Changes in thyroid volume and thyroid function in acromegaly after surgery in Chinese population

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Abstract

Background : An increased prevalence of thyroid lesions was observed in acromegaly patients. However, the change of thyroid after remission of acromegaly was not clear in Chinese populations. The aims were to assess the thyroid structure and function changes before and after transsphenoidal pituitary adenoma resection in patients with acromegaly and to investigate the correlation between GH, IGF-1, disease duration and thyroid structure and function.

Methods : We retrospectively studied 78 patients with acromegaly who underwent surgery between 2015 January and 2018 January at Peking Union Medical College Hospital. The pituitary hormone: random growth hormone (GH), nadir GH and insulin-like growth factor-1 (IGF-1); the thyroid hormone: thyroid stimulating hormone (TSH), thyroxine (T4), triiodothyronine (T3), free thyroxine (FT4) and free triiodothyronine (FT3); four parameters of thyroid metabolism: thyroid's secretory capacity (SPINA-GT), the sum activity of peripheral deiodinases (SPINA-GD), standard TSH index (sTSHI) and thyrotrophic thyroid hormone sensitivity index (TTSI); and thyroid ultrasound were assessed at baseline and 1 year after surgery.

Results : Thyroid volume was significantly positively related random GH, nadir GH, and disease duration. TSH, sTSHI and TTSI was negatively related with pituitary hormone while IGF-1 showed a significant positive association with FT4 and SPINA-GT. After transsphenoidal resection of pituitary adenoma and over 1 year follow-up, the thyroid volume decreased significantly (p=0.000). T3 (p=0.049) and FT3 (p=0.022) also decreased significantly though within normal ranges. However, no significant changes were found in nodule maximum diameter and sTSHI. Thyroid volume change was positively correlated with GH change and nadir GH change. T3 change as well as SPINA-GD change was positively associated with IGF-1 change. Though no significant difference were observed between controlled patients and those who did not achieved "control" level, control patients had a larger decline in thyroid volume along with a smaller decrease in TSH.

Conclusion: Enlarged thyroid volume, prevalent thyroid nodules, suppressive pituitary thyrotrophic function and elevated peripheral thyroid hormones are characteristic in acromegaly. A decrease in GH could have favorable effect on thyroid status on thyroid volume and thyroid hormones, while established thyroid nodules and impaired pituitary thyrotrophic function seemed to change little after surgery.

Introduction

Acromegaly is a chronic disease associated with a persistent hyper-secretion of growth hormone (GH) and subsequent elevation of insulin-like growth factor–1 (IGF–1) which is usually caused by pituitary adenoma (1). An increased prevalence of thyroid lesions was observed in acromegaly patients and raised researchers' interest (2, 3).

Goiter, a kind of thyroid lesion, was demonstrated as a common co-occurrence of acromegaly though the mechanism underlying it was not completely understood. It seems that IGF–1 could act as a thyroid

growth factor and thus could stimulate thyroid growth in acromegaly patients (4, 5). Thyroid function in acromegaly was also widely studied. Though GH was proved to modulate the activity of throxine deiodinase, which could affect thyroid hormone level in acromegaly patients, euthyroidism was seen in most acromegaly patients (6). Recently, Andreas Jostel and Johannes W. Dietrich et al proposed that traditional parameters in thyroid function test like thyroid stimulating hormone (TSH), thyroxine (T4), triiodothyronine (T3), free thyroxine (FT4) and free triiodothyronine (FT3) might influence each other and could not reflect more subtle thyroid dysfunctions. Thus, they provided four mathematical models investigating thyroid function: thyroid's secretory capacity (SPINA-GT), the sum activity of peripheral deiodinases (SPINA-GD) and, as markers of the set point, Jostel's TSH index (JTI) or standard TSH index (sTSHI) for assessment of thyrotrophic pituitary function and the thyrotrophic thyroid hormone sensitivity index (TTSI). Therefore, these four calculated parameters might reflect thyroid function in acromegaly patients though no observations were reported (7, 8).

Thyroid volume and nodules changes after treatment of acromegaly were also contradictory. Some researchers found no significant changes in thyroid volume and nodules after neurosurgery, radiotherapy, or medical treatment (6). However, Herrmann et al. observed thyroid volume decrease in both medical control and cured patients (9), and Seyfullah et al. confirmed decrease in thyroid volume and nodules volume after over 6 months somatostatin analog use (10). Data on thyroid function before and after surgery were sparse. No significant variation of thyroid stimulating hormone (TSH) was observed by Cannavo (6). Ferdinand found decreased triiodothyronine (T3), increased rT3, and unchanged thyroxine (T4) after treatment (11–14).

Considering the close relationship between acromegaly and thyroid, we conducted this study to investigate the thyroid structure and function change in acromegaly patients and their relationship in a large Chinese pituitary center. The aims of our study were: 1) to assess the thyroid structure and function changes before and after transsphenoidal pituitary adenoma resection in patients with acromegaly, 2) to investigate the correlation between GH, IGF–1, disease duration and thyroid structure and function changes.

Materials And Methods

We retrospectively analyzed data from patients who were diagnosed with acromegaly and underwent transsphenoidal pituitary adenoma resection between January 2015 and January 2018 in the Department of Neurosurgery, Peking Union Medical College Hospital (PUMCH). The inclusion criteria were as follows: (1) presented with symptoms for acromegaly; (2) patients who satisfied the diagnostic endocrine standard (fasting GH > 1 ng/ml, nadir GH > 0.4 ng/ml after oral administration of 75 g of glucose, and a fasting IGF–1 level higher than the age related reference range)(15); (3) a pituitary adenoma identified by contrast-enhanced magnetic resonance imaging (MRI); (4) underwent transsphenoidal pituitary adenoma neurosurgery in PUMCH; (5) having undergone examinations of thyroid ultrasound and thyroid hormone functional test before surgery. Exclusion criteria were: having undergone thyroidectomy, radiotherapy, or medical treatment before surgery; having pregnancy within 1

year before surgery; having ever experienced nervous or psychological disease, such as Parkinsonism and Schizophrenia.

Figure 1 showed the flow chart of participants in the present study. Seventy-eight patients were included in our study at baseline. 3 patients were diagnosed with thyroid cancer and underwent thyroidectomy or radiotherapy after neurosurgery. All of them were papillary thyroid carcinomas (PTC) confirmed by pathology, and were followed at clinic and showed no recurrence during observable period. 6 patients lost follow-up. The rest completed follow-up in our hospital 1 year after surgery including examinations of pituitary hormone test, thyroid hormone functional test and thyroid ultrasound examinations. Twenty-eight patients achieved "control" level while the rest 41 did not according to the 2014 guideline (15). Of the patients who did not meet the "control" criteria, 2 patients had residual tumors after surgery and second surgery was recommended for them, while the GH level of 3 patients remained higher than 5ng/ml (13.1, 16.6 and 33.4) and medical therapy were recommended for them. Observation were recommended for the rest 36 patients who did not achieve "control" but reached a GH level lower than 5ng/ml at 1 year after surgery. We chose the 28 controlled patients and the 36 observable not controlled patients for the postoperative analysis.

Demographics and clinical information such as: diagnosed age, body mass index (BMI) at diagnosis and disease duration (from the time of the onset of symptoms to the time of undergoing transsphenoidal pituitary adenoma neurosurgery in PUMCH) was collected from medical records.

The serum GH (random and nadir GH), IGF–1, FT4, T4, FT3, T3, and TSH levels were assessed at the time of acromegaly diagnosis and were determined using chemiluminescent immunometric assays (L2KGRH2, Siemens Healthcare Diagnostics Products Ltd., Glyn Rhonwy, Llanberis, Gwynedd LL55 4EL, UK). Random GH was defined as the fasting serum GH tested nearest to the time of diagnosis and 1 year after surgery of acromegaly. Nadir GH was defined as the lowest serum GH during the OGTT. The reference values were 0.81–1.89 ng/dl for FT4, 4.30–12.50 μg/dl for T4, 1.80–4.10 pg/ml for FT3, 0.66–1.92 ng/ml for T3, and 0.38–4.34 μIU/ml for TSH. Additionally, we evaluated four parameters of thyroid metabolism: SPINA-GT as an evaluation of thyroid's secretory capacity, SPINA-GD as a variable for the sum activity of peripheral deiodinases, sTSHI as a marker of pituitary-thyrotrophic function and TTSI as an evaluation of thyrotrophic thyroid hormone sensitivity. These parameters were calculated according to the following equations: SPINA-GT = $[\beta T \times (DT + TSH) \times TT4]/(\alpha T \times TSH)$ (reference range: 1.41–8.67 pmol/s); SPINA-GD = $[\beta 31 \times (KM1 + FT4) \times TT3]/(\alpha 31 \times FT4)$ (reference range: 20–40nmol/s); sTSHI = $[\log(TSH)+0.1345*FT4-2.7]/0.676$ (reference range: −2 to +2); TTSI = $100*TSH*FT4/24.32$ (reference of normal subjects: 136 ± 14μIU/L). Constants in the equations were as follows: βT = 1.1×10–6/s, DT = 2.75mU/L, αT = 0.1/L, $\beta 31$ = 8×10–6/s, KM1 = 5×10–7mol/L, and $\alpha 31$ = 0.026/L.

Pituitary glands were scanned by contrast-enhanced MRI using a 3.0T MRI system (MAGNETOM Skyra, Siemens Healthcare, Erlangen, Germany). Thyroid ultrasound was performed using a Philips iU22 ultrasound machine with high-frequency linear array transducers in the 8-to–15 MHz range. The characteristics of the thyroid, which included the number of nodules in the thyroid and the size,

echogenicity, margins, internal content (presence of cystic lesions), shape, and vascular pattern of the thyroid, were thoroughly documented. The volume of the thyroid gland was calculated using the sum of the volume of each lobe based on an ellipsoid model.

Statistical analysis

Categorical variables were presented as a number (percentage). Quantitative data were presented as the mean (±standard deviation) or median (±standard deviation). Normality was tested using the Kolmogorov-Smirnov and ShapiroWilk W test. Comparisons between categorical variables were performed using the chi-square test. Comparisons between numerical variables were performed using the independent sample t-test and Mann–Whitney test. The paired-samples t-test or Wilcoxon's signed-rank test was used to compare the differences between two measurements (beginning and end). Correlation between variables were conducted using Pearson or Spearman test. Analyses were performed using the Statistical Package for Social Sciences (SPSS) Version 19.0 software package (SPSS, Inc, Chicago, IL, USA). A two-sided p value <0.05 was considered statistically significant.

Results

78 patients with acromegaly were enrolled in our study. The mean age was 41.09±10.81 years, with 29 males and 49 females. The average duration of acromegaly was 76 months (Table 1). At baseline, 5 patients had normal thyroid and 73 patients had morphological abnormalities, among which 32 had benign nodules, 22 had benign nodules together with goiter, and 19 had diffuse goiter without nodules. Among patients who had nodules, 26 patients had only one nodule and 29 patients had multiple nodules. Seventy-three out of 78 patients had normal serum FT4 and FT3 levels. Of the rest, 1 had serum FT4 and FT3 over the upper end and lost follow-up 1 year later. One case had lower FT4 and 3 had lower FT3.

At baseline, we found positive relationship between thyroid volume and random GH ($r = 0.277$, $P = 0.032$), nadir GH ($r = 0.383$, $P = 0.003$), and disease duration ($r = 0.283$, $P = 0.027$). With regard to thyroid nodules, no significant relationship was found between pituitary hormone and nodule diameters. Considering relationship between pituitary hormone and thyroid function, we found negative relationship between TSH and random GH ($r = -0.230$, $P = 0.049$) and nadir GH ($r = -0.307$, $P = 0.008$). sTSHI was also negatively associated with nadir GH ($r = -0.252$, $P = 0.031$), while TTSI was negatively associated with random GH ($r = -0.229$, $P = 0.049$) and nadir GH ($r = -0.293$, $P = 0.012$) significantly. Meanwhile, IGF–1 showed a significant positive association with FT4 ($r = 0.254$, $P = 0.031$) and SPINA-GT ($r = 0.251$, $P = 0.042$) (Data not shown). In addition, patients with larger thyroid had significant lower TSH ($r = -0.335$, $P = 0.000$), sTSHI ($r = -0.321$, $P = 0.002$) and TTSI ($r = -0.340$, $P = 0.001$), as well as higher SPINA-GT ($r = 0.296$, $P = 0.005$) (Data not shown).

After transsphenoidal resection of pituitary adenoma and over 1 year follow-up, 64 patients were compared with preoperative status. For all participant, the thyroid volume decreased significantly in all patients (26.53±17.22 to 23.31±11.08 cm3, $p = 0.000$). However, no significant changes were found in

total nodule maximum diameter, single nodule maximum diameter, or multiple nodule maximum diameters. Nodule maximum diameter and single nodule maximum diameter even increased though not reach significance. In addition, at 1 year follow-up, T3 decreased significantly from 1.13±0.27 at baseline to 1.06±0.19 at follow-up ($p = 0.049$), and FT3 declined significantly from 3.12±0.57 to 2.95±0.38 ($p = 0.022$). The change of TSH, FT4, T4, SPINA-GT, SPINA-GD and TTSI showed a declined trend but were not significant while sTSHI was almost unchanged ($p = 0.772$) (Table 2). Comparing controlled patients with those who did not achieved “control”, controlled patients had a larger decline in thyroid volume along with a smaller decrease in TSH (Table 3).

Considering the change of pituitary hormone and thyroid, there were positive relationship between GH change and thyroid volume change ($r = 0.333$, $P = 0.047$) and positive association between nadir GH change and thyroid volume change ($r = 0.410$, $p = 0.014$), while IGF–1 change was not associated significantly with thyroid volume change. Considering thyroid function, only IGF–1 change was significantly positively associated with T3 change ($r = 0.286$, $p = 0.046$) as well as SPINA-GD change ($r = 0.360$, $p = 0.011$) (Figure 2). However, no significant relationship was observed between change in thyroid volume and thyroid function values (Data not shown).

Discussion

This study retrospectively investigated the thyroid structure and function changes in acromegaly patients in a large pituitary center in northern China. Our study showed that reduction in GH after surgical management for acromegaly patients could influence the size of enlarged thyroid and changed thyroid function.

Thyroid disease, especially goiter, is a frequent complication of acromegaly. Previous research showed that goiter developed in 20%–90% acromegaly patients, usually presenting as thyroid enlargement and thyroid nodularity (16, 17). However, the correlation of thyroid volume with disease duration and pituitary hormone is unclear. Gasperi et al. (16) observed thyroid volume had a positive correlation with disease duration, but not with GH and IGF–1. While Miyakawa et al. found an analogous association between higher GH, IGF–1 and thyroid volume (4). In this study, we reported thyroid abnormalities in 93.6% of acromegaly patients and found a positive correlation between thyroid volume and disease duration, serum random GH and nadir GH levels. Moreover, we found a significant decrease in thyroid volume after transsphenoidal resection of GH-secreting pituitary adenoma, and proved a positive correlation between thyroid volume reduction and random GH, nadir GH decrease, which was consistent with previous researches (9, 18). The results of our study support the theory that GH and IGF–1 could stimulate DNA synthesis and activate antiapoptotic signaling pathway in thyroid cells (19–21). The decline of thyroid volume after surgery indicated that thyromegaly might be reversible with disease control. Our study excluded those having ever received treatment with octreotide during observable period, thus proved the effect of GH, IGF–1 decrease on thyroid volume without the interference that octreotide could itself inhibit cell proliferation through SSTR2 and 5 expressing on thyroid cells (22–25). We found no correlation between thyroid volume change and IGF–1change, which may be explained by the slow descent rate of

IGF–1 after surgery. We also found that the decrease in thyroid volume was more significant in patients with longer duration, higher GH, higher nadir GH, and higher IGF–1 before treatment, which provided a value in predicting the change of thyroid volume.

Thyroid nodule change after treatment in acromegaly patients was also controversial. Cheung et al. found that nodule size did not decrease after treatment with octreotide (18), while Seyfullah K et al found a decline in nodule volume and nodule diameter after successful medical treatment for acromegaly (10). Dogansen SC et al, in addition, found nodule size increased in active acromegaly patients and found a high risk of thyroid malignancy in these patients (26). In our research, nodule maximum diameter showed no significant decrease after transsphenoidal resection of GH-secreting pituitary adenoma, indicating that decline in GH and IGF–1 might have little effect on established thyroid nodule. Thus, more attention should be paid on acromegaly patients with thyroid nodules.

To our knowledge, our study was the first to investigate parameters like SPINA-GT, SPINA-GD, sTSHI and TTSI in acromegaly patients. Traditional thyroid function tests were considered limited in evaluating thyroid function individually due to the interference of TSH and thyroid hormones (27). Thus, parameters like SPINA-GT, SPINA-GD, sTSHI and TTSI were proposed and considered stable and more reliable than thyroid function test parameters. sTSHI was demonstrated a better estimate of true pituitary thyrotrophic function which adjusting for the negative feedback inhibition of TSH by peripheral FT4 concentrations (7) and TTSI was demonstrated to be a valuable marker for estimating thyrotrophic function. Also, reliability of SPINA-GT and SPINA-GD was demonstrated higher than that of measured hormone concentrations (8). Therefore, our study was to investigate these parameters as well as traditional hormones in acromegaly patients.

Our study observed a negative relationship between nadir GH, IGF–1 levels and TSH. This negative correlation might be due to the inhibited leptin observed in active acromegaly considering the stimulating effect of leptin on TSH (28–30). The somatostatin secretion accompanied with excess GH might also suppress TSH secretion(31). In addition, the negative relationship between sTSHI, TTSI and pituitary hormones indicated an impaired pituitary thyrotrophic function in acromegaly patients more specifically. After transsphenoidal resection of pituitary adenoma, though TSH showed a declined trend, sTSHI was almost unchanged, indicating that the impaired pituitary thyrotrophic function might not recover from the decrease of GH. Thus, thyroid function should be followed-up in acromegaly patients even after remission of the disease to avoid hypothyroidism.

Though negative correlation was observed between GH or IGF–1 and TSH, an expected negative correlation between these pituitary hormones and thyroid hormones was not observed. What’s more, higher FT4 and SPINA-GT were related with higher IGF–1 and IGF–1 change was significantly positively associated with T3 change and SPINA-GD change. After surgery, decreases in T3, FT3, T4, FT4 SPINA-GT and SPINA-GD were found after surgery though some were not significant. A kind of modulation of thyroid secretion independent of TSH was proposed to explain this discrepancy. Gotzsche et al. observed the stimulation of thyroxine deiodinase by GH, which could lead to T3 increase (32, 33). Yoshinari et al.

suggested a direct stimulation of IGF–1 on thyroid secretion (34). Moreover, SPINA-GT was thought to provide an estimate for the maximum secretion rate of the thyroid gland and SPINA-GD was thought to reflect the maximum stimulated activity of step-up deiodination(8). Thus, the positive relationship between SPINA-GT and IGF–1 and decreased SPINA-GT and SPINA-GD after surgery supported this theory. In addition, thyroid volume was also an important factor influencing thyroid's secretory capacity and deiodinase activity (35). The enlarged thyroid volume in acromegaly patients and decreased thyroid size after surgery observed by us were consistent with the thyroid hormone, SPINA-GT and SPINA-GD changes. The discrepancy might also explained by a decrease in sympathetic function in acromegaly and a subsequent heightened response of thyroid tissue to TSH might explain the discrepancy of TSH impairment and peripheral thyroid function normality (36–38). These theories might explain the complex relationships between pituitary hormones and thyroid hormones observed by us.

Though no significant difference were observed between controlled patients and those who did not achieved "control" level, control patients had a larger decline in thyroid volume, with a smaller decrease in TSH. This indicated the effect of surgery on thyroid volume and TSH, and a larger sample might be implemented to compare the difference in patients with or without remission.

This study has some limitations. First, it is a retrospective study and thus a standard follow-up was failed to be established. Second, the thyroid function was estimated by regular hormone test. However, we used SPINA-GT, SPINA-GD, sTSHI and TTSI to evaluate the thyroid function. More sensitive methods such as radionuclide imaging are needed to assess thyroid function in the future.

Conclusion

Our study is the largest study implemented in Chinese population which investigated the effect of transsphenoidal resection of GH-secreting pituitary adenoma on thyroid volume and thyroid function. We found enlarged thyroid volume, prevalent thyroid nodules, suppressive pituitary thyrotrophic function and elevated peripheral thyroid secretory capacity and peripheral deiodinases in acromegaly. After transsphenoidal resection of GH secretion pituitary adenoma, a partial reverse in thyroid volume and thyroid hormones were observed, while established thyroid nodules and impaired pituitary thyrotrophic function seemeed to change little after surgery. Therefore, our study indicated that early diagnosis and regular follow-up of thyroid ultrasound and functions are necessary in acromegaly patients even after surgery.

List Of Abbreviations

GH, growth hormone; IGF–1, insulin-like growth factor–1; TSH, thyroid stimulating hormone; FT4, free thyroxine; T3, triiodothyronine; T4, thyroxine; FT3, free triiodothyronine; SPINA-GT, thyroid's secretory capacity; SPINA-GD, activity of peripheral deiodinases; sTSHI, standard Jostel's TSH index; TTSI, thyrotroph thyroid hormone sensitivity index

Declarations

Ethics approval and consent to participate

Informed consent was obtained from all individual participants included in the study. The study was approved by the Ethical Committee of PUMCH.

Consent for publication

Informed consent was obtained from all individual participants included in the study.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interest.

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Author contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Qianqian Shao, Jiayi Li and Bing Xing. The first draft of the manuscript was written by Qianqian Shao and Jiayi Li. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Tables

Table 1 Characteristics of patients with acromegaly at baseline before treatment (n=78)

Variables		Values
Age (years)/ mean (±SD[1])		41.09(±10.81)
Gender	Males/ n (%)	29 (37.2%)
	Females/ n (%)	49 (62.8%)
BMI[2] (kg/m^2)/ mean (±SD)		26.28(±4.04)
Disease duration (months)/ mean (±SD)		76.19(±67.83)
random GH[3] (ng/ml) / mean (±SD)		3.01(±5.17)
IGF-1[4] (ng/ml) / mean (±SD)		383.95(±236.05)
nadir GH (ng/ml) / mean (±SD)		1.47(±3.31)
Thyroid volume (ml)/ mean (±SD)		25.76(±15.37)
Nodule maximum diameter (cm)/ mean (±SD)		1.54(±1.26)
Single nodule maximum diameter (cm)/ mean (±SD)		0.83(±0.66)
Multiple nodule maximum diameter (cm)/ mean (±SD)		2.15(±1.34)
TSH[5] (mIU/L)/ mean (±SD)		1.39(±1.15)
FT4[6] (ng/dL)/ mean (±SD)		1.19(±0.21)
T3[7] (ng/mL)/ mean (±SD)		1.10(±0.26)
T4[8] (ug/dL)/ mean (±SD)		8.52(±2.00)
FT3[9] (pg/mL)/ mean (±SD)		3.05(±0.57)
SPINA-GT[10] (pmol/s) / mean (±SD)		5.38(±3.87)
SPINA-GD[11] (nmol/s) / mean (±SD)		17.64(±4.72)
sTSHI[12]/ mean (±SD)		-0.94(±0.74)
TTSI[13] (IU/L) / mean (±SD)		86.35(±69.57)

1. SD, standard deviation
2. BMI, body mass index
3. GH, growth hormone
4. IGF-1, growth factor-1
5. TSH, thyroid stimulating hormone
6. FT4, free thyroxine
7. T3, triiodothyronine
8. T4, thyroxine
9. FT3, free triiodothyronine
10. SPINA-GT, thyroid’s secretory capacity
11. SPINA-GD, activity of peripheral deiodinases
12. sTSHI, standard Jostel’s TSH index
13. TTSI, thyrotrophic thyroid hormone sensitivity index

Table 2 Change of thyroid structure and function after transsphenoidal resection of growth hormone-secreting pituitary adenoma (n=64)

Variables	Before treatment	After treatment	P value
	Mean (±SD[1])	Mean (±SD)	
Thyroid volume (ml)	26.53(±17.22)	23.31(±11.08)	0.009
Nodule maximum diameter (cm)	1.60(±1.30)	1.66(±1.23)	0.134
Single nodule maximum diameter (cm) (n=21)	0.83(±0.66)	0.93(±0.96)	0.499
Multiple nodule maximum diameter (cm) (n=24)	2.15(±1.34)	1.95(±1.33)	0.504
TSH[2] (mIU/L)	1.38(±0.94)	1.29(±0.89)	0.425
FT4[3] (ng/dL)	1.19(±0.18)	1.18(±0.18)	0.858
T3[4] (ng/mL)	1.13(±0.27)	1.06(±0.19)	0.049
T4[5] (ug/dL)	8.56(±2.02)	8.18(±1.54)	0.095
FT3[6] (pg/mL)	3.12(±0.57)	2.97(±0.38)	0.047
SPINA-GT[7] (pmol/s)	5.37(±3.54)	4.97(±3.07)	0.498
SPINA-GD[8] (nmol/s)	17.88(±4.62)	16.74(±3.44)	0.059
sTSHI[9]	-0.91(±0.73)	-0.93(±0.70)	0.772
TTSI[10] (IU/L)	87.61(±61.68)	82.43(±61.86)	0.439

1. SD, standard deviation
2. TSH, thyroid stimulating hormone
3. FT4, free thyroxine
4. T3, triiodothyronine
5. T4, thyroxine
6. FT3, free triiodothyronine
7. SPINA-GT, thyroid’s secretory capacity
8. SPINA-GD, activity of peripheral deiodinases
9. sTSHI, standard Jostel’s TSH index

10. TTSI, thyrotrophic thyroid hormone sensitivity index

Table 3 Comparison of change of thyroid structure and function after surgery between controlled (n=28) and not controlled patients (n=36)

Variables	Controlled	Not controlled	P value
	Mean (±SD[1])	Mean (±SD)	
Thyroid volume (ml)	-3.72(+6.28)	-2.89(+9.48)	0.458
Nodule maximum diameter (cm)	0.14(+0.72)	-0.01(+0.76)	0.406
Single nodule maximum diameter (cm) (n=21)	0.17(+0.69)	0.05(+0.67)	0.915
Multiple nodule maximum diameter (cm) (n=24)	-0.14(+0.90)	-0.27(+0.93)	0.414
TSH[2] (mIU/L)	-0.06(+0.97)	-0.11(+0.70)	0.835
FT4[3] (ng/dL)	-0.05(+0.15)	0.03(+0.13)	0.026
T3[4] (ng/mL)	-0.10(+0.31)	-0.05(+0.22)	0.509
T4[5] (ug/dL)	-0.72(+1.74)	-0.17(+1.45)	0.236
FT3[6] (pg/mL)	-0.23(+0.70)	-0.09(+0.43)	0.384
SPINA-GT[7] (pmol/s)	-0.58(±4.49)	-0.29(±4.06)	0.814
SPINA-GD[8] (nmol/s)	-0.83(±5.45)	-1.33(±3.26)	0.716
sTSHI[9]	-0.15(±0.52)	0.08(±0.56)	0.126
TTSI[10] (IU/L)	-4.25(±58.77)	-5.91(±43.41)	0.902

1. SD, standard deviation

2. TSH, thyroid stimulating hormone

3. FT4, free thyroxine

4. T3, triiodothyronine

5. T4, thyroxine

6. FT3, free triiodothyronine

7. SPINA-GT, thyroid's secretory capacity

8. SPINA-GD, activity of peripheral deiodinases

9. sTSHI, standard Jostel's TSH index

TTSI, thyrotroph thyroid hormone sensitivity index

Figures

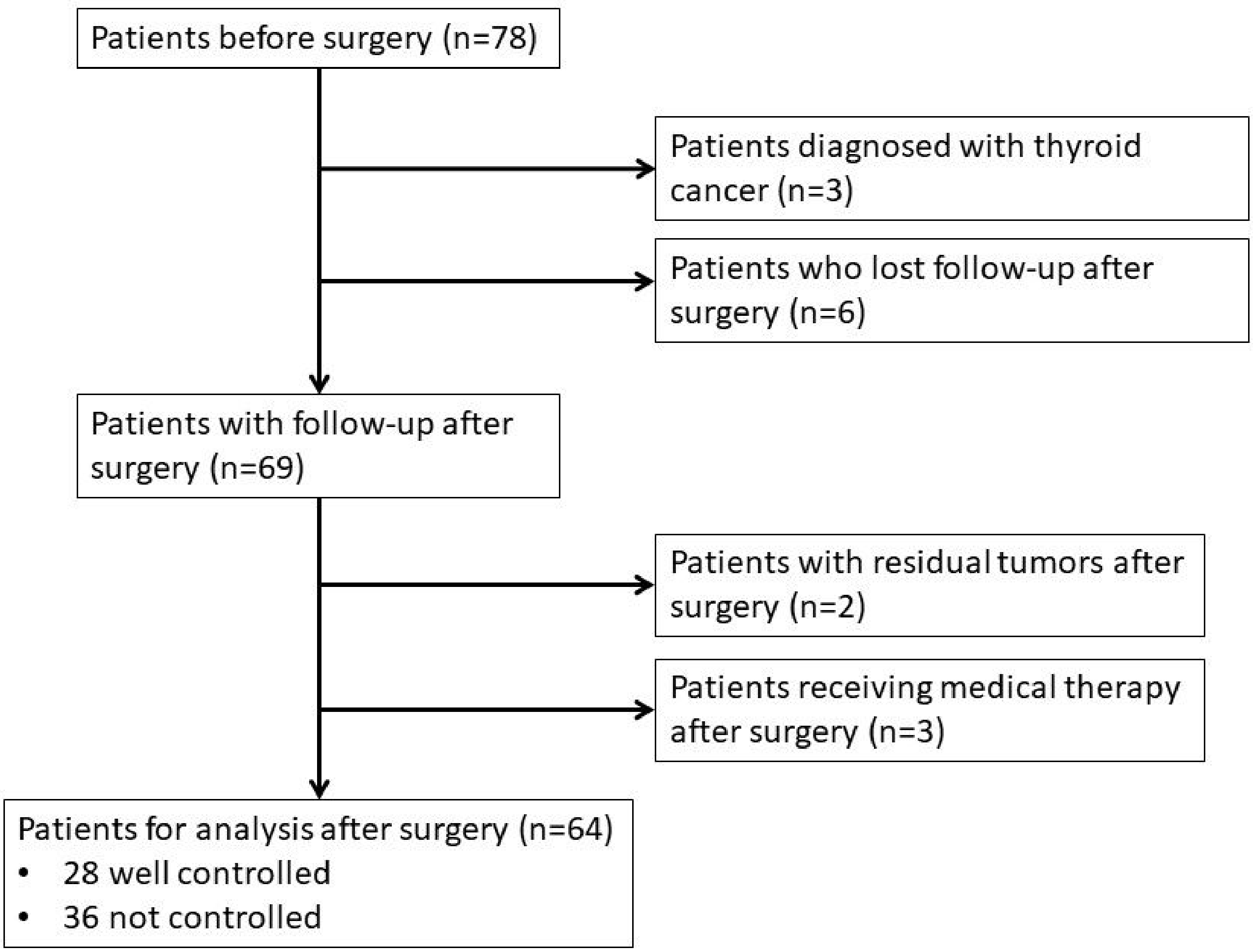

Figure 1

Flow chart of participants (n=78 at baseline and n=64 at follow-up)

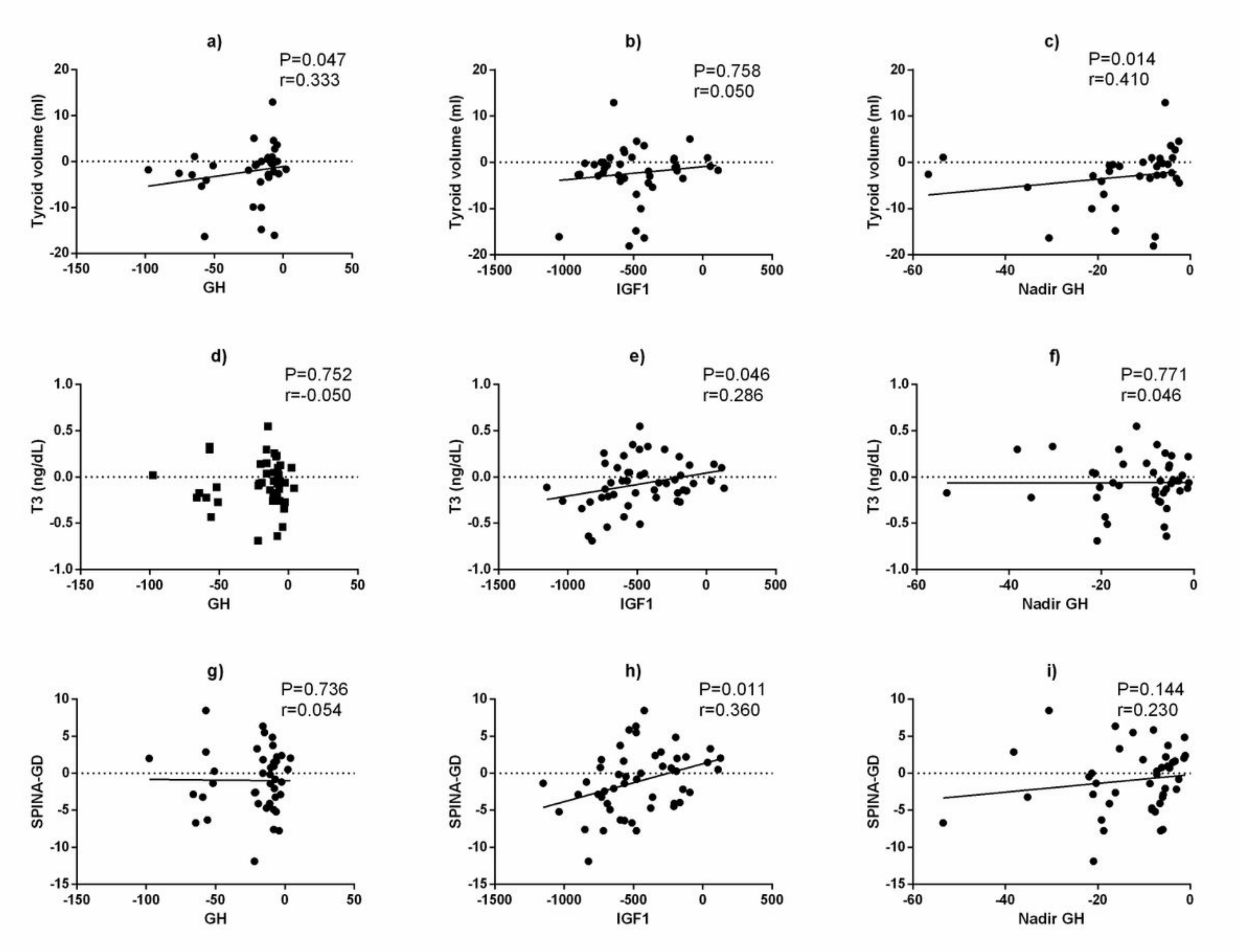

Figure 2

Correlation of changes in pituitary hormones and thyroid structure and thyroid function GH change was significantly positively related with thyroid volume change (r=0.333, P=0.047) and positive association between nadir GH change and thyroid volume change (r=0.410, p=0.014), while IGF-1 change was not associated significantly with thyroid volume change. IGF-1 change was significantly positively associated with T3 change (r=0.286, p=0.046) as well as SPINA-GD change (r=0.360, p=0.011). (Correlation between variables were conducted using Pearson or Spearman test)