



Research article

Duration of antithyroid drug treatment may predict weight gain after radioactive iodine therapy in patients with Graves' disease



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ABSTRACT

Background: Weight gain post-radioiodine (RAI) treatment is observed in patients with hyperthyroid Graves' disease. Previous studies, mostly in Caucasian patients, demonstrated excessive weight gain averaging 5–7 kg from initial presentation.

Aim: The aim of this study was to determine the extent and risk factors of weight gain in Thai patients with RAI-treated Graves' disease.

Methods: This was a 5-year retrospective study of patients with hyperthyroid Graves' disease who received RAI treatment during 2016–2020. The proportion and associated risk factors of weight gain $\geq 5\%$ in patients who was followed for at least 3 months when compared with weight at RAI administration were analyzed.

Results: There were 347 patients with Graves' disease (females 81.0%, mean age 38.8 ± 12.1 years, BMI 23.3 ± 4.0 kg/m²) who were treated with RAI. Almost all RAI-treated patients (91.9%) eventually developed hypothyroidism. During the median follow-up period of 25 months, 73.1% of them had weight gain. The mean weight change was $+2.5 \pm 4.9$ kgs when compared with weight at the time RAI administration and $+3.4 \pm 6.5$ kgs when compared with recalled body weight before the onset of hyperthyroidism. The proportion of patient in the obesity class I (BMI 25.0–29.9 kg/m²) increased from 23.6% to 28.0% and obesity class II (BMI ≥ 30.0 kg/m²) increased from 5.2% to 8.9%. Duration of antithyroid drug treatment less than 6 months after the diagnosis of hyperthyroidism was the only factor associated with weight gain $\geq 5\%$.

Conclusions: Weight gain post-RAI treatment was common, and a significant proportion of patients went on to develop obesity. Early intervention with weight management support should be employed in patients with less than 6 months of antithyroid drug treatment before RAI.

1. Introduction

Radioiodine (RAI) treatment is one of the treatment modalities for hyperthyroid Graves' disease (GD). It could be the first-line treatment in some patients or in patients with relapsed GD. The goal of RAI treatment is to induce euthyroidism [1] but hypothyroidism is usually inevitable. Post RAI weight gain is also a problem for many patients [2]. The extents of weight gain are variable and were demonstrated to associate with the severity of hyperthyroidism at presentation [3, 4].

Thyroid hormones have complex roles in both energy expenditure and food intake [5]. Restoration to euthyroidism leads to weight regain in most patients due to decreased energy expenditure with a remaining an unabated increased appetite [6, 7]. A recent study in

antithyroid-treated Japanese patients with GD showed the difference in time course of increased fat mass and lean body mass [8]. While fat mass was significantly increased very early at 1 month, lean body mass was relatively unchanged until 3–6 months. Most studies were done in antithyroid-treated or postsurgical patients [9, 10, 11, 12, 13]. Based on few studies in Caucasian subjects [4, 14], RAI-treated GD patients experienced more weight gain in comparison with the other two modalities (on average 5–7 kg from weight at the initial presentation of GD). Inadequate thyroid hormone replacement of hypothyroidism after RAI treatment could not fully explain this extent of weight regain and large inter-individual post-treatment weight trajectory exists.

To better understand the pattern of weight gain after RAI in Asian patients, the aim of this study was to determine change in body weight,

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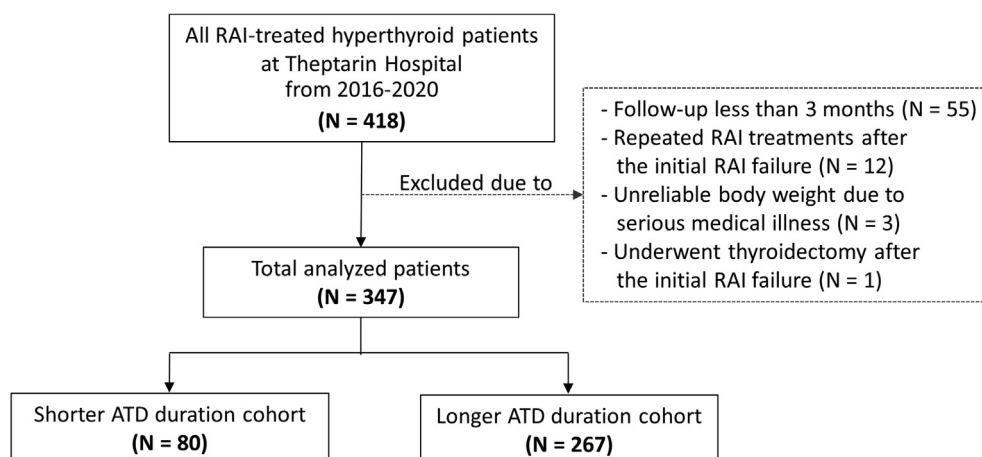


Figure 1. Study flowchart of patient selection.

weight trajectory and risk factors of weight gain during follow-up visits in a cohort of Thai patients with RAI-treated GD.

2. Materials and methods

All consecutive GD patients who were treated with RAI at Theptarin Hospital, Bangkok from 2016 to 2020 were retrospectively reviewed. Subjects were excluded if age <15 years, non-Thai ethnicity, follow-up for less than 3 months after RAI treatment, requirement of repeated RAI treatment to achieve euthyroidism or hypothyroidism, medical illnesses or taking medications which could affect weight, pregnancy during follow-up. The data included age, gender, recalled baseline body weight before the onset of hyperthyroidism, smoking status, estimated

goiter size at the time of RAI administration, and dose of RAI treatment. In our hospital, a fixed dose of RAI based on estimated thyroid size was prescribed individually to aim for hypothyroidism.

All patients included in the analysis were divided into 2 cohorts: the longer antithyroid drug duration (longer ATD duration) cohort (if RAI treatment was given after 6 months after the diagnosis of hyperthyroidism) and the shorter antithyroid drug duration (shorter ATD duration) cohort (if RAI treatment was given within 6 months after the diagnosis of hyperthyroidism). The cut-off at 6 months was chosen based on the estimated time to ensure euthyroid state before RAI therapy [15]. Anthropometric data at the time of diagnosis of hyperthyroidism, at the time of RAI administration, at 3, 6, 12, 24, 36 months after RAI and at the last visit were retrieved. Body weight was routinely

Table 1. Demographics and laboratory data of studied patients.

	Total group (N = 347)	Shorter ATD duration (N = 80)	Longer ATD duration (N = 267)	P-value
Age at the time of RAI treatment (years)	38.84 ± 12.1	39.0 ± 13.2	38.8 ± 11.8	0.866
Female (%)	281 (81.0)	64 (80.0)	217 (81.3)	0.799
Active smoking (%)	17 (4.9)	2 (2.5)	15 (5.6)	0.257
Premorbid weight (kg)	59.9 ± 12.4	60.8 ± 11.1	59.6 ± 12.8	0.450
Weight at GD diagnosis (kg)	57.0 ± 11.2	57.0 ± 9.2	57.0 ± 11.8	0.995
Weight at the time of RAI treatment (kg.)	60.9 ± 12.9	59.7 ± 10.7	61.4 ± 13.5	0.251
BMI at the time of RAI treatment (%)	23.3 ± 4.0	22.7 ± 3.5	23.4 ± 4.1	0.123
<18.5	7.5	7.5	7.5	
18.5–22.9	47.0	51.3	45.7	
23–24.9	16.7	13.8	17.6	
25–29.9	23.6	25	23.2	
≥30	5.2	2.5	6.0	
Goiter size (%)				0.503
Small	23.6	18.8	25.1	
Medium	69.5	73.8	68.2	
Large	6.9	7.4	6.7	
Smoking (%)	17 (4.9)	2 (2.5)	15 (5.6)	0.257
Total T3 levels at the time of RAI treatment (ng/dL)	129.7 ± 32.6	138.7 ± 36.5	127.0 ± 31.0	0.028
Free T4 levels at the time of RAI treatment (ng/dL)	1.4 ± 0.4	1.5 ± 0.5	1.4 ± 0.4	0.158
TSH levels at the time of RAI treatment (mIU/L)	0.6 ± 1.2	0.5 ± 1.2	0.6 ± 1.1	0.506
RAI dosage (mCi)	20.0 (15.0,21.0)	20.0 (15.0,25.0)	20.0 (15.0,20.0)	0.384
Duration of Graves' disease before RAI (months)	26.0 (7.0,60.0)	3.0 (1.0,4.8)	36.0 (18.0,75.0)	<0.001
Duration of follow-up (months)	25.0 (13.0,38.0)	26.5 (14.3,42.8)	24.0 (12.0,36.0)	0.480
Highest quartile initial FT4 (%)	51 (14.7)	28 (34.1)	23 (29.9)	0.564
Highest quartile initial T3 (%)	32 (9.2)	21 (33.9)	11 (18.0)	0.045
Duration of hypothyroid before FT4 (months)	1.0 (0,2.0)	1.0 (0,2.0)	1.0 (0,2.0)	0.947

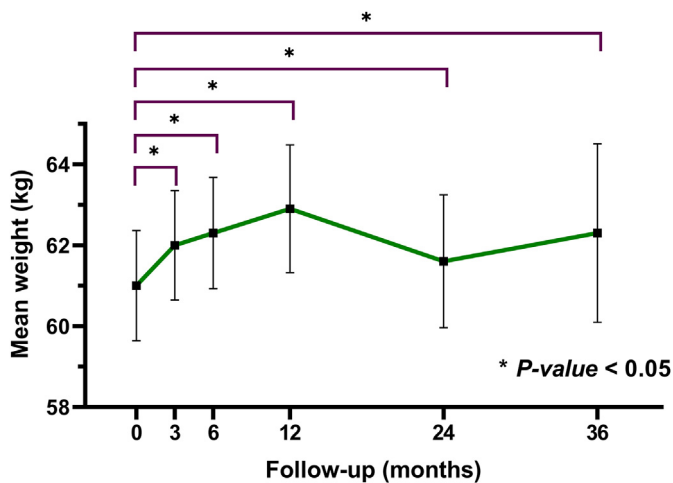


Figure 2. Mean weight trends in RAI-treated Graves' disease patients over the period of 36 months after RAI treatment (* *p*-value < 0.001).

recorded by a digital scale to the nearest 100 g while patients had minimal clothes without shoes. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. BMI was categorized based on the Asian-Pacific cutoff points [16] into underweight: <18.5 kg/m²; normal weight 18.5–22.9 kg/m²; overweight 23.0–24.9 kg/m²; obese class I 25.0–29.9 kg/m²; and obese class II ≥ 30.0 kg/m².

Initial thyroid function tests including serum total triiodothyronine (total T3), serum free thyroxine (FT4), and serum thyroid-stimulating hormone (TSH) levels were assessed. The thyroid function tests at the time of RAI administration and nadir concentrations of serum FT4 and TSH levels before the initiation of levothyroxine (LT4) were also recorded. Serum T3, FT4, and TSH levels were measured by electro chemiluminescent immunoassays (Roche Diagnostics, Indianapolis, USA). The reference ranges used for serum T3, FT4, and TSH levels were 60–177 ng/dL, 0.9–1.7 ng/dL, and 0.3–4.2 mIU/L, respectively. This study was approved by the Institutional Review Board committee of Theptarin Hospital (EC No.03/2021).

2.1. Statistical analyses

Descriptive data was reported as mean with standard deviation (SD), median with interquartile range (IQR), and number with percentage.

Quantitative variables were analyzed using Student's t-test for independent samples and qualitative variables were compared using Pearson chi-square and Fisher tests. Percentage of weight changes was calculated as (weight at the last visit – weight at the time of RAI administration)/weight at the time of RAI administration X 100. Then patients who gained weight were categorized into weight gain ≥5% or weight gain <5%. A univariate analysis of all presumed factors associated with weight gain ≥5% was conducted and a multiple regression analysis including all variables with a correlation significance of *P*-value < 0.20 obtained in the univariate analysis was performed to rule out confounding factors. Initial serum T3 and FT4 levels were transformed into the quartile category and the highest quartile was compared with the remaining quartiles for factors associated with weight gain ≥5%. Results were expressed as hazard ratios (HRs) with their 95% confidence interval (95% CI). Data processing was performed using SPSS Statistics (version 25.0, IBM Corp, Armonk, NY, USA). A two-tailed *P*-value < 0.05 was considered statistically significant.

3. Results

3.1. Patient characteristics

A total of 418 charts were reviewed; of these, 347 patients met the inclusion criteria as shown in Figure 1. Eighty cases (23.1%) received RAI treatment within 6 months after the diagnosis of GD (shorter ATD duration cohort). The baseline demographic and laboratory data in each cohort were demonstrated in Table 1. The mean age at the time of RAI administration of the total group was 38.8 ± 12.1 years (female 81.0%). The median dose of 20 mCi was given and almost all RAI-treated patients (91.9%) developed hypothyroidism. The median duration after the diagnosis of GD to the time of RAI administration was 3 months in the shorter ATD duration cohort and 36 months in the longer ATD duration cohort. In the longer ATD duration cohort, the three most common reasons to switch to RAI treatment included relapsed GD (68.3%), huge goiter (13.6%), and patient preference (7.5%). At the time of RAI administration, higher mean serum T3 level was observed in the longer ATD duration cohort (*p*-value = 0.028) but were still in the normal reference range. At the diagnosis of GD, the mean weight loss of the total group was 2.8 ± 5.7 kgs when compared with recalled pre-morbid weight. At the time of RAI administration, the mean body weight and BMI of the total group were 60.9 ± 12.9 kgs and 23.3 ± 4.0 kg/m², respectively. During the median follow-up period of 25 months, 73.1% of patients had gained weight when compared with the body weight at the time of RAI administration.

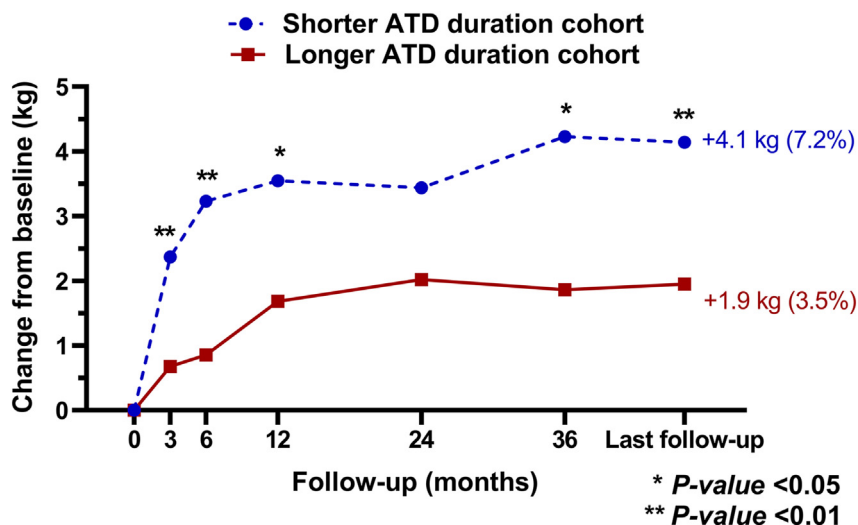


Figure 3. Comparison of mean weight trends between patients who received RAI treatment within 6 months (shorter ATD duration cohort) and patients who received RAI treatment after 6 months (longer ATD duration cohort).

3.2. Changes in weight and BMI after RAI treatment

As shown in Figure 2, most patients experienced significant weight gain after RAI treatment, with an increase from the mean weight of 60.9 kgs at baseline to 62.9 kgs at 12 months (p -value < 0.01). The weight increased early within the first 6 months after RAI treatment and continued for more than 24 months. At the last follow-up, in the total group, the mean weight change was $+2.5 \pm 4.9$ kgs when compared with weight at RAI administration. Men gained more weight than women, but the difference was not statistically significant (2.9 kgs versus 2.3 kgs, p -value = 0.405). The proportion of obesity class I (BMI 25.0–29.9 kg/m²) increased from 23.6% to 28.0% and obesity class II (BMI ≥ 30.0 kg/m²) from 5.2% to 8.9%.

3.3. Changes in weight and BMI according to timing of RAI treatment

When stratifying patients in relationship with timing of RAI treatment, patients in the shorter ATD duration cohort gained more weight after treatment more than patients in the longer ATD duration cohort as shown in Figure 3. At the last follow-up, the mean weight change was

$+4.1 \pm 6.2$ kgs in the shorter ATD duration cohort when compared with $+1.9 \pm 4.4$ kgs in the longer ATD duration cohort (p -value < 0.01). The proportion of obesity class I (BMI 25.0–29.9 kg/m²) and obesity class II (BMI ≥ 30.0 kg/m²) increased more in the shorter ATD duration cohort as shown in Figure 4 but the difference was not statistically significant.

3.4. Variables associated with weight gain $\geq 5\%$ in subgroup of patients who gained weight ($N = 254$)

As shown in Table 2, individuals with $\geq 5\%$ weight gain were more likely to be patients in the shorter ATD duration cohort and patients with longer follow-up period after RAI treatment. Receiving RAI treatment after 6 months after the onset of hyperthyroidism was the only protective factor associated with weight gain $\geq 5\%$ after the multivariate analysis with hazard ratio of 0.42 [95% CI 0.19–0.93; p -value = 0.031] as shown in Table 3. At the last follow-up, the subgroup of patients who gained weight were found to have at least 3%, 5%, and 10% weight increase from the time of RAI treatment in 72.0%, 58.3%, and 28.0%, respectively.

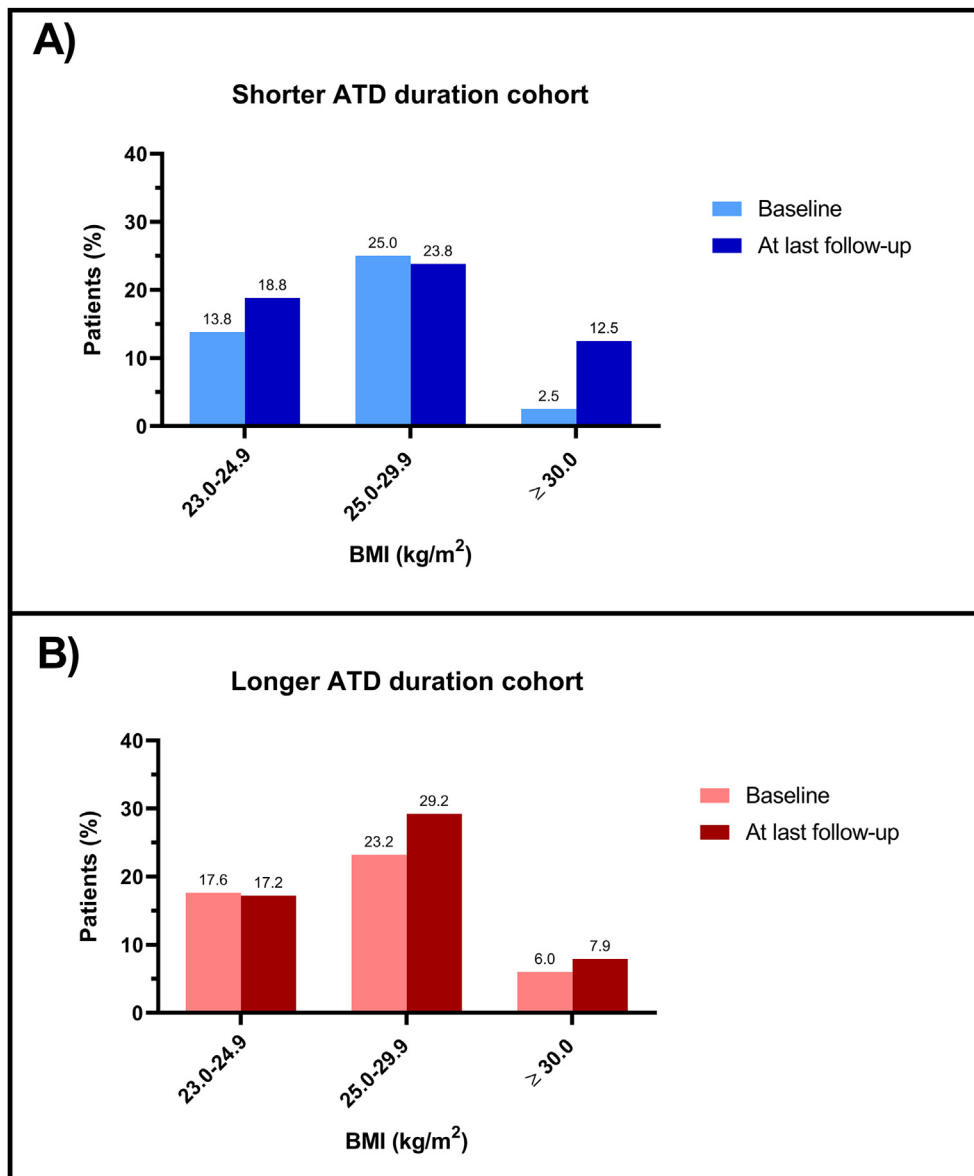


Figure 4. Comparison of each BMI category between shorter ATD duration and longer ATD duration cohort from the time of RAI treatment and the time at last follow-up.

Table 2. Comparison between patients who experienced weight gain $\geq 5\%$ and patients who experienced weight gain $< 5\%$.

	Weight gain $< 5\%$ (N = 106)	Weight gain $\geq 5\%$ (N = 148)	P-value
Age at the time of RAI treatment (years)	38.2 \pm 11.0	39.8 \pm 12.7	0.294
Female (%)	84 (79.2)	118 (79.7)	0.925
Active smoking (%)	7 (6.6)	7 (4.7)	0.793
Premorbid weight (kg)	59.3 \pm 12.6	60.1 \pm 12.1	0.599
Weight at diagnosis (kg)	56.7 \pm 11.6	56.7 \pm 10.7	0.983
Weight at the time of RAI treatment (kg)	60.8 \pm 13.5	59.4 \pm 11.9	0.366
Percentage of weight change (premorbid weight and the diagnosis of GD) (%)	-3.8 (-8.8,0)	-5.0 (-9.2,0)	0.192
BMI at the time of RAI administration (%)	23.4 \pm 4.4	22.6 \pm 3.7	0.135
<18.5	7.5	11.5	
18.5–22.9	50	48.6	
23–24.9	14.2	16.2	
25–29.9	20.8	20.3	
≥ 30	7.5	3.4	
Highest quartile initial Free T4 values (%)	17 (37.0)	23 (29.9)	0.417
Highest quartile initial Total T3 values (%)	10 (28.6)	11 (18.0)	0.229
Longer ATD duration cohort (Received RAI more than 6 months after diagnosis) (%)	88 (83.0)	100 (67.6)	0.006
Duration of hypothyroid before FT4 (months)	1.0 (0,2.0)	1.0 (0,2.0)	0.645
Duration of Graves' disease before RAI (months)	28 (9.0,59.3)	19.5 (5.0,60.0)	0.420
Duration of follow-up (months)	22.0 (10.0,31.3)	27.0 (17.0,42.8)	0.032

4. Discussions

Our present study showed that weight gain post-RAI treatment was common and a significant proportion of patients went on to develop obesity. A greater increase in body weight developed during the first 6 months after RAI treatment and continued for more than 24 months. Although most patients gained weight relatively modest (2–3 kgs) when compared with weight at RAI administration, large inter-individual weight trajectory existed. Our observed weight gain was less than in several other previous studies [4, 10, 13] which might be due to a difference in baseline body composition between Caucasians and Asians. Also, our cohort composed of mainly female at age less than 40 years which a recent study showed less increased risk of becoming obese [13]. Our data indicated that shorter duration of ATD before RAI (within 6 months after the diagnosis of GD) could be a risk factor for more weight gain after treatment.

After restoration of euthyroidism in patients with active GD, resting energy expenditure decreased markedly and weight gain is frequently observed [7, 17]. However, patients who underwent RAI treatment or post-thyroidectomy patients are more prone to gain weight even with optimum thyroid hormone replacement therapy [9]. In addition, several adipocytokines from adipocytes which control appetite was shown to be affected following the treatment for hyperthyroidism [18, 19]. Our data by multiple regression analysis indicated that duration of antithyroid drug treatment was the only factor associated with weight gain after

radioactive iodine therapy. This observation may be based on inadequate induction of euthyroid state in patients who received shorter duration of antithyroid drug treatment. This hypothesis was supported by higher mean serum T3 level in the group with shorter duration of antithyroid drug treatment. This was a retrospective study and may not have enough power to confirm significance of higher mean serum T3 level in the multiple regression analysis, but the trend was observed. Identification of high-risk patients for excessive weight gain after definitive treatments of GD based on biomarkers or metabolites should pave the way for precision medicine in the future.

Previous studies showed that more severe initial serum thyroid hormone levels correlated with the greater extent of weight gain in post-thyroidectomy patients [13, 20]. In addition, higher serum TRAb levels had been consistently shown to be higher in post-RAI treatment when compared with other treatments [21] while long-term ATD treatment could lower serum TRAb levels [22]. Recent evidence from clinical and experimental data showed that thyrotropin receptor signaling enhanced adipogenesis and involved in the transformation from brown fat to white fat [23]. In clinical practice, serum TRAb levels at the time of RAI might serve as a potential biomarker for excessive weight gain apart from worsening Graves' ophthalmopathy and exacerbation of hyperthyroidism.

Because weight gain was most pronounced during the first 6 months following RAI treatment [8, 24], implementing multidisciplinary weight management strategies to prevent obesity and achieve weight loss in

Table 3. Univariate and multivariate analysis of clinical factors and laboratory data for predicting weight gain $\geq 5\%$ after RAI treatment (N = 148).

	Univariate analysis			Multivariate analysis		
	HR	95% CI	P-value	HR	95% CI	P-value
Age ≥ 50 years at the time of RAI treatment	1.209	0.686–2.131	0.511			
Sex (Female)	0.869	0.507–1.490	0.609			
BMI ≥ 25 kg/m ²	0.639	0.395–1.033	0.068	1.237	0.519–2.948	0.632
Initial T3 values at the highest quartile (>651 ng/dL)	0.430	0.186–0.993	0.048	0.439	0.181–1.064	0.068
Initial FT4 values at the highest quartile (>7.77 ng/dL)	0.821	0.421–1.602	0.564			
Longer ATD duration cohort	0.399	0.239–0.666	0.001	0.421	0.193–0.919	0.030
Weight loss $\geq 5\%$ before the diagnosis	1.423	0.915–2.211	0.117	1.670	0.780–3.572	0.187
Duration of follow up > 24 months after RAI treatment	1.515	0.988–2.325	0.057	1.235	0.577–2.641	0.586

those with overweight/obesity is important. Currently, there is no well-designed studies to examine the effect of dietary intervention to prevent weight gain following RAI treatment. Our study had several limitations and weaknesses due to its retrospective design. We had no information on lifestyle behaviors after RAI treatment. Additional relevant parameters such as serum TRAb at the time of RAI administration, body composition analysis, menstrual status, etc. were missing in this cohort. Moreover, self-reported pre-morbid weights might not be reliable.

In conclusion, weight gain post-RAI treatment was common and a significant proportion of patients went on to develop obesity. Although large inter-individual weight trajectory existed. Our data indicated that shorter duration of ATD before RAI (within 6 months after the diagnosis of GD) could be a risk factor for more weight gain after the treatment. Discussion of the risk of excess weight gain and early intervention with weight management support should be employed during the course of treatment.

Declarations

Author contribution statement

Yotsapon Thewjitcharoen and Waralee Chatchomchuan: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Hussamon Prasatkaew and Panita Srichomchey: Conceived and designed the experiments; Analyzed and interpreted the data.

Siriwan Butadej, Soontaree Nakasatien and Ekgaluck Wanothayaroj: Conceived and designed the experiments.

Rajata Rajatanavin and Thep Himathongkam: Analyzed and interpreted the data; Wrote the paper.

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Data availability statement

Data will be made available on request.

Declaration of interests statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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