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Factors That Influence TSH Levels after Thyrogen Injection before RAI Therapy

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Purpose: Radioactive iodine therapy was used for detection and destruction of remnant normal of malignant thyroid tissue after thyroidectomy for differentiated thyroid gland cancer. To achieve a high level of TSH, discontinuation of levothyroxine is required. Discontinuation of L-T4 causes hypothyroidism, serious adverse impacts on patients, therefore, rhTSH is used. The aim of this study was to evaluate the factors influencing serum peak TSH levels after administration of rhTSH in patients with thyroid papillary carcinoma.

Methods: Retrospective review was conducted of 249 patients who underwent total thyroidectomy and subsequent RAI therapy at Kangbuk Samsung Hospital between October 2008 and February 2014. We divided patients into two groups according to the stimulated serum TSH level after administration of rhTSH (Group 1: TSH <30, Group 2: TSH ≥ 30). Clinicopathological characteristics were compared between the two groups.

Results: Serum peak TSH was negatively related to height, weight, BSA, and BMI, and positively related to LBM. A non-significant negative correlation was found between serum peak TSH and body composition.

Conclusion: Patients' weight, height, BMI, BSA, and LBM were not associated with serum peak TSH after rhTSH administration. More pharmakokinetic study of rhTSH is needed in order to find correlation between pharmacokinetic factors and TSH level.

Key Words: TSH, Thyrogen, RAI therapy

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INTRODUCTION

Radioactive iodine therapy was used to detect and destroy remnant normal or malignant thyroid tissue after thyroidectomy for differentiated thyroid gland cancer. For this reason, the patients must be stimulated by thyroid stimulating hormones (TSH) whenever a radioactive iodine (^{131}I) therapy is required, either for remnant ablation or metastatic disease. In order to achieve high blood concentrations of endogenous TSH (minimum of 30 μIU/mL), iodine restricted diet must be encountered and levothyroxine (L-T4) must be discontinued for 4~6 weeks before radioactive iodine therapy. Although transient, discontinuation of L-T4 causes hypothyroidism, which could have serious adverse impacts on the quality of life of patients as well as causing their morbidity and mortality.(*1-3*) To overcome this problem, the potential use of bovine TSH (bTSH), extractive human TSH and recombinant human TSH (rhTSH; Thyrogen®, Genzyme, USA) have been studied. TSH, a specific and potent thyroid stimulator, is essential for normal thyroid function. Early studies documented use of bTSH.(*4,5*) bTSH was used in research protocols and in clinical practice to test thyroid reserve, to stimulate ^{131}I uptake after near-total thyroidectomy in the management of thyroid cancer and to improve the quality and interpretation of thyroid nuclear medicine tests. It's

use eventually became limited, however, because of adverse reactions, including nausea, vomiting, local induration, urticaria, and even anaphylaxis.(*5-7*) Therefore, bTSH is no longer being produced for human use. These problems have been overcome by the cloning of the gene for the β-subunit of human TSH and the availability of large quantities of human TSH produced through recombinant DNA technology.(*8,9*) Two intramuscular injections of 1.1 mg of rhTSH stimulate production of thyroid hormones and thyroglobulin. Recently, individual variation of the pharmacokinetics of rhTSH has been reported.(*10,11*) In this study, we analyzed the effects of the anthropometric parameters on the serum TSH levels in patients with papillary thyroid carcinoma. Many studies investigated the influence of anthropometric factors on serum TSH levels after the administration of rhTSH. Several studies (*12*) reported that the peak of serum TSH was demonstrated to be inversely related to body weight, body mass index and body surface area. However, there are no clinical data that standard doses of rhTSH are less effective in obese patients. So the aim of this study was to evaluate the factors influencing serum peak TSH levels after administration of rhTSH in patients with papillary thyroid carcinoma.

METHODS

We investigated retrospectively two hundred and forty nine patients who were treated with rhTSH administration to induce radioiodine uptake and thyroglobulin secretion during the follow up of thyroid carcinoma from October, 2008 to February, 2014. The patients were diagnosed as differentiated thyroid carcinoma and already have been treated with total thyroidectomy. Patients with history of other malignancy were excluded. Patients were treated with a suppressive dose of L-T4. Each patient received a standard dose of 1.1 mg rhTSH intramuscularly for two consecutive days according to the conventional protocol.(*13*) Twenty-four hours after the last rhTSH injection (third day), a radioactive iodine (5 or 30 for diagnostic use vs 100 or 150 mCi for therapeutic use) is administered. ^{131}I Whole body scanning was performed on the fifth day. The whole body scans were used for detecting locoregional and/or distant metastases. Blood samples were taken before the first administration of rhTSH. We divided patients into two groups according to the stimulated serum TSH level after administration of rhTSH (Group 1 : TSH <30, Group 2: TSH ≥ 30). The patient's clinical characteristics (sex, age, height, weight, body mass index, body surface area, lean body mass) and other characteristics (TNM stage, tumor size, dosage of radioactive iodine, dosage of synthyroid, triiodothyronine (T3), free T4 (fT4), TSH, thyroglobulin (Tg), thyroglobulin antibody, microsomal antibody before rhTSH administration, TSH level after rhTSH administration) were compared between the two groups. Body mass index (BMI) was calculated as weight/height squared (kg/m^2); body surface area (BSA) was calculated as (height+weight-60)/100 (cm+kg-60)/100; lean body mass (LBM) was calculated as (0.32810*W)+(0.33929*H)−29.5336 for men, (0.29569*W)+(0.41813*H)−43.2933 for women. Serum TSH level should be minimum of 30 μIU/mL before radioactive iodine therapy for adequate evaluations and management.(*14-16*)

1) Statistical analysis

Data are presented as means±sd. Statistical analysis was performed using T test and χ^2 tests. Pearson correlation test was used to determine the independent effect of all parameters related to peak serum TSH levels. Statistical significance was defined as $P<0.05$.

RESULTS

The clinical and pathological characteristics of the study population are summarized in Tables 1 and 2. The mean age was 51.91±8.94 in group 1 and 46.60±10.04 in group 2. In addition, 56% of group 1 was females and 75% of group 2 was females. Before rhTSH administration, TSH levels were suppressed to 1.22±0.94 μIU/liter in group 1 and 1.89±1.54 in group 2. Group 1 had higher BMI (25.15±2.82 vs 23.97±3.75, P=0.14), higher BSA (1.69±0.20 vs 1.65±0.17, P=0.27), higher LBM (47.66±9.21 vs 45.63±7.74, P=0.24) than group 2 without statistical significance. By univariate analysis, serum peak TSH was negatively related to height, weight, BSA, BMI and

Table 1. Clinical characteristics of study population

	Group 1 (TSH <30)	Group 2 (TSH ≥30)	P value
Number	23	224	
Male : Female ratio	44 : 56	27 : 73	0.09
Age (yr)	51.91±8.94	46.60±10.04	0.02
Height (cm)	162.44±9.96	161.89±7.35	0.80
Weight (kg)	66.67±11.27	63.00±11.85	0.16
BMI (kg/ m^2)	25.15±2.82	23.97±3.75	0.14
BSA (m^2)	1.69±0.20	1.65±0.17	0.27
LBM (kg)	47.66±9.21	45.63±7.74	0.24

BMI = body mass index; BSA = body surface area; LBM = lean body mass.

Table 2. Pathological characteristics of study population

	Group 1 (TSH <30)	Group 2 (TSH ≥30)	P value
T stage			0.29
1a	65.2	40.2	
1b	26.1	33.0	
2	8.7	4.9	
3	0	21.9	
N stage			0.29
0	47.8	34.8	
1a	47.8	51.4	
1b	4.4	13.8	
Tumor size (cm)	1.00±0.64	1.19±0.70	0.22
Dose of synthyroid (mg)	0.17±0.03	0.17±0.03	0.70
Dose of radioactive iodine (mCi)	30.87±40.41	17.99±21.06	0.15
T3 before rhTSH	1.40±0.25	1.66±0.03	0.04
fT4 before rhTSH	1.59±0.44	1.50±0.38	0.26
TSH before rhTSH	1.22±0.94	1.89±1.54	0.04
Tg before rhTSH	37.58±123.92	29.56±77.5	0.66
TgAb before rhTSH	27.89±32.12	51.76±200.85	0.57
Microsomal Ab before rhTSH	183.62±685.77	179.85±559.51	0.98

rhTSH = recombinant human thyrotropin stimulating hormone; T3 = triiodothyronine; fT4 = free thyroxine; TSH = thyroid stimulating hormone; Tg = thyroglobulin; TgAb = thyroglobulin andibody; Microsomal Ab = microsomal antibody.

positively related to LBM (Fig. 1). A non-significant negative correlation was found between serum peak TSH and the body composition.

DISCUSSION

Total thyroidectomy and ablation of thyroid remnants with ^{131}I are followed by thyroid hormone withdrawal therapy. ^{131}I radioiodine treatment requires the stimulation of normal or pathological thyroid residual tissue. Maximum stimulation can be achieved by liothyronine (L-T3), levothyroxine (L-T4) withdrawal or by administration of rhTSH.

However, 4~6 weeks of withdrawal of L-T3 or L-T4 after thyroidectomy, causes hypothyroidism which leads to physical (*1,2*) and psychological discomforts to patients. Luster et al. (*17*) published a report comparing to elucidate clinical, quality-of-life, and pharmacoeconomic effects of hypothyroidism secondary to thyroid hormone withdrawal and rhTSH in athyroid patients with differentiated thyroid cancer (DTC). 92% had symptomatic and 85% multi-symptomatic hypothyroidism. Symptoms of hypothyrodisim includes weight gain, fatigue, sleep disturbances, difficulty concentrating, dry skin, constipation, puffy face and hands, intolerance of cold and hoarseness. Almost half of patients sought medical attention for hypothyroid complaints. At last, hypothyroidism secondary to thyroid hormone withdrawal caused important morbidity, safety risks, and productivity impairment.

In contrast, rhTSH preserves normal body functioning

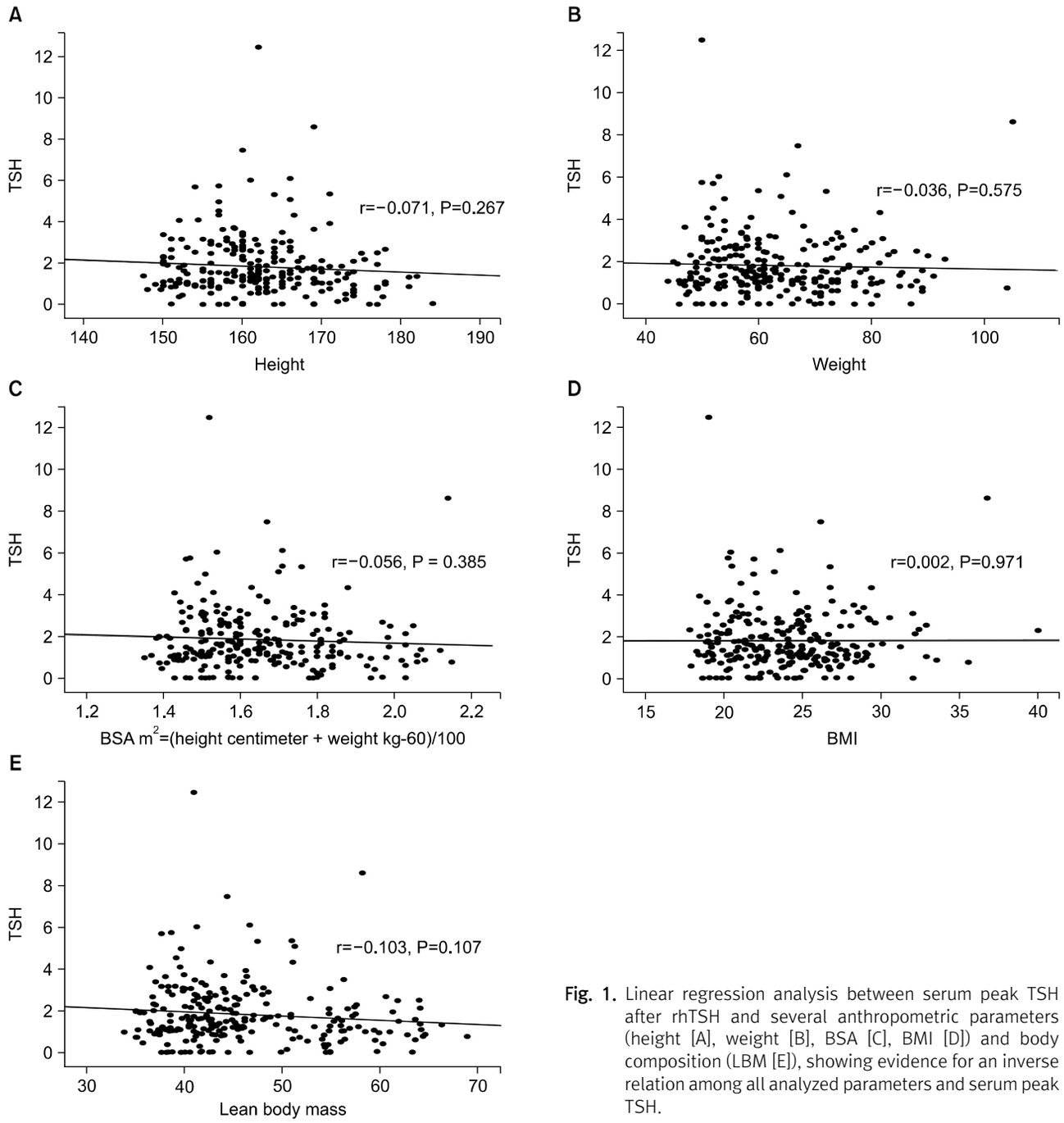

Fig. 1. Linear regression analysis between serum peak TSH after rhTSH and several anthropometric parameters (height [A], weight [B], BSA [C], BMI [D]) and body composition (LBM [E]), showing evidence for an inverse relation among all analyzed parameters and serum peak TSH.

and reduced days off work.(*18*) In addition, rhTSH decreases radiation exposure to tissue, bone and blood compared to thyroid hormone withdrawal.(*19*) Borget et al. (*20*) reported that hospital stay reduced with rhTSH. Therefore, nowadays, recombinant human TSH (rhTSH) has been proposed as an alternative method to the withdrawal of thyroid hormones in the follow-up of differentiated thyroid cancer.

The administration of rhTSH increases both radioiodine uptake and thyroglobulin secretion if normal of metastatic thyroid tissue is present after total thyroidectomy.(*21*) It is approved for diagnostic purposes such as thyroglobulin stimulus and 4- to 5-mCi ^{131}I diagnostic whole body scan. It is also used to ^{131}I ablation of the postsurgical thyroid remnant and the results of a multicentric clinical trial demonstrated that the rate of ablation is similar between rhTSH administration and withdrawl of L-thyroxine.(*22*)

The aim of our study was to evaluate the influence of

several demographic and anthropometric parameters (age, body weight, height, body mass index, body surface area and lean body mass) on serum peak TSH levels after rhTSH administration.

In our study, an inadequate increase in TSH after two-doses of rhTSH administration has been observed in twenty three patients. In those patients, the serum peak TSH levels were lower than 30 mIU/mL. These levels were considerably lower than normally required. We demonstrated that none of the anthropometric parameters were associated with serum peak TSH levels after rhTSH administration.

Other studies reported the negative linear correlation between serum peak TSH concentration and several anthropometric parameters. Vitale et al. (*10*) reported inverse relation of body surface area and serum peak TSH levels after rhTSH administration. In a multivariate regression analysis, only BSA was independently associated to serum peak TSH concentrations (standardized β coefficient= 0.721; $P < 0.0001$).

Castagna et al. (*11*) demonstrated that serum peak TSH was negatively related to lean body mass. Lean body mass is the most influencing physical parameter for the hydrophilic drugs dosage.(*23*) The most metabolic processes occur within lean tissue, and that both kidney and liver, which is responsible for drug elimination, are part of this compartment.(*24*) Because rhTSH is a hydrophilic drug,(*25*) this finding is consistent with the results.

Our results shows that mean age of group 1 was older than group 2 demonstrating that older patients tend to fail in elevation of serum TSH after rhTSH administration. However, it is inadequate to conclude that age can negatively influence on serum peak TSH level.

One of the reasons for failure of TSH elevation might be related to low iodine diet. To maximize uptake of radioiodine in the thyroid remnant and metastatic lesion after thyroidectomy, nonradioactive iodine in serum needs to be reduced. The use of such diet increases ^{131}I tumor dose (per 100mCi) in patients with differentiated thyroid cancer by 2.3-foid.(*26*) In our institute, low iodine diet starts one week before radioactive iodine therapy. However, other study questioned the traditional standard one-week protocol for restricted iodine therapy (RID) and evaluated the stringent and longer term low iodine diet (LID) to optimize protocol for out-patients.(*27*) In the report, patients with two weeks of LID were able to reduce their total iodine amount and achieved urinary iodine levels below the mean value (182.2. μg/gCr). Seventy percent of patients with two weeks of LID period achieved the adequate low iodine state. According to this report, two weeks of low iodine diet should be recommended for preparation in radioiodine study and therapy for thyroid cancer.

Another possible explanation for failure of TSH elevation is the interference of iodine content of L-T4 therapy during the administration of rhTSH. In our institute, rhTSH is used as ablation of postsurgical thyroid remnant without stopping of L-T4 administration.

However, other study reported better results for role of rhTSH in ablation of postsurgical thyroid remnants while stopping L-T4 administration.(*28*) The percentage of stimulated TSH level was higher in patients treated with rhTSH than L-T4 withdrawal [76－210 U/liter (mean, 112±11 SE) and 38－82 U/liter (mean, 51±3 SE), respectively]. The possible role of interference of iodine content in L-T4 may be explained that amount of iodine content in a daily dose of L-T4 (～50 μg). The amount of iodine in 30mCi is negligible (5 μg) compared to dose of L-T4. The iodine content in L-T4 may play role in elevation of serum TSH. In future, we should stop L-T4 administration two weeks before radioactive iodine therapy.

Other study also reported failure of TSH elevation after rhTSH administration.(*29*) Nine out of 16 patients (56.3%) showed serum TSH level ＜25 μIU/mL 96 hours after first rhTSH administration. This study explained failure of TSH elevation based on molecular biology. Kogai et al. (*30*) reported effects of TSH on Na＋/I－ symporter (NIS) messenger RNA (mRNA), protein levels in functional rat thyroid (FRTL-5) cells and correlated these with I-transport activity. When 1 μIU/mL of TSH was added to quiescent FRTL-5 cells, a 12 hour latency was observed before the onset of increased I-transport activity, which reached a maximum [approximately 27 times basal (5H medium) levels] at 72 hours. In our study, endogenous TSH levels were measured 72 hours before administration of

rhTSH. Therefore inadequate stimulation of endogenous TSH may be explained by the delay in iodine uptake. Our study had several limitations. Its retrospective design provided less strength of evidence. Another limitation is that number of patients studied was small, and these observations may not apply to a larger group of patients. Finally, investigation on thyrogen was not conducted. Failure of elevation in TSH might be contributed to defect during manufacturing of thyrogen. Further prospective studies are necessary with large population of patients.

CONCLUSION

Patients' weight, height, BMI, BSA, LBM was not associated with serum peak TSH after rhTSH administration. Appropriate timing for measuring of serum TSH level is important to avoid possibility of sub-optimal serum TSH level. In future prospective study, blood sample for serum TSH should be taken more than once after thyrogen injection to get reliable results. In future, more pharmakokinetic study of rhTSH should be accomplished to find correlation between anthropometric factors and TSH level.

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