Comparison of the Influence on the Liver Function Between Thyroid Hormone Withdrawal and rh-TSH Before High-Dose Radioiodine Therapy in Patients with Well-Differentiated Thyroid Cancer

Yeon-Hee Han · Seok Tae Lim · Kuk-No Yun ·
Sung Kyun Yim · Dong Wook Kim ·
Hwan-Jeong Jeong · Myung-Hee Sohn

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Abstract

Purpose An elevated thyroid stimulating hormone level (TSH) is essential to stimulate the uptake of radioiodine into thyroid remnants and metastases of thyroid cancer when a patient undergoes high-dose radioiodine therapy. Nowadays, recombinant human thyroid stimulating hormone (rh-TSH) is increasingly used instead of the classic method of thyroid hormone withdrawal (THW). However, beyond the therapeutic effects, clinical differences between the two methods have not yet been clearly demonstrated. The aim of this work was to investigate the effects of the two methods, especially on liver function.

Methods We identified 143 evaluable patients who were further divided into two groups: THW and rh-TSH. We first reviewed the aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels, which were measured during the admission period for total thyroidectomy. We called these liver enzyme levels “base AST” and “base ALT.” We also assessed other chemistry profiles, including AST, ALT, total cholesterol, LDL

cholesterol, alkaline phosphatase (ALP), total bilirubin (TB), and triglyceride (TG), which were measured on admission day for high-dose radioiodine therapy. We called these liver enzyme levels “follow-up AST” and “follow-up ALT.” We compared the changes in base and follow-up liver enzyme levels and the other chemistry profiles between the two groups.

Results The base AST and base ALT levels of the two groups were within normal range, and there was no significant difference between the two groups. In contrast to these base liver enzyme levels, follow-up liver enzyme levels between the two groups showed significant differences. Patients in the THW group had higher follow-up AST and ALT levels than did the rh-TSH group. Patients in the THW group also had higher levels of total cholesterol and LDL cholesterol than did the patients in the rh-TSH group. However there were no statistically significant differences in ALP, total bilirubin, and triglyceride levels between the two groups.

Conclusions In this retrospective analysis of liver function, the use of rh-TSH for high-dose radioiodine therapy had less of an effect on liver function and cholesterol levels than dose thyroid hormone withdrawal. This suggests that rh-TSH can be used effectively and safely especially for patients with metabolic syndrome.

Y.-H. Han · S. T. Lim · K.-N. Yun · D. W. Kim · H.-J. Jeong ·
M.-H. Sohn

Department of Nuclear Medicine,
Chonbuk National University Medical School and Hospital,
Jeonju, Republic of Korea

S. K. Yim

Department of Internal Medicine,
Chonbuk National University Medical School and Hospital,
Jeonju, Republic of Korea

S. T. Lim (✉) · D. W. Kim · H.-J. Jeong · M.-H. Sohn
Department of Nuclear Medicine,
Research Institute of Clinical Medicine,
Cyclotron Research Center,
Chonbuk National University Medical School and Hospital,
Jeonju, Republic of Korea
e-mail: stlim@jbnu.ac.kr

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Introduction

High-dose radioiodine therapy is a procedure to ablate normal thyroid remnant tissues and microscopic deposits of thyroid carcinoma after a total thyroidectomy for differentiated

thyroid carcinoma [1]. It has been reported to reduce the number of locoregional recurrences and to increase overall survival [2, 3]. In addition to these effects, the destruction of all thyroid cells increases the sensitivity of the serum thyroglobulin (Tg) level for detecting thyroid cancer recurrences [4].

An elevated thyroid-stimulating hormone (thyrotropin; TSH) level is essential to stimulate I-131 uptake into the normal thyroid remnants and metastatic tissues of thyroid carcinoma when a patient has undergone high-dose radioiodine therapy. Although a traditional method of preparation for the high-dose radioiodine therapy is thyroid hormone withdrawal (THW), nowadays, recombinant human thyroid-stimulating hormone (rh-TSH) is increasingly used instead. It has also been proposed that rh-TSH stimulates iodine uptake via activation of the sodium-iodine symporter and leads to sufficient I-131 uptake in thyroid remnants to allow for complete remnant ablation [5].

THW usually results in a wide range of physical and psychological side effects associated with hypothyroidism [6]. Many patients who have undergone high-dose radioiodine therapy with THW suffer from general edema, constipation, and depression. In contrast to these hypothyroid patients, euthyroid patients using rh-TSH showed better quality of life because they did not suffer from symptoms of hypothyroidism.

A prospective randomized study found that THW and rh-TSH stimulation were equally effective in preparing patients for I-131 remnant ablation [7]. Short-term recurrence rates also have been found to be similar in patients prepared with THW or rh-TSH [7]. However other clinical differences between the two methods have not been widely studied yet.

Because there is no consensus, the choice of preparation with either THW or rh-TSH has usually depended on the clinician's subjective decision or the patient's preference, and no definitive standard protocol exists.

We have become keenly aware of the absence of a standard protocol for choosing a preparation method and are

concerned about various effects of THW-induced hypothyroidism, for example, there is evidence that hypothyroidism may directly affect liver structure or function [8]. The aim of this work was to investigate the effects of the two methods especially on the liver function. We have undertaken this retrospective investigation as part of an effort to establish a standard protocol for choosing a preparation method.

Materials and Methods

All high-dose radioiodine therapies, regardless of preparation method, were performed by the same nuclear medicine department following a standard protocol. We have undertaken this retrospective investigation to review two different preparation methods and compare the chemistry profiles including liver enzyme levels. Because our research was not prospectively designed, the doses of radioactive iodine administered were not necessarily the same and no fixed follow-up period was required.

Subjects

One hundred and seventy-four patients who underwent high-dose radioiodine therapy at our nuclear medicine department from May 2009 to December 2009 were enrolled in this study. Patients had total or completion thyroidectomy carried out by a variety of surgeons, although most underwent surgery at this hospital. These patients consented to receive high-dose radioiodine therapy and were informed that the traditional method, THW, involves elevating TSH levels endogenously and that rh-TSH was an alternative option to raise TSH exogenously. Nine patients who were considered to have an incomplete radioiodine ablation at first therapy had a second high-dose radioiodine therapy during this time period.

From among these 174 patients, 31 were excluded from this study for various reasons. Twenty-seven patients who

Table 1 Clinical characteristics of the two groups

Characteristics	THW group (<i>n</i> =77)	rh-TSH group (<i>n</i> =66)	<i>p</i>
Age (years)	44.3±10.5	53.2±11.3	NS
Sex (M:F)	9:68	5:61	–
Duration of follow-up (days)	171.2±74.7	147.2±50.9	<0.05
Histology			
Papillary carcinoma	77	65	–
Follicular carcinoma	0	1	–
Surgery			
Total thyroidectomy	4	1	–
Total thyroidectomy + CND	65	52	–
Total thyroidectomy + CND + LND	8	13	–
Therapeutic dose (mCi)	155.5±18.5	158.2±19.8	NS

THW Thyroid hormone withdrawal, rh-TSH recombinant human thyroid-stimulating hormone, NS not significant, CND central neck dissection, LND lateral neck dissection

Table 2 Comparison of the liver enzyme levels between the group receiving traditional thyroid hormone withdrawal (THW) and the group receiving recombinant human thyroid-stimulating hormone (rh-TSH)

Liver enzyme	THW group (n=77)	rh-TSH group (n=66)	p
Base AST (12~33 IU/L)	19.5±4.5	20.7±4.8	NS
Follow-up AST (12~33 IU/L)	37.9±16.2	24.0±11.8	<0.05
ΔAST	19.2±17.3	3.6±12.9	<0.05
Base ALT (5~35 IU/L)	18.5±6.9	19.4±7.5	NS
Follow-up ALT (5~35 IU/L)	39.6±21.7	26.4±15.5	<0.05
ΔALT	21.8±23.0	7.2±15.6	<0.05

NS Not significant

showed high levels of liver enzymes when they underwent total thyroidectomy were excluded. Two patients with hepatitis and one patient with fatty liver were excluded because of underlying liver diseases. Another patient who took medication that could affect liver function was also excluded. On the basis of these exclusion criteria, we identified 143 evaluable patients (M:F=14:129, ages 48.4 ± 11.7 years) who were further divided into two groups, the THW group (77 patients) and the rh-TSH group (66 patients). The clinical characteristics of the two groups are summarized in Table 1.

Standard Protocol and Patient Preparation

At the nuclear medicine department, high-dose radioiodine therapy was performed following a standard protocol. Most patients were referred to the nuclear medicine department from departments of general surgery, ENT, and division of endocrinology. The decision to use I-131 dose for therapy was based on all available information, which included operation records, pathology reports, and other diagnostic studies such as neck computed tomography (CT), bone

scan, and F-18 FDG PET/CT, which were undertaken for evaluation of remnant thyroid tissues and distant metastases.

Patients in the THW group received levothyroxine therapy after total thyroidectomy. Then they were withdrawn from levothyroxine and switched to triiodothyronine for 3 weeks starting 5 weeks before the high-dose radioiodine therapy. For the last 2 weeks, patients did not take any kind of thyroid hormone medication. Their stimulated endogenous TSH levels were checked about 1 week before high-dose radioiodine therapy and were required to be above $30 \mu\text{IU/mL}$. Patients in the rh-TSH group were also placed on levothyroxine after total thyroidectomy. But instead of withdrawal of levothyroxine, they received 1.1 mg rh-TSH intramuscularly 2 days and 1 day before high-dose radioiodine therapy.

All patients in both THW and rh-TSH groups were informed about the need for low-iodine diets and what to consume and were encouraged to follow this diet from 2 weeks before high dose radioiodine therapy to 7 days after I-131 administration. On the day of high-dose radioiodine therapy, all patients underwent chest X-ray, urinalysis, and blood tests as a basic admission evaluation. After the

Fig. 1 Changes in AST (a) and ALT (b) levels for the group receiving traditional thyroid hormone withdrawal (THW) and the group receiving recombinant human thyroid-stimulating hormone (rh-TSH) on the day patients were admitted for thyroidectomy (base) and on the day they were admitted for high-dose radioiodine therapy (follow-up). The changes from base AST to follow-up AST were 19.2 ± 17.3 IU/L in

the THW group and 3.6 ± 12.9 IU/L in the rh-TSH group. The changes from base ALT to follow-up ALT were 21.8 ± 23.0 IU/L in the THW group and 7.2 ± 15.6 IU/L in the rh-TSH group. The differences between the two groups were statistically significant ($p < 0.05$). The box and whisker plots represent the range, 25th and 75th percentiles, and median

Table 3 Comparison of the other chemistry profiles between the group receiving traditional thyroid hormone withdrawal (THW) and the group receiving recombinant human thyroid-stimulating hormone (rh-TSH)
ALP Alkaline phosphatase, *NS* not significant

Chemistry profiles	THW group (<i>n</i> =77)	rh-TSH group (<i>n</i> =66)	<i>p</i>
Total cholesterol (~200 mg/dL)	249.0±50.3	166.7±31.4	<0.05
LDL cholesterol (~140 mg/dL)	149.7±40.4	93.5±27.9	<0.05
ALP (45–129 IU/L)	172.4±55.6	191.0±70.2	NS
Total bilirubin (0.2–1.2 mg/dL)	0.6±0.3	0.6±0.3	NS
Triglyceride (~200 mg/dL)	169.1±114.0	169.2±133.5	NS

patients were informed about possible complications and precautions by their attending nuclear medicine physicians, the therapeutic doses of I-131 were given orally. All patients were monitored carefully during the admission period and were discharged from the hospital 2 or 3 days after the therapeutic I-131 was administered.

Laboratory Studies

We were able to review the laboratory data of all patients in both groups. We first reviewed the AST and ALT levels that were measured when patients were admitted for total or completion thyroidectomy. We called these liver enzyme levels “base AST” and “base ALT.” We also assessed the other chemistry profiles including aspartate aminotransferase (AST), alanine aminotransferase (ALT), total cholesterol, LDL cholesterol, alkaline phosphatase (ALP), total bilirubin (TB), and triglyceride (TG), which were measured on admission day for high-dose radioiodine therapy. We called these liver enzyme levels “follow-up AST” and “follow-up ALT.” We compared the changes in base and follow-up liver enzyme levels between the two groups. We also evaluated the other chemistry profiles measured on admission day for high-dose radioiodine therapy between the two groups.

Statistical Analysis

The clinical characteristics and chemistry profiles including liver enzyme levels were compared using the unpaired Student's *t*-test. The values are presented as mean ± SD. The base and follow-up liver enzyme levels of both groups were also compared using a paired *t*-test. Statistical analyses were performed using SPSS software (version 20.0). A *p* value of less than 0.05 was considered statistically significant.

Results

The base AST and base ALT levels of the THW group were 19.5±4.5 and 18.5±6.9 IU/L and those of the rh-TSH group were 20.7±4.8 and 19.4±7.5 IU/L, respectively. All data were within the normal range, and there was no significant difference between the two groups.

In contrast to the base liver enzyme levels, follow-up liver enzyme levels between the two groups showed significant differences. Patients in the THW group had higher follow-up AST and follow-up ALT levels than did the rh-TSH group (*p*<0.05). In addition, patients in the THW group showed significant increases from base to follow-up liver enzyme levels (*p*<0.05), unlike the patients in the rh-TSH group (Table 2 and Fig. 1). The changes in base and follow-up liver enzyme levels compared using a paired *t*-test showed significant differences between groups (*p*<0.05).

Another interesting result of this study was the cholesterol levels of both groups. Patients in the THW group had much higher levels of total cholesterol and LDL cholesterol than did the patients in the rh-TSH group (*p*<0.05). There were, however, no statistically significant differences in ALP, total bilirubin, and triglyceride levels between the two groups (Table 3, Figs. 2 and 3).

No patient suffered from cholestatic jaundice, but there were five patients who had total bilirubin levels above the upper normal level (>1.2 mg/dL). Three patients were in the THW group and two in the rh-TSH group. The total bilirubin levels of the five patients ranged from 1.29 to 1.45 mg/dL, and there was no statistical association between preparation method and total bilirubin levels.

Fig. 2 Means and standard deviations of total cholesterol and LDL cholesterol for the group receiving traditional thyroid hormone withdrawal (THW) and the group receiving recombinant human thyroid-stimulating hormone (rh-TSH). The THW group has higher total cholesterol (a) and LDL cholesterol (b) levels than those of the rh-TSH group (*p*<0.05)

Fig. 3 Means and standard deviations of other chemistry profiles (ALP, total bilirubin, and triglyceride) for the group receiving traditional thyroid hormone withdrawal (THW) and the group receiving recombinant human thyroid-stimulating hormone (rh-TSH). There were no statistically significant differences between the two groups

Discussion

The liver is the major organ for cholesterol metabolism, and the thyroid hormones play an integral role in hepatic lipid metabolism [8]. Thyroid hormones accelerate the expression of LDL receptors on the hepatocytes [9] and increase the activity of lipid-lowering liver enzymes, resulting in a reduction in low-density lipoprotein levels [10]. This is well correlated with the results of our study showing that the patients in the rh-TSH group, who were in euthyroid state, showed lower total cholesterol and LDL cholesterol levels than the THW group.

Hypothyroidism may also be responsible for cholestatic jaundice due to decreased bilirubin and bile excretion [11]. In the experiment by Van et al., the activity of bilirubin UDP-glucuronyltransferase decreased, resulting in a reduction in bilirubin excretion [12]. They also suggested that a reduction in bile flow can be attributed to an increase in membrane cholesterol-phospholipid ratio and diminished membrane fluidity, which affects a number of canalicular membrane transporters and enzymes [12]. In this study, there was no significant difference in total bilirubin levels between the two groups. There were five patients who had high total bilirubin levels over the upper normal limit (1.2 mg/dL). Three of these patients belonged to the THW group and the other two belonged to the rh-TSH group. However the total bilirubin levels only ranged from 1.29 to 1.45 mg/dL, and no patients showed signs or symptoms related to cholestatic jaundice. Based on these results, we suggest that high-dose radioiodine therapy prepared by THW is a low-risk procedure in terms of cholestatic jaundice. All patients in the THW group discontinued taking thyroid hormone medication for only 2 weeks, and we suppose that this short period of hypothyroidism has less of an effect on bilirubin metabolism. Recent studies have also shown that the hepatic dysfunction associated with hypothyroidism can be reversible over some weeks with thyroxine replacement, with no liver damage [13, 14].

One study by Menzel et al. explained that rh-TSH spared the patient the drawbacks of being in a hypothyroid state

and thus not only avoided personal discomfort but also reduced the time period during which the patient could not work or maneuver sophisticated or dangerous equipment [15].

Furthermore, it is also well known that severe hypothyroidism causes increased permeability of the vascular endothelium, resulting in effusions and ascites [16]. Preparation by rh-TSH may be a safe choice for patients who have pleural effusions or ascites.

Recent studies have shown that iodine clearance rates are generally faster in patients receiving rh-TSH compared with patients who were in a hypothyroid state after THW [17]. Although the follow-up liver enzyme levels in this study were checked before administration of radioactive iodine, we expect that the faster clearance of radioactive iodine in the patients prepared by rh-TSH may have less of an effect on liver function.

Another study on iodine biokinetics showed the effective half-life in the remnant thyroid tissue was significantly longer after rh-TSH than THW, reducing radiation exposure to the rest of the body and to the general public who come in contact with such patients [18]. In these patients, the efficacy of radioiodine treatment is related to the radiation dose delivered to remnant and neoplastic thyroid tissue [19]. However, the significant radiation doses delivered to extra-thyroidal tissues may induce side effects such as nausea and vomiting, sialadenitis and xerostomia, loss of taste, and bone marrow insufficiency [19]. In this respect, rh-TSH can be an effective ablative preparation with reduced incidence of several side effects.

One study recommended formal whole-body and blood dosimetry for patients over 70 years old and patients with large-volume radioiodine-avid disease, if administration of radioiodine activity exceeding 7.4 GBq (200 mCi) is considered [20]. This is because empiric radioactive iodine dosing regimens frequently exceed maximum tolerated activity levels in elderly patients [20]. Because preparation with rh-TSH has a longer effective half-life in the remnant thyroid tissue with reduced radiation exposure to the rest of

the body [18], not only patients with metabolic syndrome, but also elderly patients and those with large thyroid remnants can more safely undergo rh-TSH than THW.

This study has several limitations. Because it was an uncontrolled retrospective study, the duration of follow-up between the day of base liver enzyme test and follow-up chemistry test differed among patients (Table 1). The shortest term was 1 month and the longest was 18 months. In addition, we were not able to evaluate the changes in free T4 and TSH levels because almost no patients in either group underwent a blood test for free T4 and TSH. For these reason, we could not collect chemistry data such as total cholesterol, LDL cholesterol, ALP, and total bilirubin measured during admission for total thyroidectomy.

Conclusion

In this retrospective analysis of liver function, the use of rh-TSH for high-dose radioiodine therapy had less effect on liver function and cholesterol profiles than dose thyroid hormone withdrawal. This suggests that rh-TSH can be used effectively and safely especially in patients with metabolic syndrome.

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Conflict of interest None.

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