% (Group A1). This iodide-induced hypothyroidism would be troublesome in cases of Hashimoto thyroiditis [1, 2, 5, 6] but might be beneficial to GD ameliorating hyperthyroidism. It was very important to keep the serum iodide level above the threshold for the WC effect, avoiding the tapering method usually performed in MMI therapy. The KI dosage could be reduced later when TBI became negative or patients had nearly achieved remission. It was interesting to find that TBI and RAII were significantly higher in Group A1 or Group B1, compared with Group A2 or Group B2, respectively (Table 1). It was suggested that the more stimulated thyroid was ironically more susceptible to KI probably due to the higher incorporation of iodine into the thyroid [2].

When the serum TSH level remained suppressed, re-elevation of the serum thyroid hormone levels within 180 days or escape was observed in 33%–37% of Group B and in 82% of Group C (Table 1, Fig. 2). Escape was observed in none of the patients in Group A, suggesting the importance of TSH in avoiding the escape phenomenon. The precipitating role of TSH in the WC effect has been suggested in cases of reversible iodide-induced hypothyroidism in humans [2, 5, 6] as well as in iodine-deficient rat [40].

Regarding the factors associated with KI sensitivity and recovered TSH response (Group A) compared with Groups B & C, a multivariate logistic regression analysis suggested that the age, TGHA, MCHA, thyroid volume and freeT3 level before treatment were significant factors (Table 2).

Elderly patients (>65 years old) were sensitive to KI treatment and escape was observed only in 11% (Table 3). The KI sensitivity in elderly patients might be explained by 1) mild GD suggested by a low fT4 and fT3 level before treatment, and 2) an increased NHI level during 100 mg KI treatment, possibly due to the senile impairment of the renal function. Iodide-induced hypothyroidism was frequently observed in patients with renal dysfunction (2, 5). Wolff and Chaikoff originally reported that nephrectomy prolonged the inhibitory effect of excess iodide in rats [54]. The serum creatinine level and effective glomerular filtration rate (eGFR) in the euthyroid patients in our clinic was 0.6 ± 0.1 mg/dL and 96 ± 19 mL/min in younger patients (<40 years old, n = 99) and 0.8 ± 0.5 mg/dL and 67 ± 19 mL/min in older patients (>65 years old, n = 353), respectively (unpublished data), suggesting a significantly impaired renal function (p < 0.0001) in elderly patients, corresponding to their increased serum NHI levels during 100 mg KI treatment.

The NHI level measured in the patients taking 100 mg KI was 10–50 μM (Table 4). The higher serum NHI level in Group A1 and B1 than in other groups might suggest a greater suppressive effect of KI with increasing dosage, although the overlap of the NHI level between groups suggested differing sensitivities to KI among patients. The serum NHI level during 100 mg KI treatment was >50 μM in only 1 patient (Table 4). Considering the requirement of >50 μM iodide for a complete WC effect shown in animal experiments [36, 42], a greater antithyroid effect may be expected with higher doses of KI.

KI-resistant patients or continuous TSH suppression with escape were more frequent among patients with a larger thyroid volume (≥40 mL) and higher fT3 level (>10 pg/mL) than among other patients (Tables 2, 3). However, it must be mentioned that even in such severe cases of GD, 10%–20% of patients were KI-sensitive without TSH suppression or escape (Group A). A multivariate logistic regression analysis suggested that an increased fT3 level rather than an increased fT4 level would be a better predictor of KI resistance or escape (Table 1). T3 predominant synthesis and secretion is a good marker of the thyroid gland being strongly stimulated with high turnover of both Tg and iodide, as found in cases of iodine deficiency [55].

Regarding the early response to KI, KI resistance (Group C) was frequent when the time until the
normalization of the serum $fT_4$ or $fT_3$ level was >60 days or escape from the acute KI effect occurred (Table 3-II). About 42.7% of the escaped patients belonged to Group C. When treating GD with KI, the timing for adding MMI is important. If patients fail to achieve euthyroid status within 60 days or escape occurs, it may be better to begin combined KI and MMI therapy.

The important conclusion from this study was that KI resistance or escape from the KI effect could be overcome either by combined KI and MMI therapy (Fig. 3) or RI therapy. The inhibitory effect of MMI on the thyroid gland depending on the iodine intake is very complicated [56, 57]. MMI was also considered to be actively incorporated into the thyroid gland, but the active transport mechanism for MMI was different from that for iodide [21, 41]. After the administration of 5–15 mg MMI in addition to 100 mg KI in this study, the time required for the normalization of the serum $fT_4$ level was 49 (28–70) days, which was shorter than 54 (30–100) days observed when GD patients were initially treated by 15 mg MMI monotherapy [34]. The prevalence of iatrogenic hypothyroidism during treatment was 36.5% during combined KI and 5–15 mg MMI therapy in this study (Fig. 2), much higher than 10.8% found in 15 mg MMI treated patients [34]. The additive effect of excess iodide and MMI was strongly suggested [58].

Regarding RI therapy, KI therapy may interfere with the efficacy of RI therapy, which is quite concerning. However, most of the excess iodide that did not enter the thyroid gland was rapidly excreted into the urine, as reported previously [17] and confirmed in this study (Table 4). After RI treatment in Groups B and C, 86% of the patients achieved a euthyroid- or hypothyroid status with a decrease in thyroid volume. It was then concluded that KI therapy did not interfere with the efficacy of RI.

The prognosis of the patients initially treated with 100 mg KI was significantly much better in Group A than in Groups B or C (Fig. 4), which was confirmed by both a $\chi^2$ test and a multivariate logistic analysis. When the patients were initially treated with 15 mg MMI in the same way, the long-term prognosis was not significantly different, regardless of the initial response to MMI [34]. It was then suggested that physiological inhibition of the thyroid function by KI rather than pharmacological inhibition by MMI more closely correlated with the long-term prognosis in GD.

Of note, the prognosis in the patients with a suppressed TSH level despite a low $fT_4$ level (Group B1) was poor. Even if the serum $fT_4$ level decreased smoothly, the prognosis was still poor if the TSH remained suppressed, as was also noted in the patients initially treated with 15 mg MMI [34]. The inappropriately suppressed hypothalamus-pituitary system might be attributed to TSH receptor antibody (TRAb) activity or strong GD activity [59]. The significance of prolonged TSH suppression and TBII positivity on the poor prognosis of GD was also found in MMI treated patients [34].

Regarding goiter size, the estimated thyroid volume after drug treatment was <40 mL in more than 80% and ≥160 mL in only 0.7% of the patients in this study, almost the same results as found in the patients initially treated with 15 mg MMI [34].

Considering the sensitivity of the patients with chronic thyroiditis to excess iodide [1, 2, 6], KI sensitivity can be expected in patients with positive antithyroid antibody. However, no correlation was noted between escape and the prevalence of TGHA or MCHA. Unexpected findings were that, compared with Groups B & C, positive TGHA was more frequent (72.9% vs. 67.6%; with the exception of Group B1) and positive MCHA less frequent (66.0% vs. 80.0%) in Group A (Tables 1, 2).

Regarding the long-term prognosis, it was interesting to find that MCHA was an only significant predictor of spontaneous hypothyroidism following GD, considering the report that GD may evolve into chronic thyroiditis in patients in permanent remission [60]. The role of antithyroid antibody on the clinical course of GD should be re-evaluated in the future.

Regarding the strategy for GD treatment depending on the early response to 100 mg KI, KI treatment could be continued in Group A. Nearly 80% remission or spontaneous hypothyroidism could be expected. If the serum $fT_4$ and $fT_3$ levels do not normalize within 60 days, the patients may belong to Group B or C (Table 3). Combined KI and MMI therapy is then recommended, as a 33%–82% chance of escape is expected later (Table 1). The chance of achieving remission may be about 50% (Fig. 4). If patients are resistant to this combined therapy and do not wish to continue ATD or KI for a long time [33], especially patients with an increasing thyroid volume exceeding 80 mL, which was noted in about 5% of the patients, RI can be recommended in the early stage of treatment.

This study was conducted in an iodine-sufficient area. Jod-Basedow or iodine-induced hyperthyroidism is well-known risk of administering iodine for endemic goiter [61]. The effect of a large amount of iodine in GD in an iodine-deficient area is unclear. Considering the results of animal experiments [40], a large amount of iodine may inhibit the organification of iodide, even in iodine-deficient human thyroid glands. However, it remains important to eradicate iodine-deficiency issues. Excess or more than adequate iodine, which suppresses the stimulated thyroid, is a better condition than an iodine deficient one, which induces universal hypothyroidism [52]. As for the KI dosage, sensitivity to KI varies.
among individuals. Since KI has no serious side effects, as shown in this study, and is economically inexpensive, it may be best to start with a more than sufficient dosage (exceeding the threshold for WC effect) in order to clearly evaluate the iodine-sensitivity of the patient. If the patient is resistant to such a large amount of KI, it is best to add MMI early.

The study was limited by the fact that about 15% of the patients dropped out within 2 years after the initiation of the treatment.

In conclusion, the serum $fT_4$ levels declined in all patients with GD following KI therapy. Among GD patients treated with 100 mg KI, 34% were KI-sensitive with detectable TSH and a good prognosis, 50% were KI-sensitive with TSH suppression and 16% were KI-resistant. KI was immediately excreted into urine without clearly evaluate the iodine-sensitivity of the patient. If the "KI or RI" strategy for the treatment of GD without suppressing patients. KI-resistant and escaped patients were able to be treated with a combination of KI and a small dosage MMI, or RI, as usual. We can minimize the use of thionamide with serious side effects by adopting the “KI or RI” strategy for the treatment of GD without impending serious symptoms, until more sophisticated therapies, such as immunomodulators or small-molecule TSH receptor antagonists become available [62]. KI is the least expensive modality without any serious side effects. When we use drugs with serious side effects, such as MMI, it is better to try to reduce the dosage [63]; however, when we use drugs that are relatively inexpensive with extremely rare side effects, such as KI, a sufficient dosage may be administered from the beginning.

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