



저작자표시 2.0 대한민국

이용자는 아래의 조건을 따르는 경우에 한하여 자유롭게

- 이 저작물을 복제, 배포, 전송, 전시, 공연 및 방송할 수 있습니다.
- 이차적 저작물을 작성할 수 있습니다.
- 이 저작물을 영리 목적으로 이용할 수 있습니다.

다음과 같은 조건을 따라야 합니다:



저작자표시. 귀하는 원저작자를 표시하여야 합니다.

- 귀하는, 이 저작물의 재이용이나 배포의 경우, 이 저작물에 적용된 이용허락조건을 명확하게 나타내어야 합니다.
- 저작권자로부터 별도의 허가를 받으면 이러한 조건들은 적용되지 않습니다.

저작권법에 따른 이용자의 권리는 위의 내용에 의하여 영향을 받지 않습니다.

이것은 [이용허락규약\(Legal Code\)](#)을 이해하기 쉽게 요약한 것입니다.

[Disclaimer](#) 

The Changing Pattern of Urine Iodine
Excretion with Low Iodine Diet during
Preparation for RAI Ablation in Thyroid
Cancer Patients; A Prospective
Comparative Study of Thyroxine
Withdrawal vs. rhTSH using Groups

Sang-Wook Kang

Department of Medicine

The Graduate School, Yonsei University



연세대학교
YONSEI UNIVERSITY

The Changing Pattern of Urine Iodine
Excretion with Low Iodine Diet during
Preparation for RAI Ablation in Thyroid
Cancer Patients; A Prospective
Comparative Study of Thyroxine
Withdrawal vs. rhTSH using Groups.

Directed by Professor Woong Youn Chung

The Doctoral Dissertation
submitted to the Department of Medicine,
the Graduate School of Yonsei University
in partial fulfillment of the requirements for the degree
of Doctor of Philosophy

Sang-Wook Kang

December 2017

This certifies that the Doctoral Dissertation
of Sang-Wook Kang is approved.

Thesis Supervisor : Woong Youn Chung

Thesis Committee Member#1 : Eun Jig Lee

Thesis Committee Member#2 : Jae Bok Lee

Thesis Committee Member#3: Yoon Woo Koh

Thesis Committee Member#4: Mijin Yun

The Graduate School
Yonsei University

December 2017

ACKNOWLEDGEMENTS

The author thank our colleagues from Yonsei University College of Medicine who provided insight and expertise that greatly assisted the research, although they may not agree with all of the interpretations/conclusions of this paper.

I especially thank Dr. Woong Youn Chung (Surgery, Yonsei University College of Medicine), Dr. Eun Jig Lee (Internal medicine, Yonsei University College of Medicine), Dr. Jae Bok Lee(Surgery, Korea University School of Medicine), Dr. Yoon Woo Koh (Otolaryngology, Yonsei University College of Medicine), Dr. Mijin Yun (Nuclear Medicine, Yonsei University College of Medicine) for sharing their pearls of wisdom with us during the course of this research, and special reviews for their so-called insights.

I would also like to show my sincere gratitude to Dr. Haiyoung Son, and Dr. Eun Jeong Ban for assistance with patient enrollment and gaining informed consent, and Dr. Zeng Yap for comments that greatly improved the manuscript.

I also thank the study patients whose cooperation, sacrifices, and trust were critical to evaluating this advance in management of this increasingly common disease.

I hereby attest that the study was funded by Sanofi-Genzyme Co. and disclose financial relations with Sanofi-Genzyme Co. The study, however, is not modified by the entity nor reflects particular interests. The authors whose names are listed in this study certify that they have no affiliations or involvement with Sanofi-Genzyme and declare no conflicts of interests with the entity.

<TABLE OF CONTENTS>

ABSTRACT	1
I. INTRODUCTION	3
II. MATERIALS AND METHODS	4
1. STUDY DESIGN	4
2. INCLUSION AND EXCLUSION CRITERIA	6
3. ASSESSMENT	6
III. RESULTS	7
IV. DISCUSSION	11
V. CONCLUSION	15
REFERENCES	16
ABSTRACT(IN KOREAN)	20

LIST OF FIGURES

Figure 1. Schematic urine sample collection schedule	7
Figure 2. Changing patterns of the UIE on both groups	11

LIST OF TABLES

Table 1. Clinicopathological characteristics of two groups	8
Table 2. Patterns of UIE during 14 days of LID.	9
Table 3. Urinary I/Cr ratio at the day of 7 th and 14 th of LID	9
Table 4. Patterns of UIE in inadequately prepared patients (N=6)	10
Table 5. Patterns of UIE in adequately prepared patients (N=88)	10

ABSTRACT

The Changing Pattern of Urine Iodine Excretion with Low Iodine Diet during Preparation for RAI Ablation in Thyroid Cancer Patients; A Prospective Comparative Study of Thyroxine Withdrawal vs. rhTSH using Groups
Sang-Wook Kang

*Department of Medicine
The Graduate School, Yonsei University*

(Directed by Professor Woong Youn Chung)

Background: Radioactive iodine ablation (RAI) is usually performed after total thyroidectomy for well-differentiated thyroid cancer to reduce disease relapse and disease-related death in high risk group. However, RAI treatment requires many weeks of preparation, including thyroxine withdrawal and low iodine diet (LID), which may be very uncomfortable for some patients. This is especially noticeable in Korea and Japan, where iodine intake is relatively high. Adhering to the strict and complex LID diet is often difficult because the diet is unpalatable for many patients. With this in mind, we investigated the optimal period of iodine restriction for RAI treatment in an area with iodine rich diet through analyzing the changing pattern of urine iodine excretion (UIE) during LID, and evaluated whether there is any difference in the UIE levels between two differently prepared groups.

Materials: A total of 94 patients who underwent total thyroidectomy and RAI ablation were enrolled in the study. All patients were prospectively allocated into the two study groups according to the patient's preference (thyroxine withdrawal or using rhTSH for TSH stimulation). Informed consent was obtained from all patients. For the evaluation of the changing patterns of UIE,

we collected 6 and 7 separate spot urine specimens during the LID period (0, 3rd, 5th, 7th, 10th, 14th days in the withdrawal and 0, 3rd, 7th, 10th, 11th, 12th, 14th in the rhTSH group) accordingly. We also analyzed the pattern and differences in UIE during LID between the two groups.

Result: There was no statistically significant difference in the clinicopathologic characteristics except for the tumor size and lymph node (LN) status between the two groups. In the withdrawal group, the median values of the morning UIE (I/Cr ratio) serially reduced with time, and the I/Cr ratios on the 7th and 14th day were 18.3 (4.2-908.6) and 17.9 $\mu\text{g/gCr}$ (4.3-190.4), respectively. The adequate preparation rate on the 7th and 14th day for UIE (cutoff value 100 $\mu\text{g/gCr}$) were 93.3% and 93.3%, respectively. In rhTSH group, I/Cr ratios on the 7th day and 14th day were 48.0 (10-95) and 45.7 (19.2-388.8), and the adequate preparation rates were 91.8% and 93.8%, respectively.

Conclusion: One week of strict LID is sufficient preparation for RAI ablation in areas with iodine rich diet. The one-week schedule of LID can be safely applied to patients prepared with either thyroxine withdrawal or patients using rhTSH.

Key words: low iodine diet (LID), radio-active iodine (RAI) ablation, urine iodine excretion, thyroid cancer.

The Changing Pattern of Urine Iodine Excretion with Low Iodine Diet during Preparation for RAI Ablation in Thyroid Cancer Patients; A Prospective Comparative Study of Thyroxine Withdrawal vs. rhTSH using Groups

Sang-Wook Kang

*Department of Medicine
The Graduate School, Yonsei University*

(Directed by Professor Woong Youn Chung)

I. INTRODUCTION

The prevalence of differentiated thyroid cancer is high and rising globally.¹⁻⁴ Following total thyroidectomy for well-differentiated thyroid cancer, RAI treatment is given to high risk patients to reduce disease relapse and disease related death. Apart from ablating the remaining thyroid and cancer cells, RAI is also used to diagnose the presence of remnant thyroid or metastatic disease.^{2,4}

RAI treatment however, requires many weeks of preparation which causes some discomfort to the patients. For optimal RAI treatment, serum thyroid stimulating hormone (TSH) level should be above 30 μ U/ml prior to the treatment. In order to reach this level, the administration of thyroid hormone has to be stopped, and a dietary program that limits the intake of iodine should be implemented.⁵⁻⁷ The iodine restriction diet prior to RAI treatment should be given to all patients for a period of 1-2 weeks or more.⁸ The purpose of iodine restriction is to increase the expression of the sodium-iodine symporter (NIS) in the thyroid follicular cells by lowering the iodine concentration within the body. It also minimizes the competitive handling by NIS of non-radioactive iodine instead of the radioactive iodine.⁹

Due to the complexity of the low iodine diet (LID), it is not easy for patients to follow the instructions while living their ordinary lifestyles. This is a significant issue especially in Korea and Japan, where iodine intake is relatively high. Many patients have difficulty following the complex LID schedule because the menu is devoid of food that constitute their daily diet. It is also not a diet that is particularly palatable to the patients. Therefore, recently, the suggestion of a more moderate and less stringent dietary menu, as well as opinions regarding the reduction in the period of the strict dietary restriction, are being considered.

10, 11

The recommended period of iodine restriction diet prior to RAI varies depending on several major guidelines, and there is no uniform standardized method till this day. Although there are a great number of on-going researches both within and outside of Korea to find the optimal period for iodine restriction, ^{5, 9-12} there is limited reliable clinical data on the internal iodine accumulation level before and after the RAI treatment and their association with the iodine restriction dietary program. Therefore, the primary purpose of this research was to investigate the urinary iodine excretion pattern during the 2-week period of iodine restriction. This research could suggest the optimal period of iodine restriction from the current 2 weeks to a shorter period by investigating the changes in iodine excretion. We also evaluated whether there is any difference in the UIE level between two differently prepared groups.

II. MATERIALS AND METHODS

1. *Study design*

Patients from Seoul and Gyeonggi provinces who were planned to receive RAI treatment after total thyroidectomy at Yonsei University Health System, Seoul, Korea from May 2013 to October 2013 were enrolled. The enrolled patients

were divided into two groups. One group, which is the withdrawal group, discontinued administration of the levothyroxine for 4 weeks before the RAI treatment. The other group, the recombinant human thyroid stimulating hormone (rhTSH) group, continued to receive levothyroxine, but were administered 0.9 mg rhTSH injections for 2 days before receiving the RAI treatment. Both groups went through the iodine restriction diet for 2 weeks before the RAI treatment.

The number of research subjects was initially calculated to be 50 patients for each group, based on the results from similar researches regarding the changes of iodine excretion measured during LID, and also after discussion with our department statistician. During the study period, 5 patients in the withdrawal group and 1 in the rhTSH group could not reach the target point (failed to gather the urine samples), and dropped off from this study. Hence the final number of subjects for the thyroxine withdrawal group and the rhTSH group were 45 and 49, respectively.

During the 2 weeks of iodine restriction diet, the withdrawal group visited the hospital 6 times on the 0th, 3rd, 5th, 7th, 10th, and 14th days, whereas the rhTSH group visited the hospital on the 0th, 3rd, 7th, 10th, 11th, 12th, 14th day, for the spot urine collection. The simple urine iodine and iodine/creatinine ratios were measured and the mean and median values and standard deviation from the results of all patients were calculated. The change in iodine excretion level was analyzed. The points where its level fall below the cut off value (I/Cr ratio < 100 ($\mu\text{g/gCr}$)), as suggested by major guidelines, were noted. All subjects underwent the RAI treatment afterwards. The Institutional Review Board (IRB) of Yonsei University College of Medicine reviewed and approved the protocol for this prospective study (IRB number 4-2012-0431). Research participants gave signed, informed consent, which was confirmed by the IRB, after receiving an explanation of the study purpose.

2. *Inclusion and exclusion criteria*

According to the Revised American Thyroid Association management guidelines (2009) and the Revised Korean Thyroid Association Management Guidelines (2011), the inclusion criteria for this clinical research was defined as patients who were newly diagnosed with differentiated thyroid cancer, underwent total or near total thyroidectomy and were going to receive the radioactive iodine treatment. The patients who have significant medical disease such as renal dysfunction, or take medications which contain iodine or affect the renal function were excluded. Cases with extra-thyroidal invasion (T4), lateral neck node metastasis (N1b), and distant metastasis (M1) were also excluded from this study.

3. *Assessment*

The spot urine specimens were collected 6 to 7 times for 2 weeks between the starting day of iodine restriction diet and the final day. The simple I and I/Cr ratios were measured.¹² Although the method has some disadvantages in showing diurnal changes compared to the 24-hour urine specimen, it was decided that measuring the iodine excretion volume with Chemical method (Sandell–Kolthoff reaction) by using the microplate format based on discussion with Laboratory Medicine Department of Severance Hospital would overcome the issue. This method was adopted by the EQUIP (Ensuring the Quality of Urinary Iodine Procedures) of CDC (Centers for Disease Control and Prevention) and validated.¹³ According to the Vanacor et al., when compared with the 24-hour urine specimen, the spot urine specimen collected between lunch and dinner is least affected by the diurnal changes. Hence the clinic visiting time during the research was set between 1p to 5pm.¹⁴ To identify the change in iodine excretion pattern during the 2-week period of iodine restriction diet, iodine excretion volumes in both the withdrawal and rhTSH groups were measured.

III. RESULTS

Figure 1 shows the schedule of urine sample collection during the 14-day LID period. In the thyroxine withdrawal group, the spot urine specimens were collected 6 times for 2 weeks from the starting day of iodine restriction diet until the final day. The first morning urine was collected on Day 0,3,5,7,10 and 14 in the thyroxine withdrawal group. In the rhTSH treated group, the first urine samples were obtained on Day 0,3,7,10,11,12 and 14. Adequate urine iodine excretion (UIE) was defined as I/Cr ratios below 100 $\mu\text{g/gCr}$.

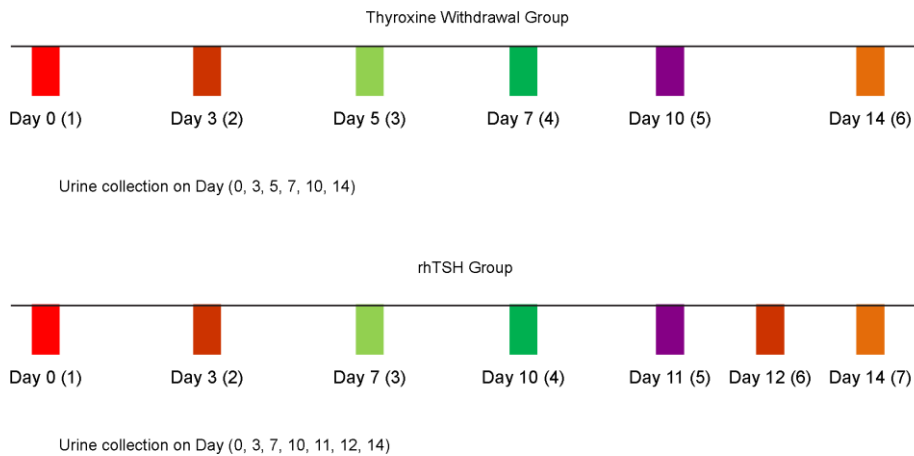


Figure 1. Schematic urine sample collection schedule

There was no statistically significant difference in the clinicopathological characteristics except the tumor size and LN status between the rhTSH group and the withdrawal group, suggesting that the patient participants were well-balanced between the two groups (Table 1). The tumor size was bigger in withdrawal group (withdrawal vs. rhTSH; 1.47 ± 1.12 vs 1.10 ± 0.62 , $P=0.006$), and LN positive rate was higher in withdrawal group (withdrawal vs. rhTSH;

71.1% vs. 46.9%, $P=0.029$) compared to the rhTSH group. The discrepancy in pathologic status between the two groups was a result of the group allocation. The study group allocation was mainly decided by the patient's preference after the operation, and the patients who had advanced disease had shown the tendency to choose the withdrawal group for the RAI treatment preparation.

Table 1. Clinicopathological characteristics of two groups

	rhTSH(N=49)	Withdrawal (N=45)	P-value
Age (mean)	41.6±8.3	43.2±9.8	0.135
Gender	4 (8.2%)	4 (8.9%)	0.594
Male	45 (91.8%)	41 (91.1%)	
Female			
BMI	23.78±3.45	23.44±3.20	0.484
Peak TSH (mU/L)	110.8±38.1	82.1±49.7	0.107
Just before ablation			
Tumor size (cm)	1.10±0.62	1.47±1.12	0.006
Histology	45 (91.8%)	42 (93.4%)	0.281
PTC	4 (8.2%)	1 (2.2%)	
FTC		1 (2.2%)	
FVPTC		1 (2.2%)	
SVPTC (solid variant)			
LN status	26/23	13/32	0.029
Negative	26 (53.1%)	13 (28.9%)	
Positive	23 (46.9%)	32 (71.1%)	
Stage I	36(73.5%)	24(53.3%)	0.058
III	12(24.5%)	21(46.7%)	
IV	1(2%)		

Table 2 and 3 display the UIE patterns during the two weeks of LID. The median values of the spot UIE serially reduced with time. Median values of the I/Cr ratio on the 7th and on the 14th day were 48.0µg/gCr (range 10-95) and

45.7 (range 19.2-388.8), respectively in the rhTSH group, whilst they were 18.3 (range 4.2-908.6) and 17.9 (range 4.3-190.4) respectively, in the withdrawal group. The rate of adequate UIE for RAI treatment were 91.8% vs. 93.8% (7th vs. 14th day) in the rhTSH group, and 93.3% vs. 93.3% in the withdrawal group, respectively.

Table 2. Patterns of UIE during 14 days of LID.

	0 day	3rd day	5th day	7th day	10th day	11th day	12th day	14th day
	I/Cr ratio (µg/gCr)	I/Cr ratio (µg/gCr)	I/Cr ratio (µg/gCr)	I/Cr ratio (µg/gCr)	I/Cr ratio (µg/gCr)	I/Cr ratio (µg/gCr)	I/Cr ratio (µg/gCr)	I/Cr ratio (µg/gCr)
rhTSH (N=49)								
Mean	519.7±718.7	92.2±141.8		49.3±20.3	61.7±37.2	106.8±232.3	80.3±118.7	59.5±56.9
Median	282.1	56.6		48.0	52.9	54.3	48.6	45.7
Range	(40.5~4546.2)	(18.4~773.6)		(10~95)	(20.5~173.8)	(18.8~1414.6)	(25.7~802.2)	(19.2~388.8)
Adequate UIE				45 (91.8%)				46 (93.8%)
Withdrawal (N=45)								
Mean	822.9±1104.3	56.7±132.2	24.6±16.3	51.6±137.5	40.5±56.6			32.6±39.2
Median	350.9	31.1	22.0	18.3	21.2			17.9
Range	(27.5~5410.2)	(8.9~901.1)	(2.0~80.0)	(4.2~908.6)	(4.5~263.6)			(4.3~190.4)
Adequate UIE				42 (93.3%)				42 (93.3%)

Table 3. Urinary I/Cr ratio at the day of 7th and 14th of LID

	I/Cr ratio (µg/g Cr)	Adequate UIE	I/Cr ratio (µg/g Cr)	Adequate UIE
	7 th day of LID	portion at 7 th day	14 th day of LID	portion at 14 th day
rhTSH (N=49)	Mean : 49.3±20.30 Median : 48.0 Range : 10~95	45 (91.8%)	Mean : 59.5±56.9 Median : 45.7 Range : 19.2~388.8	46 (93.8%)
Withdrawal	Mean : 51.6±137.5	42 (93.3%)	Mean : 32.6±39.2	42 (93.3%)

(N=45)	Median : 18.3 Range : 4.2~908.6	Median : 17.9 Range : 4.3~190.4
--------	------------------------------------	------------------------------------

There were several patients who broke the LID schedule due to poor compliance. The notable increase in their UIE (3 in the rhTSH and 3 in the withdrawal group) indicates that the patients consumed food with high iodine content more than once during the LID period. All the patients admitted to that during follow-up interviews. (Table 4). After analysis of the 88 patients who were compliant with their diet and hence had appropriate UIE levels, we found that the pattern of UIE was quite dramatic without much difference between the two groups. (Table 5). This is highlighted in Figure 2, where a significant drop in median UIE is seen during the LID period, suggesting that adequate UIE level required for RAI can be achieved within 3 days after starting LID in both groups.

Table 4. Patterns of UIE in inadequately prepared patients (N=6)

	0 day	3rd day	5th day	7th day	10th day	11th day	12th day	14th day
	I/Cr ratio	I/Cr ratio	I/Cr ratio	I/Cr ratio	I/Cr ratio	I/Cr ratio	I/Cr ratio	I/Cr ratio
	($\mu\text{g/gCr}$)	($\mu\text{g/gCr}$)	($\mu\text{g/gCr}$)	($\mu\text{g/gCr}$)	($\mu\text{g/gCr}$)	($\mu\text{g/gCr}$)	($\mu\text{g/gCr}$)	($\mu\text{g/gCr}$)
rhTSH								
A	850.50	125.00		205.20	160.00	140.00	91.70	177.60
B	291.90	96.20		66.70	59.70	38.30	57.90	388.80
C	229.90	70.70		60.30	56.10	32.30	75.80	167.10
Withdrawal								
D	3448.10	901.10	133.90	908.60	254.70			190.40
E	81.60	140.70	69.60	242.70	263.60			161.40
F	353.80	16.40	29.20	16.70	24.70			114.50

Table 5. Patterns of UIE in adequately prepared patients (N=88)

	0 day	3rd day	5th day	7th day	10th day	11th day	12th day	14th day
	I/Cr ratio	I/Cr ratio	I/Cr ratio	I/Cr ratio	I/Cr ratio	I/Cr ratio	I/Cr ratio	I/Cr ratio
	($\mu\text{g/gCr}$)	($\mu\text{g/gCr}$)	($\mu\text{g/gCr}$)	($\mu\text{g/gCr}$)	($\mu\text{g/gCr}$)	($\mu\text{g/gCr}$)	($\mu\text{g/gCr}$)	($\mu\text{g/gCr}$)
rhTSH								
(N=46)								
Mean	523.8±738.6	91.9±146.4		49.4±20.3	59.8±35.5	90.3±204.2	74.3±116.0	47.4±18.4

Median	271.5±515.6	55.9±38.6		47.0±30.5	50.9±30.8	54.3±26.9	47.1±32.9	45.0±20.7
Range	(40.5~4546.2)	(18.4~773.6)		(10~95)	(20.5~173.8)	(18.8~1414.6)	(25.7~802.0)	(19.2~94.0)
Adequate UIE				43 (93.3%)				46 (100%)
Withdrawal (N=42)								
Mean	789.3±1058.6	35.5±26.3	23.7±15.2	27.5±29.4	30.4±31.6			23.8±19.9
Median	300.4±807.7	30.4±22.8	22.0±20.9	18.2±25.1	20.5±20.1			16.2±24.5
Range	(27.5~5410.2)	(8.9~141.0)	(2.0~80.0)	(4.2~170.8)	(4.5~157.6)			(4.3~94.0)
Adequate UIE				41 (97.6%)				42 (100%)

Figure 2 dramatically shows the changing patterns of the median UIE values during the LID period, and it reveals that the adequate UIE level can be achieved within 3 days after starting LID on both groups.

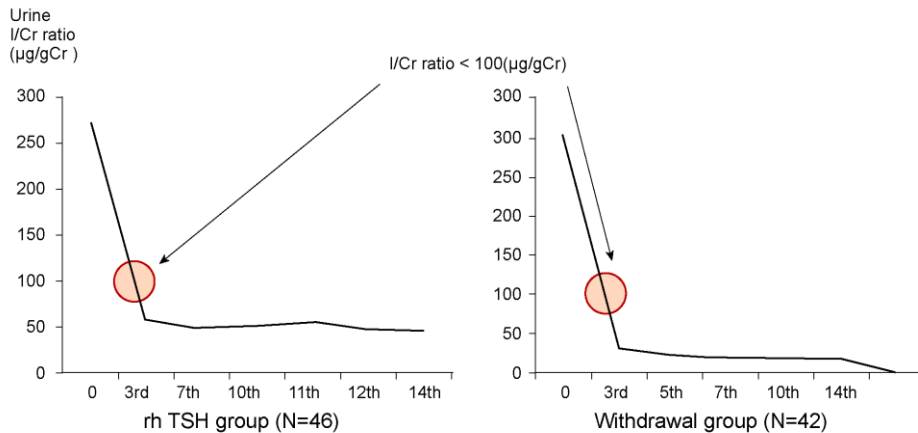


Figure 2. Changing patterns of the UIE on both groups

IV. DISCUSSION

RAI ablation is frequently performed worldwide to reduce the recurrence rate and prolong survival of moderate to high risk patients with well-differentiated

thyroid cancer.⁹

For optimal RAI treatment, proper elevation of TSH level and iodine restriction are prerequisites. Normal thyroid tissue has preferential capability to accumulate iodine via the sodium-iodine symporter (NIS), whereas thyroid cancer cells have decreased expression of NIS and relatively reduced ¹³¹I uptake compared to normal follicular cells.^{15,16} In order to overcome this problem, iodine restriction and TSH elevation are used to increase the expression of the sodium-iodine symporter (NIS) and hence augment the ¹³¹I accumulation in the thyroid cancer cells.^{17,18}

Thyroxine withdrawal should be conducted to increase the serum TSH to an appropriate level before RAI treatment. This however results in symptoms of hypothyroidism which are quite debilitating for the patients. Thus in recent practices, rhTSH injections are used to achieve similar TSH elevation without rendering the patients hypothyroid.^{17,18} Many research papers have shown that the efficacy of RAI treatment after the injection of rhTSH is similar to the withdrawal group.^{6,7,17,18} In addition, many clinical researches are currently actively investigating and proving that the rhTSH is effective in maintaining the euthyroid status as well as retaining the patients' quality of life.^{6,7,17,18}

Iodine restriction with a LID is always necessary 1-2 weeks before RAI treatment.^{8,9} Even though there are a number of on-going studies trying to determine the most optimal period and extent of iodine restriction world-wide, there is no standardized protocol for the LID prior to RAI which takes account of the racial differences, endemic dietary habits, and composition of iodine in the local food yet. Duration of the diet is also an important factor that needs to be tailored to the local people's dietary preferences. Most Koreans and Japanese usually consume significant amount of seafood and regional food which are rich in iodine. Therefore, for these people, LID is one of the most troublesome and difficult process to follow during RAI treatment regardless of the dosage.

Patients often complain of difficulties in maintaining the LID for extended periods of time. Thus, attempts to reduce the duration of LID are of clinical importance, especially in iodine-rich areas.

In this study, we attempted to confirm the optimal period of iodine restriction for RAI treatment in iodine rich diet through analyzing the changing pattern of UIE during LID, and evaluated whether there is any difference in the UIE level between two differently prepared groups. There is some limitation using spot urine I/Cr compared to the 24-hour urinary iodine analysis. The 24-hour urine iodine analysis is the gold standard method for evaluating iodine status in the body.¹⁹ However, this method is really inconvenient patients, and practically impossible to be used for measurement of the changing pattern of UIE throughout the LID period. It is true that the spot urine iodine concentration can be influenced by diurnal variation, urinary volume, fluid intake, and renal function.^{20,21} In order to compensate for the limitation of spot urine, the iodine to creatinine ratio (I/Cr) of spot urine can alternatively be used for the evaluation of iodine status in the body, and it has been proven to reflect the 24-hour urinary iodine concentration.²² By using the I/Cr ratio of spot urine, iodine status of the patient can be easily and reliably evaluated.

In terms of the timing of the urine collection, Kim et al. used the morning spot urine for the evaluation of the iodine status of the body.²² However, UIE usually follows a circadian rhythm and is lowest between the hours of 8:00 AM and 11:00 AM; thus, a morning spot urine could potentially result in an underestimation of iodine status.^{20,23} According to the Vanacor group, when compared with the 24-hour urine iodine analysis, spot urine specimen collected during the afternoon time has the best correlation with the 24-hour value. Hence we set the urine collection time between 1pm to 5pm.¹⁴

In this study, the cutoff value of the adequate UIE for RAI treatment was chosen as urine I/Cr ratio $<100\mu\text{g/gCr}$ based on major guidelines.^{11,12,24,25} The

European Association of Nuclear Medicine Therapy Committee recommended adequate UIE level for RAI treatment as urine iodine concentration <100 mcg/l or urine I/Cr < 100 mcg/gCr, and many other studies have also suggested using the same value as a reflection of adequate LID preparation.^{11,12,24,25}

In this study, we found that there was a decreasing pattern of UIE (spot urine I/Cr ratio) during the 2 weeks of low iodine diet. The changing pattern of UIE demonstrated that adequate UIE (<100 μ g/gCr) was achieved within several days, and the UIE was maintained at this low level to the end of the LID period in both groups. Our study corresponds with previous reports which were also from Korea.^{22,26} Lee et al. showed that 95.9% (187/195) of patients can achieve adequate UIE for RAI treatment after 1 week of LID. Kim et al. also revealed that satisfactory UIE level can be achieved within 6 days of LID, suggesting that for RAI ablation preparation, one week of strict LID might be sufficient.^{24,25} In our study, considering the changing pattern of the UIE, we argue that one-week schedule of LID can be also safely applied to the patients using rhTSH.

We assessed the median value rather than the mean value for the purpose of maintaining the accuracy of the data. The drastic increase in I/CR ratio in the middle of the LID was due to the failure of compliance to the LID schedule by several participants in both groups. This explains the abnormality of the mean value of the rhTSH group on the 11th& 12th day (Table 2 & 4). The violation of diet schedule was confirmed through follow-up phone calls by a nurse. To prevent data distortion by skewed distribution when using the mean, the data generation through the median values was inevitable (Figure 2).

Since this study was mainly done through simple urine collection, there was no potential harm or any adverse reactions involving the subjects during the study period. However, we conducted a safety assessment for further evaluation.

Based on the regular check-ups and consultations by physicians and nurses during each visit, no adverse reactions or serious adverse events were reported. Even though we were unable to show any difference in the UIE pattern between the two groups, from the physicians' perspective, the withdrawal group experienced more discomfort and fatigue compared to the rhTSH group due to hypothyroidism.

V. CONCLUSION

Further study regarding the therapeutic outcome- ablation success rate is necessary to check the effect of one week LID. However, in terms of total body iodine level, one week of strict LID is sufficient preparation for RAI ablation in an area with iodine rich diet. This one-week schedule of LID can also be safely applied to patients prepared with rhTSH.

REFERENCES

1. Sawka AM, Thephamongkhon K, Brouwers M, Thabane L, Browman G, Gerstein HC. Clinical review 170: a systematic review and metaanalysis of the effectiveness of radioactive iodine remnant ablation for well-differentiated thyroid cancer. *J Clin Endocrinol Metab* 2004;89:3668–76.
2. Jonklaas J, Sarlis NJ, Litofsky D, Ain KB, Bigos ST, Brierley JD, Cooper DS, Haugen BR, Ladenson PW, Magner J, Robbins J, Ross DS, Skarulis M, Maxon HR, Sherman SI. Outcomes of patients with differentiated thyroid carcinoma following initial therapy. *Thyroid* 2006;16:1229–42.
3. Sawka AM¹, Brierley JD, Tsang RW, Thabane L, Rotstein L, Gafni A, Straus S, Goldstein DP. An updated systematic review and commentary examining the effectiveness of radioactive iodine remnant ablation in well-differentiated thyroid cancer. *Endocrinol Metab Clin North Am* 2008;37:457–80.
4. Mazzaferri EL, Jhiang SM. Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. *Am J Med* 1994;97:418–28.
5. Ju DL, Park YJ, Paik HY, Kim MJ, Park S, Jung KY, Kim TH, Choi HS, Song YJ. Dietary evaluation of a low-iodine diet in Korean thyroid cancer patients preparing for radioactive iodine therapy in an iodine-rich region. *Nutr Res Pract* 2016;10(2):167-74.
6. Pacini F, Ladenson PW, Schlumberger M, Driedger A, Luster M, Kloos RT, Sherman S, Haugen B, Corone C, Molinaro E, Elisei R, Ceccarelli C, Pinchera A, Wahl RL, Leboulleux S, Ricard M, Yoo J, Busaidy NL, Delpassand E, Hanscheid H, Felbinger R, Lassmann M, Reiners C. Radioiodine ablation of thyroid remnants after preparation with recombinant human thyrotropin in differentiated thyroid carcinoma: results of an international, randomized, controlled study. *J Clin Endocrinol Metab* 2006; 91(3): 926-32.

7. Lippi F, Capezzone M, Angelini F, Taddei D, Molinaro E, Pinchera A, Pacini F. Radioiodine treatment of metastatic differentiated thyroid cancer in patients on L-thyroxine, using recombinant human TSH. *Eur J Endocrinol* 2001;144(1):5-11.
8. Kim WB, Seok JW, Kim MH, Kim BI, Park YJ, Lee KE, Lee SM, Lee YS, Jung KH, Jo YS, Cheon GJ, Chung JH, Kang SJ. Korean Thyroid Association guidelines for patients undergoing radioiodine therapy for differentiated thyroid cancers (First edition, 2012). *J Korean Thyroid Assoc* 2013;6:12-25.
9. Li JH, He ZH, Bansal V, Hennessey JV. Low iodine diet in differentiated thyroid cancer: a review. *Clin Endocrinol (Oxf)* 2016;84(1):3-12.
10. Lee J, Yun MJ, Nam KH, Chung WY, Soh EY, Park CS. Quality of life and effectiveness comparisons of thyroxine withdrawal, triiodothyronine withdrawal, and recombinant thyroid-stimulating hormone administration for low-dose radioiodine remnant ablation of differentiated thyroid carcinoma. *Thyroid* 2010; 20(2): 173-9.
11. Tomoda C, Uruno T, Takamura Y, Ito Y, Miya A, Kobayashi K, Matsuzuka F, Amino N, Kuma K, Miyauchi A. Reevaluation of stringent low iodine diet in outpatient preparation for radioiodine examination and therapy. *Endocr J* 2005; 52(2):237-40.
12. Park JT 2nd, Hennessey JV. Two-week low iodine diet is necessary for adequate outpatient preparation for radioiodine rhTSH scanning in patients taking levothyroxine. *Thyroid* 2004; 14(1):57-63.
13. Choi J, Kim HS, Hong DJ, Lim H, Kim JH. Urinary iodine and sodium status of urban Korean subjects: a pilot study. *Clin Biochem.* 2012; 45(7-8):596-8.
14. Vanacor R, Soares R, Manica D, Furlanetto TW. Urinary iodine in 24 h is associated with natriuresis and is better reflected by an afternoon sample. *Ann Nutr Metab* 2008;53(1):43-9.

15. Ringel MD, Anderson J, Souza SL, Burch HB, Tambascia M, Shriver CD, Tuttle RM. Expression of the sodium iodide symporter and thyroglobulin genes are reduced in papillary thyroid cancer. *Mod Pathol* 2001;14:289–96.
16. Smanik PA, Ryu KY, Theil KS, Mazzaferri EL, Jhiang SM. Expression, exon-intron organization, and chromosome mapping of the human sodium iodide symporter. *Endocrinology* 1997;138:3555–8.
17. Haugen BR, Pacini F, Reiners C, Schlumberger M, Ladenson PW, Sherman SI, Cooper DS, Graham KE, Braverman LE, Skarulis MC, Davies TF, DeGroot LJ, Mazzaferri EL, Daniels GH, Ross DS, Luster M, Samuels MH, Becker DV, Maxon HR 3rd, Cavalieri RR, Spencer CA, McEllin K, Weintraub BD, Ridgway EC. A comparison of recombinant human thyrotropin and thyroid hormone withdrawal for the detection of thyroid remnant or cancer. *J Clin Endocrinol Metab* 1999;84:3877–85.
18. Ladenson PW, Braverman LE, Mazzaferri EL, Brucker-Davis F, Cooper DS, Garber JR, Wondisford FE, Davies TF, DeGroot LJ, Daniels GH, Ross DS, Weintraub BD. Comparison of administration of recombinant human thyrotropin with withdrawal of thyroid hormone for radioactive iodine scanning in patients with thyroid carcinoma. *N Engl J Med* 1997;337:888–96.
19. Baloch Z, Carayon P, Conte-Devolx B, Demers LM, Feldt-Rasmussen U, Henry JF, LiVosli VA, Niccoli-Sire P, John R, Ruf J, Smyth PP, Spencer CA, Stockigt JR; Guidelines Committee, National Academy of Clinical Biochemistry. Laboratory medicine practice guidelines. Laboratory support for the diagnosis and monitoring of thyroid disease. *Thyroid* 2003;13:3–126.
20. Rasmussen LB, Ovesen L, Christiansen E. Day-to-day and within-day variation in urinary iodine excretion. *Eur J Clin Nutr* 1999;53:401–7.
21. Vejbjerg P, Knudsen N, Perrild H, Laurberg P, Andersen S, Rasmussen LB, Ovesen L, Jørgensen T. Estimation of iodine intake from various urinary iodine measurements in population studies. *Thyroid* 2009;19:1281–6.

22. Kim HK, Lee SY, Lee JI, Jang HW, Kim SK, Chung HS, Tan AH, Hur KY, Kim JH, Chung JH, Kim SW. Usefulness of iodine/creatinine ratio from spot-urine samples to evaluate the effectiveness of low-iodine diet preparation for radioiodine therapy. *Clin Endocrinol (Oxf)* 2010;73:114–8.
23. Als C, Helbling A, Peter K, Haldimann M, Zimmerli B, Gerber H. Urinary iodine concentration follows a circadian rhythm: a study with 3023 spot urine samples in adults and children. *J Clin Endocrinol Metab* 2000;85:1367–9.
24. Luster M, Clarke SE, Dietlein M, Lassmann M, Lind P, Oyen WJ, Tennvall J, Bombardieri E; European Association of Nuclear Medicine (EANM). Guidelines for radioiodine therapy of differentiated thyroid cancer. *Eur J Nucl Med Mol Imaging* 2008;35:1941–59.
25. WHO. Iodine Status Worldwide: WHO Global Database on Iodine Deficiency. WHO, Geneva 2004.
26. Lee M, Lee YK, Jeon TJ, Chang HS, Kim BW, Lee YS, Park CS, Ryu YH. Low iodine diet for one week is sufficient for adequate preparation of high dose radioactive iodine ablation therapy of differentiated thyroid cancer patients in iodine-rich areas. *Thyroid* 2014;24(8):1289-96.

ABSTRACT(IN KOREAN)

분화 갑상선 암에서 방사성 요오드 치료를 위한 저 요오드 식이
기간 중 체내 요오드 함량을 반영하는 소변 요오드 배설량의
변화 양상; 갑상선 호르몬 중단군과 rhTSH 사용군의 전향적
비교 연구

<지도교수 정 용 윤>

연세대학교 대학원 의학과

강 상 옥

배경: 분화 갑상선 암으로 갑상선 전 절제술을 받은 후 고 위험군인 경우 술 후 암의 재발과 그로 인한 사망률을 낮추기 위해 일반적으로 방사성 요오드 치료가 필요하다. 하지만 동위 원소 치료를 위해서는, 일정 기간의 갑상선 호르몬 중단과 저 요오드 식이가 필요하며, 이는 환자에게 다양한 불편감을 유발한다. 특히 한국이나 일본처럼 요오드 섭취가 높은 지역에서는 저 요오드 식이 기간 중 환자들의 입맛에 맞는 음식을 찾기 힘든 관계로 많은 환자들이 심한 불편감을 호소하고 있다. 본 연구에서는 저 요오드 식이 기간 중 체내 요오드 함량을 반영하는 소변 요오드 배설량의 변화 양상을 분석함으로써, 방사성 요오드 치료를 위한 저 요오드 식이의 적절한 기간을 확인하고, 갑상선 호르몬의 중단군과 rhTSH 사용군 간의 차이가 있는지 보고자 한다.

방법: 본 연구는 분화 갑상선 암으로 갑상선 전 절제술 후 방사성 동위 원소 치료가 필요한 94명의 환자를 대상으로 하였다. 모든 환자들은 충분한 설명과 동의 하에 환자의 선택에 따라 전향적으로 갑상선 호르몬 중단군과 rhTSH 사용군으로 배정되었다. 저 요오드 식이 기간 중 소변 요오드 배설량의 변화 양상을 보기 위해 각 환자당 6~7회의 개별 일회성 소변 샘플을 수집 하였으며, 각 군간의 변화 양상과 차이점을 분석하였다. (갑상선 호르몬 중단군의 경우 0, 3, 5, 7, 10, 14일째, rhTSH 사용군의 경우 0, 3, 7, 10, 11, 12, 14 일째 소변 채취)

결과: 두 군간 임상병리적 인자에서는 종양의 크기와 림프절 전이여부 외에 의미 있는 차이가 없었다. 호르몬 중단군의 경우 소변 요오드 배설량의 중앙값이 시간에 따라 순차적으로 감소하였으며, 7일째, 14일째 I/Cr 비는 각각 18.3 (4.2~908.6), 17.9 $\mu\text{g/gCr}$ (4.3~190.4) 이었다. 요오드 치료에 적합한 소변 요오드 배설량을 보인 환자들은 (기준값 100 $\mu\text{g/gCr}$ 미만) 7일째 93.3%, 14일째 93.3%였다. rhTSH 사용군에서는 7일째, 14일째 소변 I/Cr 비의 중앙값이 48.0 (10~95), 45.7 (19.2~388.8)로 나타 났으며, 적합한 요오드 배설량을 보인 환자는 7일째 91.8%, 14일째 93.8% 였다.

결론: 분화 갑상선암에서 수술 후 방사성 요오드 치료를 위한 저 요오드 식이의 기간은 요오드를 많이 섭취하는 지역에서도 1주일이면 충분할 것으로 사료되며, 이것은 rhTSH를 사용한 군에서도 안전하게 적용될 수 있다.



핵심되는 말: 저 요오드 식이, 방사성 동위 원소 치료, 소변
요오드배설량, 갑상선 암.