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High Serum Levels of Thyroid-Stimulating Hormone and Sustained Weight Gain in Patients with Thyroid Cancer Undergoing Radioiodine Therapy

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Background and Objectives: The extent of weight gain and its association with clinical factors in patients undergoing radioiodine therapy for differentiated thyroid cancer remain unclear. We analyzed clinical factors related to sustained weight gain after serum thyroid-stimulating hormone (TSH) stimulation for radioiodine (I-131) therapy. **Materials and Methods:** The study population included 301 adult patients who underwent total thyroidectomy followed by radioiodine therapy and visited the thyroid clinic regularly. Group 1 received a single radioiodine therapy treatment, while group 2 received multiple radioiodine treatment. Data on transient weight gain, defined as weight gain that resolved (±5%) within 1 year after radioiodine therapy, were collected from medical records. Sustained weight gain was defined as body mass index after treatment (BMI_{post}) − BMI before treatment (BMI_{pre}) ≥2 kg/m^2 more than 1 year following radioiodine therapy. Subjective symptoms were scored by questionnaire. Logistic regression analysis was performed using various clinical and laboratory factors to identify risk factors associated with sustained weight gain. **Results:** Two hundred and fifty-nine (86%) patients showed transient weight gain and 23 (8%) patients showed sustained weight gain. TSH at therapy and T4-on TSH differed significantly in all patients and in the patients in group 1 with sustained weight gain. The proportion of patients with basal BMI≥25 kg/m^2 in group 1 with sustained weight gain also differed significantly. Univariate analysis revealed that high serum levels of TSH at therapy (≥100 μIU/mL) and hypercholesterolemia were associated with sustained weight gain in group 1. Multivariate analysis showed that TSH at therapy levels ≥100 μIU/mL was associated with sustained weight gain in group 1. Of 283 patients remaining after excluding those with insufficient TSH suppression during follow-up, T4-on TSH levels were lower in the sustained weight gain group compared to those without sustained weight gain. TSH at therapy levels ≥100 μIU/mL were significantly associated with sustained weight gain in multivariate analysis. **Conclusion:** Most patients (86%) had transient weight gain after TSH at therapy, while 8% of patients showed sustained weight gain. Univariate and multivariate analysis revealed relatively high TSH levels (≥100 μIU/mL) to be a risk factor for patients that received a single dose of radioiodine therapy. Insufficient T4 dose was not associated with sustained weight gain.

Key Words: Radioiodine therapy, I-131, Weight gains, TSH at therapy, Hypercholesterolemia

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Introduction

Radioiodine (I-131) therapy has been widely used for management of patients with well-differentiated thyroid cancer.[1,2] Since elevated serum TSH levels enhance iodine uptake in thyroid cancer cells, serum TSH levels are typically stimulated prior to radioactive iodine therapy. Serum TSH levels can be increased simply by discontinuing thyroid hormone therapy in patients that have undergone total thyroidectomy. In these cases, high TSH stimulation is accompanied by hypothyroidism. The symptoms of hypothyroidism include increased body weight. Although recombinant TSH can be used for this pretreatment, its high cost and poor availability are obstacles to its widespread use.

The importance of sustained weight gain after two weeks withdrawal of thyroid hormone has not been well studied in patients with differentiated thyroid cancer (DTC). Some patients show severe and sustained weight gain despite a return to normal or even suppressed serum TSH levels. Reports on hypothyroidism related to weight change in postoperative DTC are scarce. Sohn et al.[3] observed that only female patients with DTC showed significant gains in weight and body mass index (BMI) during long-term follow-up after initial treatment. Patients administered recombinant TSH did not gain significant weight during follow-up. In these cases, recombinant TSH may be a treatment of choice.

In the present study, we evaluated the patterns of weight gain in patients undergoing radioiodine therapy. TSH levels and various clinical factors were analyzed in order to elucidate their relationships with weight gain.

Materials and Methods

Patient Characteristics

Korean patients who visited Seoul National University Hospital between July 2012 and December 2012 were enrolled in this study. The design of this study and exemption of informed consent were approved by the Institutional Review Board of our institution. A total of 311 patients with DTC received radioiodine therapy post-operatively and were followed for more than 1 year. Ten patients were excluded due to not responding to the questionnaire, irregular follow-up, or insufficient TSH stimulation (<30 μIU/mL). Finally, 301 patients (69 men, 232 women) were included (53.4±12.2 years of age). Regular 6-month follow-up was performed in all patients. Patients were classified by the number of radioiodine therapy sessions administered; 83 patients received a single radioiodine treatment (group 1; median follow-up: 6 years) and 218 patients received multiple radioiodine treatments (group 2; median follow-up: 9 years). The mean number of multiple radioiodine therapies was 3.0±2.6. Most patients (92%) had been diagnosed with papillary thyroid cancer. Recurrent thyroid cancer or metastatic thyroid cancer were confirmed by follow-up ^{131}I-therapy or diagnostic scan, ultrasonography, computed tomography (CT) or positron emission tomography-CT (PET/CT). Diabetes mellitus, hypertension, hypercholesterolemia and cardiovascular disease were present in 6%, 18%, 7%, and 2% of patients. About three-quarters of the patients reported that they exercised, and 24% reported following calorie restriction diets. The patient characteristics are listed in Table 1.

In order to stimulate TSH levels, levothyroxine (LT4) was discontinued for 4 weeks before radioiodine therapy. Triiodothyronine (T3) was then administered for 2 weeks; this T3 replacement was discontinued for the last two weeks before radioiodine therapy. In addition, patients were instructed to follow a low-iodine diet for the last two weeks before radioiodine therapy.[4]

Definition of Sustained Weight Gain and Transient Weight Gain

Sustained weight gain was defined as more than 2 kg/m^2 increase in BMI at the 1-year follow-up. Basal BMI (BMI_{pre}) was measured before serum TSH elevation. BMI_{post} was defined as the BMI at the 1-year follow-up after radioiodine therapy. Transient weight gain was defined as weight gain that resolved within 1 year after radioiodine therapy. Restored body weight was

Table 1. Patient clinical characteristics (n=301)

Characteristics	Group 1	Group 2	p
Age (years)	53.7±11.6	53.3±12.4	0.353
Sex			
Male	15	54	0.283
Female	68	164	
Pathology			
Papillary	82	194	0.019
Follicular	0	16	
Papillary and follicular	1	8	
Underlying disease			
Diabetes mellitus	6	12	0.591
Hypertension	15	39	1.000
Hypercholesterolemia	9	12	0.128
Cardiovascular disease	2	3	0.618
Tuberculosis	2	4	0.669
Liver disease	1	1	0.207
Exercise			
No	17	59	0.299
Yes	66	159	
Calorie restriction			
No	64	165	0.881
Yes	19	52	

within ±5% of basal body weight. BMI was defined as body mass (kg) divided by the square of their height (m).

Questionnaire

Each subject was interviewed after 1 year follow-up post ^{131}I-therapy and answered a detailed questionnaire regarding subjective discomfort due to sustained weight gain. Medical conditions, calorie restriction, and exercise were included. Participants were considered positive for exercise when they reported having engaged in moderate or vigorous physical activity for more than one hour per day. We surveyed subjective discomfort scores of sustained weight gain associated with TSH at therapy. The scores were classified into five categories based on a visual analog scale: 1, none; 2, mild; 3, moderate; 4, severe; and 5, extreme discomfort. These subjective discomforts were due to the physical discomforts of weight gain, including ill-fitting clothing, difficulty walking, and difficulty climbing stairs.

Anthropometrical Measurements

Weight and height were measured at our clinic, with the patients wearing light clothing without shoes. Basal body weights before elevation of TSH period for radioiodine therapy were obtained from electronic medical charts. Asian populations BMI 25 kg/m^2 was used as the cut-off value for obesity in this study, and participants were classified into two groups for analysis.[5)]

TSH Measurement

Regular follow-ups were conducted every 6 months. Serum levels of TSH were measured (μIU/mL; reference range, 0.4-4.1; BRAHMS Diagnostica, Berlin, Germany). T4-on TSH level was defined as the average of several TSH levels during the regular 6-monthly follow-ups. TSH at therapy levels were averaged in cases of patients with multiple radioiodine therapies.

Statistical Analysis

Statistical analysis was performed using a commercial statistics package (MedCalc 9.5; MedCalc Software, Belgium). Chi-squared tests were used to evaluate the correlation between subjective discomfort scores and sustained weight gain. Chi-squared and independent t-tests were used to evaluate binary and continuous parameters for sustained weight gain, respectively. Univariate and multivariate logistic regression analyses were used to identify parameters significantly associated with sustained weight gain. Odds ratios and p values were obtained, and p values <0.05 were considered statistically significant. The relationships between TSH levels and sustained weight gain were tested by ROC curve. The cutoff values of stimulated and T4-on TSH were 100 and 0.9, respectively.

Results

Patient Characteristics

A significant number of patients experienced weight gain. Of 301 patients, 259 (86%) showed transient weight gain, and 23 patients (8%) showed sustained weight gain (Table 2). In group 1, nine (11%) patients had sustained weight gain. In group 2, 14 patients (6%) had sustained weight gain.

Subjective discomfort scores are listed in Table 3.

Table 2. Patient characteristics related to weight gain

Characteristics	Group 1	Group 2	Value n (%) or mean±SD
Basal BMI			
BMI<25 kg/m^2	63	159	222 (74%)
BMI≥25 kg/m^2	20	59	79 (26%)
Transient weight gain			
Yes	73	186	259 (86%)
No	10	32	42 (14%)
Sustained weight gain ($BMI_{post}-BMI_{pre}$≥2 kg/m^2)			
Yes	9	14	23 (8%)
No	74	204	278 (92%)
TSH at therapy	121.4±72.4	145.8±73.8	139.7±74.0
T4-on TSH	0.905±1.880	1.414±2.999	1.274±2.744

BMI: body mass index, BMI_{post}: body mass index after treatment, BMI_{pre}: body mass index before treatment, SD: standard deviation, TSH: thyroid stimulating hormone

Table 3. Subjective discomfort scores for sustained weight gain after TSH at therapy

Subjective discomfort	Sustained weight gain		p
	(-)	(+)	
No - moderate	254	9	<0.0001*
Severe and extreme	24	14	

*p<0.05: Chi-squared test between two groups
TSH: thyroid stimulating hormone

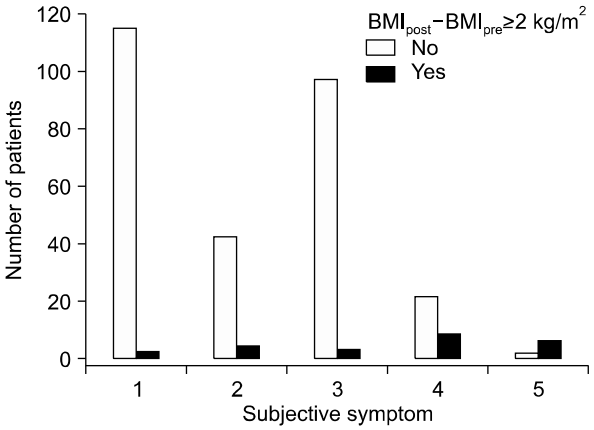

Fig. 1. Number of patients with and without sustained weight gain according to subjective symptom scores. Subjective discomfort scores were categorized using a visual analog scale: 1, none; 2, mild; 3, moderate; 4, severe; and 5, extreme discomfort. The numbers of patients with and without sustained weight gain for each score were: 115 vs. 2 (1.7%) in score 1, 42 vs. 4 (8.7%) in score 2, 97 vs. 3 (3%) in score 3, 22 vs. 8 (26.7%) in score 4, and 2 vs. 6 (75%) in score 5.

The proportion of patients with sustained weight gain was significantly higher in the severe and extreme discomfort groups (p<0.0001). Sustained weight gain ($BMI_{post}-BMI_{pre}$<2 kg/m^2) was frequently observed in patients with high subjective symptom scores (Fig. 1). Scores of 1, 2, 3, 4, and 5 were reported in 1.7%, 8.7%, 3%, 26.7% and 75% of patients (p<0.05).

Comparisons of TSH at Therapy and T4-on TSH Levels According to the Presence of Sustained Weight Gain

The cutoff values of TSH at therapy and T4-on TSH were determined by ROC curve analysis (Fig. 2). Of 301 patients, TSH at therapy levels differed significantly between patients with and without sustained weight gain (180.1±97.8 and 136.2±70.8, respectively; p=0.022) (Table 4). The T4-on TSH levels also differed significantly between these groups (2.1±3.6 and 1.2±2.7, respectively; p=0.021) (Table 4). Of 83 patients in group 1, stimulated and T4-on TSH levels and the proportion of individuals with basal BMI ≥25 kg/m^2 differed significantly between patients with and without sustained weight gain (p=0.015, p<0.001, and p<0.0001, respectively) (Table 4, Fig. 3).

Evaluation of Factors Associated with Sustained Weight Gain

Univariate analysis revealed that TSH at therapy levels ≥100 μIU/mL and hypercholesterolemia were

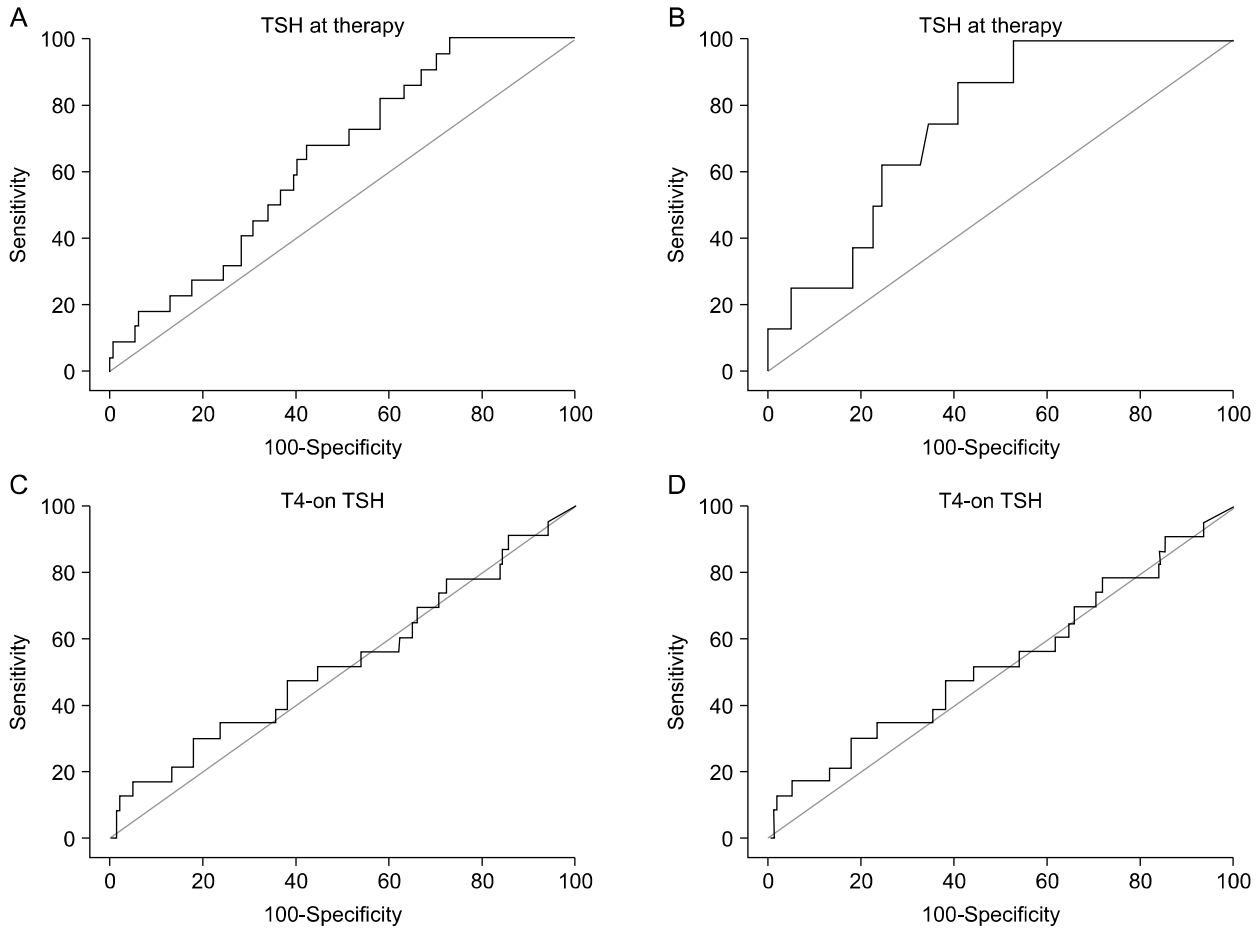

Fig. 2. ROC curves for the evaluation TSH cutoff values. (A) The TSH at therapy cutoff value overall was 87.35 μIU/mL (sensitivity 100 and specificity 27.17). (B) The TSH at therapy cutoff value in group 1 was 100 μIU/mL (sensitivity 100 and specificity 47.54). (C) The T4-on TSH cutoff value overall was 1.73 μIU/mL (sensitivity 30.43 and specificity 82.37). (D) The T4-on TSH cutoff value in group 1 was >0.90 μIU/mL (sensitivity 100 and specificity 27.17).

significantly associated with sustained weight gain in group 1 (Table 5). However, no significant factors were revealed in group 2. Meanwhile, TSH at therapy levels ≥100 μIU/mL was a significant factor in multivariate analysis (Table 6). The proportions of patients with sustained weight gain according to group are shown in Fig. 4. The proportions were higher in patients with TSH at therapy levels ≥100 μIU/mL in group 1, group 2 and overall ($p<0.05$).

Analysis of Patients with Insufficient TSH Suppression During Follow-up

T4-on TSH levels were higher among patients with sustained weight gain than those without sustained weight gain (Table 4). Eighteen patients had high T4-on TSH levels (>4.1 μIU/mL). Of the 283 patients remaining after excluding these 18 patients, the T4-on TSH levels were lower in the sustained weight gain group than those in the no sustained weight gain (Table 7). Hypercholesterolemia was a significant factor in univariate analysis. However, TSH at therapy levels ≥100 μIU/mL was a significant factor associated with sustained weight gain (Tables 7, 8) in multivariate analysis. This finding raises questions on the effects of TSH. Furthermore, insufficient T4 dose was not associated with sustained weight gain.

Discussion

In this study, a significant number of thyroid cancer patients experienced weight gain after TSH at therapy. We found that 86% and 8% had transient and sus-

Table 4. Comparisons of clinical factors according to the presence of sustained weight gain

Characteristics	Sustained weight gain		p	Sustained weight gain		p
	(−)	(+)		(−)	(+)	
Overall				Group 1		
Sex (female)	214	18	0.888	62	6	0.210
Diabetes mellitus	18	0	0.209	6	0	0.378
Hypertension	48	6	0.290	12	3	0.210
Hypercholesterolemia	18	3	0.236			
Cardiovascular disease	5	0	0.5173	2	0	0.620
Tuberculosis	6	0	0.477	2	0	0.620
Liver disease	2	0	0.773	1	0	0.727
Exercise	207	18	0.687	58	8	0.463
Calorie restriction	65	6	0.769	18	1	0.376
Basal BMI≥25 kg/m^2	72	7	0.635	16	4	0.137
TSH at therapy (μIU/mL)	136.2 (95% CI 127.4−144.9)	180.1 (95% CI 136.7−223.5)	0.022§	112.9 (95% CI 96.9−128.9)	185.8 (95% CI 93.9−277.8)	0.015§
T4-on TSH (μIU/mL)	1.20 (95% CI 0.892−1.518)	2.10 (95% CI 0.526−3.68)	0.021§	0.738 (95% CI 0.449−1.027)	2.28 (95% CI −1.124−5.692)	<0.001§

Categorical data: Chi-squared test between two groups
§p<0.05 : Independent samples t-test between two groups
BMI: body mass index, CI: confidence interval, TSH: thyroid stimulating hormone

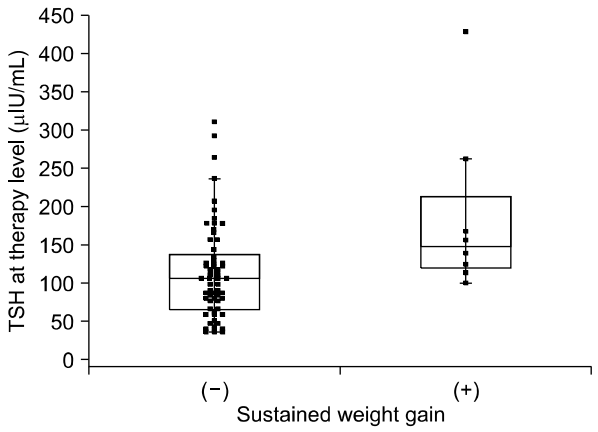

Fig. 3. TSH at therapy levels differed significantly between patients in group 1 with (185.8±109.9 μIU/mL) and without sustained weight gain (112.9±62.4 μIU/mL) (p=0.015). The central box in the plot represents the TSH at therapy values from the lower to upper quartiles (25 to 75 percentiles). The middle line represents the median of stimulated TSH. The horizontal line extends from the minimum to the maximum value, excluding outlier values, which are displayed as separate points.

tained weight gain, respectively. Relatively high TSH at therapy serum levels (≥100 μIU/mL) was a risk factor for sustained weight change among patients who received one dose of radioiodine therapy. Insufficient T4 dose was not a causative factor of sustained weight gain.

Weight gain due to hypothyroidism has been underestimated in post-operative DTC patients. Various metabolic and cardiovascular diseases such as hypertension,[6] diabetes mellitus, and cardiorenal metabolic syndrome[7] are related to obesity.[8] Moreover, weight gain has an economic impact in terms of increasing the medical and cosmetic costs.[9] The pathophysiology of weight gain in hypothyroidism is complex and unclear. It includes genetics, environment, behavior, diet, exercise,[10] and physiologic factors.[11]

It is possible for patients to develop severe problems after repeated short-term myxedema states. In general, there were no specific symptoms of complications two weeks after discontinuation of T4. However, 8% of patients in the current study experienced sustained weight gain with symptomatic discomfort. Recently, cosmetic needs for good and healthy shape have been elucidated. Therefore, assessment of clinical factors associated with sustained weight gain is important. The results of the current study exclude the possibility that high TSH (insufficient T4) was asso-

Table 5. Univariate analysis of risk factors associated with sustained weight gain

Factors	Group 1	p	Group 2	p
	Odds ratio (95% CI)		Odds ratio (95% CI)	
TSH at therapy ≥100 μIU/mL	3.15 (1.05–9.53)	0.041*	2.20 (0.22–22.20)	0.474
T4-on TSH >0.9 μIU/mL	0.00 (0.00–0.00)	0.986	0.87 (0.26–2.90)	0.827
Sex (male)	2.58 (0.57–11.78)	0.241	1.12 (0.11–11.34)	0.926
Age (50–59 years)	1.02 (0.24–4.43)	0.979	0.47 (0.06–3.55)	0.471
Recurrent or metastatic thyroid cancer	0.00 (0.00–0.00)	0.329	0.00 (0.00–0.00)	0.544
Diabetes mellitus	0.00 (0.00–0.00)	0.231	0.00 (0.00–0.00)	0.356
Hypertension	2.58 (0.57–11.78)	0.241	1.05 (0.10–10.62)	0.967
Hypercholesterolemia	5.67 (1.12–28.57)	0.049*	0.00 (0.00–0.00)	0.496
Exercise	2.21 (0.26–18.97)	0.432	1.14 (0.11–11.53)	0.910
Calorie restriction	0.39 (0.05–3.32)	0.339	3.53 (0.47–26.72)	0.234
Basal BMI ≥25 kg/m^2	2.90 (0.70–12.08)	0.154	2.78 (0.37–20.92)	0.326

*Statistically significant factors ($p<0.05$)
BMI: body mass index, CI: confidence interval, TSH: thyroid stimulating hormone

Table 6. Multivariate analysis of risk factors associated with sustained weight gain in group 1

Factors	Odds ratio (95% CI)	p
TSH at therapy ≥100 μIU/mL	3.22 (1.06–9.79)	0.039*
Hypercholesterolemia	1.77 (0.46–6.79)	0.404
Basal BMI ≥25 kg/m^2	1.61 (0.64–4.06)	0.317

*Statistically significant factors ($p<0.05$)
BMI: body mass index, CI: confidence interval, TSH: thyroid stimulating hormone

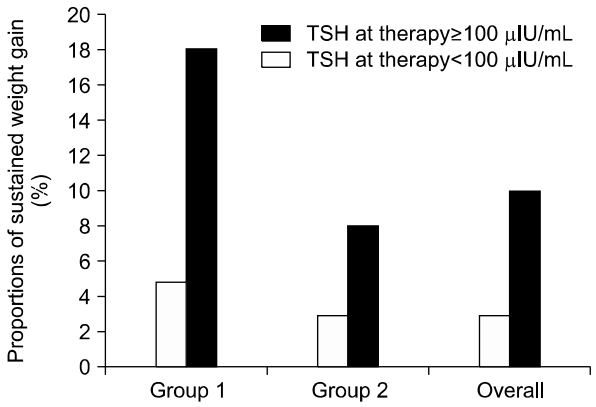

Fig. 4. Proportions of sustained weight gain ($BMI_{post}-BMI_{pre}\geq 2$ kg/m^2) were higher in TSH at therapy levels ≥100 μIU/mL in group 1, group 2, and overall. The values for the proportions of patients in groups 1 and 2 with sustained weight gain for TSH at therapy levels above and below 100 μIU/mL were 5% and 18%, and 3% and 8%, respectively, and 3% and 10% overall.

ciated with sustained weight gain.

Previous studies have evaluated the relationship between weight gain and thyroid function. Excess weight gain is a common complication after correction of thyrotoxicosis. Patients treated for hyperthyroidism reportedly gained weight continuously for at least 6 months after attaining a euthyroid status.[12,13] In addition, patients treated for primary hypothyroidism showed no significant weight loss and could not achieve their basal body weight.[14] Previous studies have reported different levels of weight gain in variable groups. Overweight and obese groups showed increased weight gain compared to the normal weight group among patients treated for thyrotoxicosis,[15] while menopausal women showed the highest weight gain among euthyroid patients undergoing thyroidectomy.[16] Similarly, individual heterogeneity caused divergent results between dyslipidemic and glycemic controls.[17] In this study, TSH at therapy ≥100 μIU/mL in group 1 was significantly associated with sustained weight gain in both univariate and multivariate analysis. We observed more complex patterns of weight gain or loss in group 2. Patients in group 2 experienced hypothyroidism for longer periods due to frequent therapies, and showed variable levels of TSH stimulation compared to those in group 1. Although TSH at therapy levels ≥100 μIU/mL was not a significant factor in group 2, this lack of significance could be due to variable responses to TSH at therapy. Tables 7 and 8 show that insufficient hormone replacement was not

Table 7. Comparisons of clinical factors according to the presence of sustained weight gain in 283 patients with well-controlled T4-on TSH levels

Characteristics	Sustained weight gain		p
	(–)	(+)	
Overall			
Basal BMI ≥25 kg/m^2	65	5	0.869
TSH at therapy (μIU/mL)	136.5 (95% CI 127.3–145.6)	185.8 (95% CI 136.0–235.5)	0.015§
T4-on TSH (μIU/mL)	0.740 (95% CI 0.628–0.851)	0.605 (95% CI 0.240–0.967)	0.332
Group 1			
Basal BMI ≥25 kg/m^2	15	3	0.188
TSH at therapy (μIU/mL)	113.8 (95% CI 97.3–130.2)	188.5 (95% CI 78.9–298.1)	0.010§
T4-on TSH (μIU/mL)	0.578 (95% CI 0.391–0.765)	0.093 (95% CI −0.003–0.189)	<0.001§

§p<0.05: Independent samples t-test between two groups
BMI: body mass index, CI: confidence interval, TSH: thyroid stimulating hormone

Table 8. Univariate and multivariate analysis of risk factors associated with sustained weight gain in 78 patients in group 1 with well-controlled T4-on TSH level

Factors	Odds ratio (95% CI)	p
Univariate		
TSH at therapy >100 μIU/mL	7.50 (0.86–65.52)	0.069
T4-on TSH <0.303 μIU/mL	0.00 (NA)	0.997
Hypertension	3.75 (0.74–18.95)	0.110
Hypercholesterolemia	8.25 (1.49–45.82)	0.016*
Basal BMI ≥25 kg/m^2	2.85 (0.57–14.14)	0.200
Multivariate		
TSH at therapy ≥100 IU/mL	16.33 (1.21–220.26)	0.035*
Hypercholesterolemia	2.48 (0.26–23.23)	0.426
Hypertension	5.27 (0.54–51.42)	0.153
Basal BMI ≥25 kg/m^2	6.14 (0.76–49.64)	0.089

*Statistically significant factors (p<0.05)
BMI: body mass index, CI: confidence interval, TSH: thyroid stimulating hormone

correlated with sustained weight gain in this study. Therefore, we hypothesize that different responses to TSH stimulation due to unidentified individual factors could lead to sustained weight gain.

The basic mechanism of weight gain in hypothyroidism remains unknown. A possible role of TSH and TSH receptors (TSHR) in regulating adipose tissue metabolism has been suggested in several reports.[18–20] TSHR has been identified in a number of tissues, including the brain, testes, kidney, heart, bone, thymus, lymphocytes, adipose tissue, and fibroblasts.[21] Likewise, the expression of TSHR in obese mice and obese human subcutaneous adipose tissues was positively correlated with BMI.[22] Additionally, obese persons with an euthyroid status showed a positive correlation between BMI and TSH levels.[23]

Differential activation of TSHR could be a mechanism that explains differences in weight gain, while modifications in TSHR activity may affect body composition. TSHR expression is upregulated during adipogenesis.[24] Higher levels of TSHR transcripts were observed in both Graves' opthalmopathy orbital fat[25] and fat undergoing differentiation due to increased cAMP in response to TSH activation.[26] Individuals with germline mutations in the TSHR gene may demonstrate differences in body composition parameters.[27] Although the expression levels of TSHR in human adipose tissues is always less than that in thyroid tissues, differential activity of TSHR might be a key mechanism in regulating body composition. Our patients showed significant correlations between weight gain and TSH levels. Additionally, we speculate that changes in TSHR may be a mechanism that leads to sustained severe weight gain.

There are other complex mechanisms of weight gain that include both peripheral and central factors. Many investigators have investigated potential mechanisms of energy intake and expenditure. Recently, a close evolutionary relationship between peripheral and hypothalamic neuropeptides was reported.[28] The hypothalamus, the central controller of hunger, mediates regulation of long- and short-term dietary intake via synthesis of various orexigenic and anorectic neuropeptides. Long-term regulation is provided by the

main circulating hormones leptin and insulin, which control food intake and energy storage. Patients with hypothyroidism had decreased leptin levels, which may contribute to decreased energy expenditure.[29] Although the findings are controversial, insulin was positively correlated with TSH levels in patients with hypothyroidism.[30] Feeding behavior is controlled by a series of short-term hormonal and psychological signals derived from the gastrointestinal tract, such as cholecystokinin and ghrelin. However, ghrelin, known as an appetite-stimulatory signal, does not seem to be crucial for maintenance of energy homeostasis. Ghrelin-knockout mice have a normal body size and composition, which implies that this hormone has only a small effect on body weight.[28,31] Furthermore, ghrelin levels appear to be related to insulin resistance.[32]

This study has several limitations. First, this is a retrospective study; therefore, it is possible that patients had biased recall memories about their subjective symptoms despite careful observation. Second, laboratory data on levels of leptin, ghrelin, insulin, and other variable neuropeptides regulating appetite and energy expenditure were not obtained. Third, quantitative body weight data were only obtained in preparation for radioiodine therapy and irregularly during follow-up clinical visits. More regular measurements of weight to evaluate transient and sustained weight gain are recommended in future studies. To elucidate the clinical significance of multiple radioiodine therapies on weight gain, a comparison study using multiple groups with similar radioiodine therapy doses might be informative. To evaluate the basic mechanism of weight gain, further biologic research on TSH and TSHR is required.

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