Restriction of dietary Iodine does not ameliorate the early effect of anti-thyroid drug therapy for Graves’ disease in an area of excessive iodine intake

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ABSTRACT. The close relationship between iodine intake and the effects of anti-thyroid drugs (ATD) for Graves’ disease (GD) has been well established. However, it remains unknown whether restriction of dietary iodine improves the effect of ATD. This study aimed to clarify this issue in Japanese patients with GD who routinely ingest large amounts of dietary iodine. We performed a prospective clinical study in 81 patients with newly diagnosed GD who were divided into an iodine restricted group and a control group. Urinary iodine, thyroid hormones and TSH receptor antibody were measured during the first 8 weeks of ATD therapy. Urinary iodine concentrations in the iodine restricted group were significantly lower than in the control group (p=0.043). However, there were no significant differences in the decrease of thyroid hormones and TSH receptor antibody between the two groups. Restriction of dietary iodine does not ameliorate the effect of ATD therapy for GD in an area of excessive iodine intake.

INTRODUCTION
Several lines of evidence have suggested that variation in iodine intake affects the efficacy of anti-thyroid drugs (ATD) in patients with Graves’ disease (GD). Azizi et al. (1) demonstrated that the efficacy of ATD to decrease thyroid hormone levels in patients with GD in an area of iodine deficiency was superior to that in an area of iodine sufficiency (1). In addition, Taurog et al. (2) demonstrated that intra-thyroid degradation of propylthiouracil and methylmercaptomidazole (MMI) in vitro were influenced markedly by intra-thyroid iodide content, and that chronic exposure to excessive iodine resulted in a decrease of propylthiouracil uptake into thyroid cells and rapid excretion of the drug (2). These results indicated that there is a close relationship between iodine intake and the effectiveness of ATD in the treatment of GD.

Japan is a country with excessive iodine intake, due to both consumption of seaweeds and use of condiments containing kelp. It has also been shown that there is a large variation in both diurnal and regional consumption of iodine in the Japanese population (3-5). Although a large proportion of GD patients utilize ATD therapies in Japan compared with alternative approaches (6), the degree to which variations in iodine intake affect the efficacy of ATD has yet to be determined. The notion that iodine restriction in an area of excessive iodine intake may enhance the effectiveness of ATD therapy for GD therefore remains an important issue.

The aim of this study was to elucidate whether restriction of dietary iodine ameliorates the early effect of ATD therapy in patients with GD in an area of excessive iodine intake. We compared thyroid hormone and thyrotropin receptor antibody (TRAAb) during MMI therapy between GD patients with and without dietary iodine restriction. The present investigation also monitored the degree of iodine restriction using a new method for measuring urinary iodine.

Key-words: Iodine restriction, Graves’ disease, anti-thyroid drug, urinary iodine, excessive iodine intake.

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MATERIALS AND METHODS
Patients
Eighty-one patients with newly diagnosed GD, who had visited the Kuma Hospital for the first time between October 2000 and February 2002, consented to participate in this prospective clinical study. The diagnosis was based on elevated levels of free T₄ (FT₄) (>1.60 ng/dl) and free T₃ (FT₃) (>3.7 pg/ml), associated with decreased TSH (<0.5 mU/l), a positive TSH receptor antibody (TRAb) titer (>15%), and/or a level >40% in a radiiodine uptake (RAIU) test. Exclusion criteria included pregnancy, ongoing immuno-suppressive treatment, complication of psychiatric or other serious disease, poor drug-compliance and the patients’ preference for surgery or radioiodine therapy.

Intervention
A physician in charge instructed the 81 patients on how to restrict dietary iodine, using a legend of popular Japanese foods and drugs containing iodine, such as kelp, soup extracts, seaweed, seafood, iodine glycerin gargling solution and contrast medium. The patients were also informed that iodine restriction would likely be of therapeutic benefit. After these explanations, the patients determined voluntarily whether or not they would restrict dietary iodine. The patients who chose to restrict dietary iodine were directed to strictly avoid taking the foods included in the above legend during the first 8 weeks of treatment.

Evaluation
Initially, all patients were treated with 15 mg MMI daily during the first 8 weeks, except for 2 patients. Urinary iodine (UI), urinary creatinine (Ucr), FT₄, FT₃ and TRAb were measured during the first 8 weeks of treatment to assess the degree of iodine restriction and the efficacy of treatment. Patients in the iodine restricted (IR) group with a UI/Ucr >500 µg/(g•cr)⁻¹ after 4 to 8 weeks of treatment were excluded, as we considered they were unable to restrict their daily iodine intake according to our instructions. Seventy patients were determined as eligible for evaluation of MMI efficacy during the early phase of treatment, with 11 patients being excluded. Of these 11, 8 patients did not meet the criteria concerning iodine restriction, 1 due to poor drug-compliance, 1 underwent an operation for papillary carcinoma of the thyroid gland, while the other patient stopped the IR diet. Of the 70 eligible patients, 23 received β-blockers with MMI during the first several weeks, 8 exhibited drug eruption that improved following administration of a histamine H1 receptor antagonist, and 2 developed mild hypothyroidism 4 weeks after treatment that caused us to decrease the dose of MMI. Informed consent was obtained from all patients, and the study protocol was approved by the Ethics Committee of Kuma Hospital.

Laboratory tests
The UI concentration was measured with a simple microplate method (Hitachi Chemical Co., Ibaragi, Japan). The mean intra- and inter-assay coefficients of variance (CV) for UI with iodine concentrations >100 µg/l were ≤10%. For UI concentrations over the range 30-100 µg/l, the mean intra- and inter-assay CV were ≤20%. Ucr concentrations were measured using an enzyme assay (Daichi Chemical Co., Tokyo, Japan) with a mean intra- and inter-assay CV ≤5%.

Serum concentrations of TSH, FT₄ and FT₃ were measured with a microparticle enzyme immunoassay (ARCHITECT TSH, FT₄ and FT₃, Dainabot Co., Tokyo, Japan). The normal range for serum TSH was 0.50-5.00 mU/l with mean intra-assay and inter-assay CV ranging from 1.1-5.0 and 1.7-5.3%, respectively. The normal range for serum FT₄ was 0.70-1.60 ng/dl with mean intra-assay and inter-assay CV ranging from 2.3-5.3 and 3.6-7.8%, respectively. The normal range for serum FT₃ was 1.7-3.7 µg/ml with mean intra-assay and inter-assay CV ranging from 1.4-2.2 and 2.3-5.0%, respectively. Serum TRAb activity was measured by a radioiodide uptake assay (Cosmic Co., Tokyo, Japan) that had mean intra-assay and inter-assay CV ranging from 1.2-7.3 and 1.2-5.5%, respectively. The normal range for TRAb was set below 15%. Anti-thyroglobulin was measured by a hemagglutination technique using a thyroid test kit (Fujirebio Inc., Tokyo, Japan) and anti-microsomal antibodies (TGHA and MCHA) by a microsome test kit (Fujirebio Inc.)

Other parameters
The volume of the thyroid gland was measured by ultrasonography, as reported previously (7), while RAIU values were measured 24 h after oral administration of 100 µCi [¹³¹I], or 8-14 µCi of [¹²³I], and expressed as a percentage of the administered dose. A value between 10-40% was classified as normal.

Statistical analysis
The Mann-Whitney U-test was used to compare the data on age, FT₄, FT₃, TRAb, UI/Ucr, thyroid volume, RAIU value, and observation period, while comparison of data on gender, and positive ratio of TGHA and MCHA were conducted using Fisher exact test. The sequential changes in UI/Ucr, FT₄, FT₃ and TRAb between the two groups were compared by two-way repeated-measures analysis of variance (ANOVA). When a significant difference was found using ANOVA, a comparison was made at each measurement point using the Mann-Whitney U-test. JMP software (SAS Institute Japan Inc, Tokyo, Japan), version 5.0.1, was used for all statistical analyses.

RESULTS
To evaluate the influence of iodine restriction on early efficacy of MMI, we compared the data of 31 patients in the IR group and 39 patients in the control group. The characteristics of the patients in the two groups are summarized in Table 1, which demonstrates that age, gender, UI/Ucr, TGHA, MCHA, TSH, FT₄, FT₃, TRAb, thyroid volume and RAIU were similar in both groups at baseline. The median (1st-3rd quartile) concentration of UI/Ucr in the IR group was 220 (142-440) µg/(g•cr)⁻¹ prior to treatment, 207 (127-317) µg/(g•cr)⁻¹ 4 weeks after treatment, and 150 (101-213) µg/(g•cr)⁻¹ 8 weeks after treatment. At the same times, median UI/Ucr concentrations in the control group were 195 (122-581) µg/(g•cr)⁻¹, 299 (170-671) µg/(g•cr)⁻¹ and 339 (143-968) µg/(g•cr)⁻¹, respectively. As shown in Figure 1, a significant difference was observed in UI/Ucr concentrations between the two groups (p=0.043). Post-hoc analyses using the Mann-Whitney U-test