

Effect of a Low Iodine Diet vs. Restricted Iodine Diet on Postsurgical Preparation for Radioiodine Ablation Therapy in Thyroid Carcinoma Patients

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Purpose: The radioiodine ablation therapy is required for patients who underwent a total thyroidectomy. Through a comparative review of a low iodine diet (LID) and a restricted iodine diet (RID), the study aims to suggest guidelines that are suitable for the conditions of Korea. **Materials and Methods:** The study was conducted with 101 patients. With 24-hour urine samples from the patients after a 2-week restricted diet and after a 4-week restricted diet, the amount of iodine in the urine was estimated. The consumed radioiodine amounts for 2 hours and 24 hours were calculated. **Results:** This study was conducted with 47 LID patients and 54 RID patients. The amounts of iodine in urine, the 2-week case and 4-week case for each group showed no significant differences. The amounts of iodine in urine between the two groups were both included in the range of the criteria for radioiodine ablation therapy. Also, 2 hours and 24 hours radioiodine consumption measured after 4-week restrictive diet did not show statistical differences between two groups. **Conclusion:** A 2-week RID can be considered as a type of radioiodine ablation therapy after patients undergo a total thyroidectomy.

Key Words: Thyroid carcinoma, iodine diet, radioiodine ablation therapy

INTRODUCTION

Due to increased desire for regular medical check-ups along with the development of diagnostic technology, the prevalence rate of thyroid carcinoma has shown an increase domestically. For women, the incidence rate of thyroid cancer had the second highest percentage following breast cancer according to the domestic incidence rate of cancer in 2005.¹ Differentiated thyroid carcinoma, the most commonly occurring type of thyroid carcinoma, is a malignant tumor with a relatively favorable prognosis compared to other cancers.^{2,3} For treatment, radioiodine ablation therapy applying iodine-131 (¹³¹I) is done for patients who have undergone a total thyroid-

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ectomy. Patients are then monitored by neck ultrasonography and measuring the thyroglobulin antigen (Tg-Ag) levels in the blood. In positive thyroglobulin antibody (Tg-Ab) patients, a diagnostic radioiodine whole body scanning (dWBS) can also be useful.⁴ For effective radioiodine ablation therapy, a low iodine diet (LID) is implemented for a certain period.⁵ Normally, a LID restricts the daily consumption of iodine to less than 50 ug; the recommendations released by the American Thyroid Association (ATA) in 2006 advise carrying out a 1–2 week restricted diet before radioiodine ablation therapy.⁶ However, as Korea is surrounded on three sides by the sea and because Koreans are exposed to relatively more iodine containing food, people consume 468.9 ug of iodine per day, more than the average amount consumed by Americans, which is 195 ug.⁷ Against this background, we considered that new recommendations, different from those of the ATA, should be made for Korean patients. When implementing a LID for patients, most of them complain about the unpleasantness of maintaining the diet, and their quality of life is greatly affected by it. Therefore, some hospitals implement a restricted iodine diet (RID) that limits the daily consumption of iodine, only partially, to 50–100 ug.⁸

Kim, et al.⁷ reported the effectiveness of a 1-week LID by comparing a 1-week LID vs. a 2-week LID, and Tomoda, et al.⁹ reported the effectiveness of a 2-week LID by comparing a 1-week RID vs. a 1-week LID vs. a 2-week LID. However, neither study compared RID to LID under the same conditions, which made many centers hesitate to apply their results in a clinical setting. For this reason, many Korean doctors still prefer 4-week LID despite ATA guide line. This is a preliminary study to compare 2-week vs. 4-week according to restricted diet methods by analyzing urine samples and treatment outcomes for patients with differentiated thyroid carcinoma who previously underwent a total thyroidectomy and undergo radioiodine ablation therapy.

MATERIALS AND METHODS

Patients

Among 108 patients who had undergone a total thyroidectomy for differentiated thyroid carcinoma and agreed to participate in the research at the Thyroid Cancer Clinic of the College of Medicine at Yonsei University from March of 2009 to May of 2010, 101 patients who followed the diet in principle were included in this study. Patients with progressive or relapsing thyroid carcinoma were excluded. When

the patient visited the hospital on the seventh day after their operation, they were given an explanation of the research objective. If they agreed, the patient was selected as a subject, in the order of their hospital visit. Patients who did not follow the research plan were excluded from analysis. Research objectives were determined considering the opinions from diagnostic imaging results, those from surgical findings in operative field, and the histopathology results after the surgeries. Once this was determined, the study proceeded. All of the patients were hypothyroid status due to 4 weeks of T4 withdrawal.

Study design

For this study, the Research Institute of Food & Nutritional Sciences at Yonsei University provided meal plans for LID and RID and the Department of Nutrition at Shinchon Severance Hospital educated the patients about the diet.^{7,9,10}

1) The Department of Nutrition and the nutrition coordinators for the research provided the subjects with information about the diet and instructed them on how to keep diet records. They also provided diet guidelines and sample meal plans. Moreover, the patients were trained to keep records on two days during the week and on one day over the weekends. Diet guidelines and specific lists of approved and restricted foods provided to the patients are shown in Table 1 and 2.

2) Measurement of the amount of urine iodine was done after a 4-week restricted diet as well as a 2-week restricted diet. For 24 hours, urine was collected without preservatives. After waking up at 6 in the morning on Monday, the first urine sample was rejected. The sample came from the second production of urine. Urine samples were collected until the morning on Tuesday, and patient brought them to the hospital. A urine creatinine was determined. Urinary iodine was measured by Ion Selective Electrode method. An Orion EA 940 ion meter (Orion Research, Boston, MA, USA), equipped with an Orion 94-53 iodide-specific ion electrode, and an Orion 90-03 double-junction reference electrode, was used for determination of iodine. The standard solution was 0.1 M NaI, and the ionic strength was adjusted with 5 M NaNO₃. The creatinine in the urine was analyzed by the Jaffe method using Kyobuto company's creatinine kit (Kyobuto, Tokyo, Japan).¹¹ The measured figure of urine iodine was divided by the amount of urine creatinine to calculate the rate of I/Cr (ug/gCr). 30 mCi was administered on Wednesday. Scanning and thyroid function examinations were conducted on Friday. Thyroid uptake was performed at 2 hours and 24 hours after I-131 adminis-

tration. At this time, with the cooperation of the Department of Nuclear Medicine, the amount of radioiodine consumption was calculated and the difference between the two groups was confirmed. The amount of consumption (%) was calculated by comparing consumption at the neck based on consumption at the thigh. Thyroid uptake was measured using Koroid thyroid uptake system (SeYong NDC, Ltd., Seoul, Korea) equipped with single NaI (TI) scintillator with PM tube and lead shielded collimator. Briefly, the probe was placed approximately 30 cm from neck for thyroid uptake counts and thigh for body background counts. Calibration was done using a known radioiodine dose from neck phantom.

Radioiodine uptake (RAIU) was calculated using the following equation:

$$\text{RAIU} = \frac{\text{neck counts (cpm)} - \text{thigh counts (cpm)}}{\text{administered counts (cpm)} - \text{background counts (cpm)}}$$

Statistics

The targeted number of subjects was determined to be 92 according to a power analysis of a non-inferiority test done on the difference of the two means by the Department of Biostatistics, however, after confirming no difference between the two groups by conducting homoscedasticity for an intermediate verification when 50% of the targeted number was filled, recruitment of research subjects was closed. A paired t-test and a chi-square test were carried out using SPSS v12.0 for Windows (SPSS Inc., Chicago, IL, USA) in order to compare and analyze the results and the remedial values between the two groups.

Table 1. Diet Guidelines for the RID

Group	Approved	Restricted
Seaweed and seafood		All types of seaweed and seafood (laver, sea mustard, sea tangle, seaweed fusiforme, seastaghorn, sea mustard, shrimp, crab, etc.)
Meat and fish	Beef, pork, chicken (max. 200 g)	Fish and shellfish ham, sausage, fish paste
Milk and dairy products	Milk and dairy products (choose one: milk, ice-cream, cheese, yogurt), 1 cup of milk less than 200 mL	
Eggs	General egg (1 per day or less)	Eggs containing iodine (iodine egg, seaweed egg, etc.)
Grains	All types	
Fruits and vegetables	All fruits and vegetables	

RID, restricted iodine diet.

General Instructions: 1. Restrict seaweeds and fish, which are high in iodine; 2. The maximum amount of consumption for beef, pork and chicken is 200 g in total per day; 3. Do not use salt containing iodine (Ex: sea salt); 4. Avoid processed, imported, fast foods and eating out as much as possible; 5. Do not take vitamin/mineral supplements during the RID period. Specific list of approved and restricted foods.

Table 2. Diet Guidelines for the LID

Group	Approved	Restricted
Seaweed and seafood		All types of sea vegetable (laver, sea mustard, sea tangle, seaweed fusiforme, seastaghorn, sea mustard) and sea food (crab, oyster, shrimp, etc.)
Fish and shellfish		All types of fish and shellfish
Meat	Beef, pork, chicken (max. 100 g)	Ham, sausage, fish paste
Eggs	General egg (1/2 per day or less)	Eggs containing iodine (iodine egg, seaweed egg, etc.)
Dairy products		Milk and dairy products, soymilk
Grains	All types	Cereal with red food coloring, bread
Fruits and vegetables	All types of raw fruits and vegetables	Juice with red food coloring, canned
Others		Stock, anchovy stock, udon soup, instant noodles soup, etc.

LID, low iodine diet.

General Instructions: 1. Restrict seaweed (laver, sea mustard, sea tangle, seaweed fusiforme, seastaghorn, etc.) and fish; 2. Do not use salt containing iodine (Ex: sea salt); 3. Avoid processed and imported foods as much as possible; 4. Do not take vitamin/mineral supplements during the LID period; 5. Avoid eating out and fast foods as much as possible; 6. Avoid consuming stock, anchovy stock, udon soup, instant noodle soup, etc.; 7. Avoid food containing red food coloring (confectionery, candy, juice, cereal, etc.) and drugs (cough syrup, etc.) as much as possible; 8. Avoid salted food (salted fish, pickled vegetables, sauce, food containing liquid sauce) as much as possible. Specific list of approved and restricted foods.

Ethics statement

This study was approved by the Institutional Review Board of the Severance Hospital Institutional Review Board (IRB No. 4-2008-0646).

RESULTS

Analysis of the clinical characteristics of patients

The total number of applicants for the research was 108, including 52 patients on a LID and 56 patients on a RID, but 5 from the LID group and 2 from the RID group were excluded because they did not adhere to the diets. According to the analysis of clinical characteristics of the 47 patients on a LID and the 54 patients on a RID, there were no statistical differences in terms of their age, gender, capsule invasion, the maximal size of tumor, multifocality, bilaterality, central node invasion, lateral neck node invasion, distant metastasis, and serum thyroglobulin level which proved that the subjects for the study were suitably selected (Table 3).

Analysis of characteristics according to the TNM stage

The patients' TNM stages were classified based on the 7th edition of the American Joint Committee on Cancer (AJCC).¹² The number of patients in Stages I and III were 37 (36.6%) and 58 (57.4%), respectively, which accounted for 94.0% of the total number of patients. There was no statistical difference between the LID and RID groups (Table 4).

Comparison of the urinary I/Cr and urine creatinine for the LID and RID groups

According to the paired t-test, no statistical differences existed in the urine I/Cr and urine creatinine values in each group according to diet duration (Table 5).

Comparison of radioiodine consumption between the LID and RID groups

Consumption of radioiodine after 4 weeks of diet restriction showed no statistical difference between the two groups at 2 and 24 hours after consuming radioiodine (Table 6).

DISCUSSION

Although there have been differing opinions regarding treatments for differentiated thyroid carcinoma, many institutes perform radioiodine ablation therapy after a total thyroidec-

tomy.¹³ Radioiodine ablation therapy with an application of ¹³¹I has been utilized to treat or examine residual thyroid tissue or metastasized thyroid carcinoma after a total thyroidectomy since Keston, et al.¹⁴ reported that radioiodine is consumed in tissues in which differentiated thyroid carcinoma had metastasized.¹⁵ To increase radioiodine uptake, thyroid-stimulating hormone (TSH) range can be increased by stopping thyroid hormone therapy or by injecting recombinant human TSH (rhTSH). Moreover, by decreasing the concentration of iodine through a LID, the sensitivity of residual thyroid tissues toward TSH can be increased. In turn, consumption of radioiodine can be increased. Moreover, by increasing sodium iodide symporter (hNIS), specific activity of radioiodine can be increased.^{16,17} Residents in regions lacking

Table 3. Clinical Characteristics of the Patients

	Total	Diet	
		Low iodine diet	Restricted iodine diet
Age (yrs)	52.0 (23–73)	52.0 (23–73)	51.5 (24–72)
Gender			
Male	13	6	7
Female	88	41	47
Capsule invasion (%)			
No	24 (23.8)	12 (50.0)	12 (50.0)
Yes	77 (76.2)	35 (45.5)	42 (54.5)
Maximal size (cm)	0.9 (0.2–4.0)	0.9 (0.3–4.0)	0.8 (0.2–3.0)
Multifocality (%)			
No	60 (59.4)	27 (45.0)	33 (55.0)
Yes	41 (40.6)	20 (48.8)	21 (51.2)
Bilaterality (%)			
No	71 (70.3)	30 (4.23)	41 (57.7)
Yes	30 (29.7)	17 (56.7)	13 (43.3)
Central node invasion (%)			
No	62 (61.4)	28 (45.2)	34 (54.8)
Yes	39 (38.6)	19 (48.7)	20 (51.3)
Lateral neck node invasion (%)			
No	101 (100)	47 (46.5)	54 (53.5)
Yes	0 (0)	0 (0)	0 (0)
Distant metastasis (%)			
No	101 (100)	47 (46.5)	54 (53.5)
Yes	0 (0)	0 (0)	0 (0)
Serum Tg* (ng/mL)		1.69 (0.2–14.26)	1.28 (0.21–92.07)

TSH, thyroid-stimulating hormone.

*Median serum thyroglobulin antigen level with TSH suppression off status.

iodine have a daily urine iodine (I/Cr) of <50 ug/gCr on average, while people living in areas with a normal amount of iodine consumption show >100 ug/gCr. Hence, many institutions consider daily urine iodine (I/Cr) <50 ug/gCr amounts as the optimal figure for measurement when a patient undergoes radioiodine ablation therapy. Meanwhile, Park and Hennessey¹⁸ estimated a range as high as <100 ug/gCr as appropriate.^{19,20} Many institutions limit the daily amount of iodine consumption to <50 ug for a LID and 50–100 ug for a RID prior to radioiodine ablation therapy.²¹ According to the recommendations published by the ATA in 2006, the restricted diet should be implemented 1–2 weeks before radioiodine ablation therapy.⁶ In Korea's case, however, people consume 468.9 ug on average, which is more than the average consumption of iodine per day for Americans (195 ug), and

Table 4. Characteristics According to TNM Stage

	Total	Diet	
		Low iodine diet	Restricted iodine diet
T stage (%)			
T1	21 (20.8)	9 (42.9)	12 (57.1)
T2	3 (3.0)	3 (100)	0 (0)
T3	72 (71.3)	33 (45.8)	39 (54.2)
T4a	5 (5)	2 (40.0)	3 (60.0)
N stage (%)			
N0	62 (61.4)	28 (45.2)	34 (54.8)
N1a	39 (38.6)	19 (48.7)	20 (51.3)
M stage			
M0	101 (100)	47 (46.5)	54 (53.5)
Over all stage (%)			
I	37 (36.6)	15 (40.5)	22 (59.5)
II	1 (1.0)	1 (100)	0 (0)
III	58 (57.4)	29 (50.0)	3 (50.0)
IVa	5 (5.0)	2 (40.0)	3 (60.0)

Table 5. Comparison of Urinary I/Cr and Urine Creatinine Values for the LID and RID Groups According to Diet Duration

Diet	Duration		<i>p</i> value
Low iodine diet			
Urine I/Cr (ug/gCr)*	2 wks	28.6 (23.6)	0.253
	4 wks	35.0 (33.0)	
Urine creatinine (mg/dL)*	2 wks	110 (85.4)	0.295
	4 wks	94.3 (81.3)	
Restricted iodine diet			
Urine I/Cr (ug/gCr)*	2 wks	35.8 (35.2)	0.884
	4 wks	35.0 (31.0)	
Urine creatinine (mg/dL)*	2 wks	103.1 (93.2)	0.530
	4 wks	112.9 (91.9)	

LID, low iodine diet; RID, restricted iodine diet.

*Mean standard deviation.

almost identical to the average amount consumed by Japanese, at 544 ug.^{7,22,23} Moreover, Koreans are exposed to relatively more food with high iodine content such as seaweed and fish. Accordingly, rather than following the recommendations of the ATA, many institutions actually apply a longer duration to the restricted diet, considering the characteristics of Korea. Regarding restricted diets, because Koreans and Japanese normally enjoy meals that are high in iodine, LID causes considerable discomfort to patients in terms of their quality of life. Thus, some studies on RIDs have been published in Korea and Japan.^{8,9} We prepared meal plans for RIDs and LIDs that are suitable for conditions in Korea by requesting the Research Institute of Foods and Nutritional Science at Yonsei University. For the durations of the restricted diets, the analyses were conducted for 2 and 4 weeks, which are used mostly in Korean institutions, not based on 1- and 2-week diets in foreign cases. In general, to measure urine iodine (I/Cr), urine is collected in the morning on the day of hospitalization for radioiodine ablation therapy, or urine collected by the patient over a period of 24 hours is used. Research thus far has used the urine produced in the morning on the day of the procedure instead of the 24-hour concentrated urine in order to measure I/Cr due to the objections of patients; however, because the output of iodine to urine strongly depends on the iodine concentration in the blood for the urine in the morning sample, it is difficult to measure the amount of I/Cr as precisely as with the 24-hour concentrated urine.^{24,25} In this study, we strictly trained patients to visit the hospital and deliver 24-hour concentrated urine on the 2nd and 4th week of the restricted diets. The urine iodine calculation was calculated by dividing it with the amount of creatinine. As the measured amount can differ according to individual body water contents when using urine iodine that is not revised by creatinine, it is not easy to differentiate if the figure truly reflects the amount of iodine in the body. Thus, it should be revised by urine creatinine.^{18,24} Urine creatinine can differ according to gender and age. In general, given that men and the young have more muscle tissue than women and the elderly, urine I/Cr tends to increase with age, and women tend to have higher figures than to men.^{26,27} In the present study, the ratio of males to females was 1:6.8 and the average age was 53 (range: 23–72) for the LID group, whereas the ratio of males to females was 1:6.7 and the average age was 51.5 (24–72) for the RID group; there was no statistical difference between the two. Hence, statistical bias can be minimized. One possible problem when selecting research subjects was that the

Table 6. Comparison of Radioiodine Consumption between the LID and RID Groups

Radioiodine uptake	Diet		<i>p</i> value
	LID	RID	
After 2 hrs (%) [*]	1.95 (0.67)	1.83 (0.83)	0.811
After 24 hrs (%) [*]	2.78 (2.62)	2.69 (4.05)	0.721

LID, low iodine diet; RID, restricted iodine diet.

^{*}Mean standard deviation.

volume of residual thyroid tissues can be slightly different because the operation methods can vary according to the institution in the case of cooperative research at multiple institutions. This can cause statistical bias. We conducted our research with patients undergoing surgeries with the same operation methods at a single institution, which should minimize statistical prejudice. To compare the amount of urine I/Cr, the amounts at the 2nd and 4th weeks were compared for each group. In the LID group, the average amount of urine I/Cr for the 2nd and 4th weeks were 28.6 ug/gCr (3.7–107) and 35.0 ug/gCr (3.5–185.9), respectively, showing a rather lower I/Cr average amount for a 2-week restricted diet, but with no statistical meaning. The amount of urine I/Cr was >100 ug/gCr in one case of the 2-week restricted diet and in two cases of the 4-week restricted diet. This might have occurred because the average amount of urine creatinine was 110 mg/dL (11.7–452.7) for the 2-week restricted diet, which is higher than the figure of 94.3 mg/dL (19.7–419.5) for the 4-week restricted diet. However, it should be considered that compliance for some of the patients decreased as the duration of the diet was extended. In the RID group, the average amounts of urine I/Cr measured at the 2nd and the 4th week were 35.8 ug/gCr (3.7–142.3) and 35.0 ug/gCr (1.9–152.6), showing a slightly lower amount for the 4-week restricted diet, but this had no statistical importance. This arose because the average amount of urine creatinine for the 2-week diet was 103.1 mg/dL (11.1–378.7), which was less than that of the 4-week diet, at 112.9 mg/dL (11.6–452.7). The amount of urine I/Cr was >100 ug/gCr for four cases in the 2-week restricted diet group and two cases in the 4-week restricted diet group. The LID figure for amount of urine I/Cr was less in the 2-week restricted diet than the RID, whereas in the 4-week diet, the two groups showed same amount. However, both figures were included in the range of <50 ug/gCr, which is the required amount for radioiodine ablation therapy. I-131 whole body scan was performed once at 2 days after I-131 administration, and thyroid uptake was performed at 2 hours and 24 hours after I-131 administration, with both showing no

statistical gaps. The amount of radioiodine consumption was calculated using gamma-rays from the regions where the thyroids were removed, based on the thigh data after a request to the Department of Nuclear Medicine of Severance Hospital at Yonsei University. Results showed no statistical differences in the amounts of urine I/Cr or urine creatinine in each group between the 2-week and 4-week restricted diet groups, and no differences between the RID and LID groups. Moreover, as for the amounts of radioiodine consumption for a 4-week restricted diet, the two groups did not show a difference. Therefore, with systematic education for the patients, RID for 2 weeks can be considered for radioiodine ablation therapy after a total thyroidectomy. Moreover, it is expected that this may improve patient quality of life. In this study, the consumption amount was measured only for a 4-week restricted diet. Rather than conducting research with different patients and dividing them into 2-week and 4-week restricted diet groups, we thought it to be more accurate to work with the same patients. Moreover, if they were to be included in the range of optimal figures for treatment with little difference in urine I/Cr, we considered that the gap in the amount of radioiodine consumption would not be significant. Although patients with progressive or relapsing thyroid carcinoma were excluded, we hope that the RID can be expanded by analyzing the prognosis related to a restricted diet through monitoring of research subjects in the future.

In this study, the amounts of urine iodine and urine creatinine were compared and analyzed by setting 2-week and 4-week diet durations for the LID and RID group, and there were no differences between the durations; a comparison between the two diets also showed no differences. The two diets did not show any difference in the amounts of radioiodine consumption for a 4-week restricted diet. Therefore, when developing an adaptability plan for patients using the LID for radioiodine ablation therapy, it is reasonable to consider a 2-week RID after ensuring strict education for the patients, in order to improve their quality of life.

Furthermore, if patients do not receive proper diet education, they may proceed with ambiguous iodine restriction between the RID and LID. For the application of the RID in a clinical setting, the importance of thorough patient education cannot be overemphasized.

This is a preliminary study showing that 4-week LID and RID are unnecessary. Although we did not apply objective method to analyzing the quality of life, it is quite possible that it made patient's quality of life worse.

In extension of this preliminary results, we are in a pro-

cess to compar 1-week vs. 2-week according to restricted diet method and to obtain objective data to recommend application in clinical setting, including the method of analyzing the quality of life.

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