# Clinical study on the status of transient thyrotoxicosis after surgery for secondary hyperparathyroidism patients with end-stage renal disease

**Baoshan Zou**
the First affiliated Hospital of Chongqing Medical University
**Jiashuo Liu**
The First Affiliated Hosiptal of Chongqing Medical University
**Hong Li**
The First Affiliated hospital of Chongqing Medical University
**Zhou Xu**
The First Hospital of Chongqing Medical university
**Hao Li**
The First Hospital of Chongqing Medical University
**Hongyuan Li**
The First Affiliated Hospital of Chongqing Medical University
**Kainan Wu**
The firat Affiliated Hospital of Chongqing Medical University
**Lingquan Kong** ( huihuikp@163.com )
Chongqing Medical University First Affiliated Hospital https://orcid.org/0000-0001-5705-9001

**Research article**

**Keywords:** chronic kidney disease, end-stage renal disease, secondary hyperparathyroidism, thyrotoxicosis, parathyroidectomy

**Posted Date:** September 12th, 2019

**DOI:** https://doi.org/10.21203/rs.2.14358/v1

# Abstract

Background: Secondary hyperparathyroidism (SHPT) is a common complication of end-stage renal disease (ESRD)and part of SHPT patients need receive parathyroidectomy (PTX). However, as an important postoperative complication of SHPT, thyrotoxicosis has received little attention. Therefore, in this article, we aimed to study the status of transient thyrotoxicosis after PTX for SHPT patients with ESRD and normal thyroid function.

Methods: A total of 36 SHPT patients with preoperative normal thyroid function, normal thyroglobulin(Tg) and normal thyroid antibodies receiving PTX were enrolled from the Department of Endocrine and Breast Surgery, the First Affiliated Hospital of Chongqing Medical University, from January 2017 to January 2019. Tg, high sensitivity thyrotropin stimulating hormone(sTSH), triiodothyronine(T3), free triiodothyronine(fT3)thyroxine(T4) and free thyroxine(fT4) were evaluated the day before PTX and on day 1, 3 and 5 after PTX. Besides, all enrolled patients were evaluated whether there are symptoms associated with thyrotoxicosis.

Results: Among the 36 SHPT patients, 3 case (8.3%), 14 cases (38.9%) and 24 cases (66.7%) had suffered thyrotoxicosis at the first, third and fifth day after surgery, respectively. Serum FT4 level increased significantly (1.5 times higher than the normal maximum) from pre-operation (0.66±0.14 ng/dl, normal range: 0.59-1.25ng/dl) to the third day after operation (2.13±2.16 ng/dl, p0.001) and then gradually decline, but still higher than the normal maximum on day 5 after surgery (1.40±0.59 ng/dl, p 0.001). The frequencies of serum sTSH lower than the normal level gradually increased from the first day 11.1% to fifth day 66.7% after surgery. Serum Tg level increased significantly (4 times higher than the normal maximum) from pre-operation (8.43±6.26, normal range: 0.00-50.03ng/ml)to the first day after operation 213.07±157.69, p0.001) and then gradually decline, but still relatively higher than the normal maximum on day 5 after surgery (67.70±97.43ng/ml, p0.001).

Conclusion: Transient thyrotoxicosis is a common postoperative complication of parathyroidectomy for SHPT patients with ESRD and normal thyroid function, and it is necessary for clinicians to evaluate the perioperative thyroid function to make early diagnosis and appropriate prevention and treatment of thyrotoxicosis.


# Background

The prevalence of chronic kidney disease (CKD) has reached 8%–16% worldwide and the prevalence of end-stage renal disease (ESRD) is highly unacceptable, especially in developing countries[1,2]. The incidence of ESRD in developing countries is about 150 per million population[3]. Hemodialysis is a necessary conservative treatment way for ESRD[4]. Secondary hyperparathyroidism (SHPT), as the common complication of ESRD, has increased steadily correspondingly[5]. SHPT occurs as a result of a series of abnormalities in mineral metabolism that cause an increase in parathyroid hormone (PTH) secretion[6,7]. Most SHPT patients can be treated with drugs such as calcimimetics, synthetic vitamin D

analogs, calcitriol. However, approximately 10% of patients with ESRD need to receive parathyroidectomy (PTX) for SHPT[8]. Normally, clinicians are more concerned with recurrent laryngeal nerve damage, hemorrhage, infections, arrhythmia, and electrolyte disturbances after parathyroidectomy, such as hypocalcemia, hyperkalemia, hypophosphatemia, and hypomagnesemia[9]. However, as an important postoperative complication of secondary hyperparathyroidism, transient thyrotoxicosis is often ignored by clinicians. Thyrotoxicosis is a common disease caused by excessive circulating thyroid hormone. Symptoms of overt thyrotoxicosis include sweating, polydipsia, heat intolerance, tremor, nervousness, anxiety, fatigue, palpitations, chest pain, dyspnoea, nausea and vomiting[10]. Most importantly, transient thyrotoxicosis is associated with increased risk of atrial fibrillation, heart failure, and angina, which increases the risk of postoperative death in SHPT patients[11]. However, only a few studies have focused on thyrotoxicosis as a result of PTX in patients with SHPT[12,13]. We aimed to identify the status of transient thyrotoxicosis and thyroxine fluctuations after PTX for SHPT patients with ESRD and normal thyroid function.

## Methods

A total of 36 SHPT patients with preoperative normal thyroid function receiving PTX were enrolled for analysis from Department of Endocrine and Breast Surgery, the First Affiliated Hospital of Chongqing Medical University, Chongqing, China, from January 2017 to January 2019 (Table 1). This study was approved by the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University. The inclusion criteria include that SHPT patients received parathyroidectomy +autotransplantation under the general anaesthesia and all enrolled patients have been assured with the normal thyroid function, normal thyroglobulin(Tg) and normal thyroid antibodies (such as thyrotrophin receptor antibody, TRAb; thyroid peroxidase antibody, TPOAb; anti-thyroglobulin antibodies, TGAb) before surgery. The exclusion criteria were those patients with previously known thyroid dysfunction (such as thyroiditis, hyperthyroidism), preoperative thyroid medication, prior thyroid surgery or parathyroid surgery. We assessed thyroid biochemical indicators in the morning before surgery and on day 1, 3 and 5 after surgery to compare changes in thyroid function. The biochemical indicators include Tg, high sensitivity thyrotropin stimulating hormone(sTSH), triiodothyronine(T3), free triiodothyronine(fT3), thyroxine(T4) and free thyroxine(fT4). Thyrotoxicosis was biochemically defined as serum sTSH below the normal minimum as well as fT4 above the normal maximum[14]. Additionally, we also need to assess the thyroid antibodies (such as TRAb, TPOAb, TGAb) in the morning before and after surgery to exclude out their abnormal changes.

# Statistical Methods

The levels of thyroid biochemical indicators are displayed in the form of mean ±standard deviation. The SPSS software (Version 22.0) was used to analyze differences of the biochemical indicators before and after surgery. P value of less than 0.05 was represented statistically significant.

# Result

Among the 36 SHPT patients, 3 case (8.3%), 14 cases (38.9%) and 24 cases (66.7%) suffered thyrotoxicosis at the first, third and fifth day after surgery, respectively (Table 2). Serum FT3 level increased significantly (≥2.5 times higher than the normal maximum) from pre-operation ≥3.01±0.38 pg/ml, normal range: 2.14–4.21pg/ml≥to the first day after operation (10.93±7.05 pg/ml, p≥0.001) and then gradually decline, but still higher than the normal maximum on day 3 (7.62±4.97 pg/ml) and day 5 (5.15±2.72 pg/ml) after surgery, respectively (Table 3 & Figure 1). Serum FT4 level increased significantly (≥1.5 times higher than the normal maximum) from pre-operation 0.66±0.14 ng/dl, normal range: 0.59–1.25ng/dl) to the third day after operation (2.13±2.16 ng/dl, p≥0.001) and then gradually decline, but still higher than the normal maximum on day 5 after surgery (1.40±0.59 ng/dl, p≥0.001) (Table 3 & Figure 2).

The mean value of serum sTSH always fluctuated within the normal range (Table 3 & Figure 3), but the frequencies of serum sTSH lower than the normal level gradually increased from the first day≥11.1%≥ to fifth day ≥66.7%≥ after surgery (Table 2). A total of 24 patients with complete Tg data, all of which were higher than normal maximum on the first day after surgery (Table 2), and the serum Tg level increased significantly (≥4.8 times higher than the normal maximum) from preoperation (8.43±6.26, normal range: 0.00–50.03ng/ml)to the first day after operation (213.07±157.69, p≥0.001) and then gradually decline, but still relatively higher than the normal maximum on day 5 after surgery (67.70±97.43 ng/ml, p≥0.001). (Table 3).

# Discussion

In our center, we usually perform total parathyroidectomy ± auto-transplantation for the dialysis patients who have persistent secondary hyperparathyroidism (PTH levels >800 pg/mL) and are accompanied by clearly related signs and symptoms and refractory to medical therapies. In the previous study, we found that thyrotoxicosis was an important postoperative complication of parathyroidectomy for SHPT patients[13], while only a few studies have focused on thyrotoxicosis as a result of PTX in patients with SHPT[12,13].

In this study, all the SHPT patients have normal thyroid function, normal Tg and normal thyroid antibodies (such as TRAb, TPOAb and TGAb) and have no preoperative thyroid medication, prior thyroid surgery or parathyroid surgery. It shows the common occurrence of thyrotoxicosis in these SHPT patients after surgery, 3 case (8.3%), 14 cases (38.9%) and 24 cases (66.7%) suffered thyrotoxicosis at first, third and fifth day after surgery, respectively (Table 2), suggesting that thyrotoxicosis was a common postoperative complication of parathyroidectomy for SHPT patients. All biochemical indicators of thyroid function have changed significantly after surgery. The frequencies of serum fT4 higher than the normal level are≥58.3%≥, ≥77.8%≥ and≥52.8%≥ on the first, third and fifth day after surgery, respectively (Table 2). The frequencies of serum sTSH lower than the normal level gradually increased from the first day≥11.1%≥ to fifth day ≥66.7%≥ after surgery (Table 2). It indicates that thyroid hormone is abnormally released from the first day after surgery and the change of serum sTSH is later than that of fT4. This may be due to the

massive release of thyroid hormone, and need time to inhibit the secretion of sTSH. Research has shown that Tg is a good marker to evaluate the palpation thyroiditis[15]. Similarly, our study also showed that, there are 24 patients with complete thyroglobulin data, the vast majority of the Tg levels were higher than the normal maximum on the first day after surgery (Table 2).

It has been reported that the occurrence of transient hyperthyroidism after parathyroidectomy for patients with primary hyperparathyroidism is 20% to 29%[16,17]. Our study shows that the occurrence of transient thyrotoxicosis after parathyroidectomy in SPTH patients was obviously higher than that in primary hyperparathyroidism.

Thyrotoxicosis is caused by excessive circulating thyroid hormones for some reason. The common reasons include excessive production by the thyroid gland (as in Graves' disease), excessive production outside the thyroid, or loss of storage function and leakage from the gland[18]. The most likely reason for this study is mechanical insult during the surgery which causes transient loss of storage function. It shows that parathyroid exploration could provide sufficient stimulation for thyroid to release thyroid hormone.

Thyrotoxicosis affects many different important organs, including neuromuscular, cardiovascular, pulmonary, gastrointestinal and skin[19,20]. Transient thyrotoxicosis is associated with increased risk of atrial fibrillation, heart failure, and angina, which increases the risk of postoperative death in SHPT patients. Some case reports have reported symptoms such as increased metabolism and atrial fibrillation in patients with thyrotoxicosis after surgery of SHPT[12,13]. When thyrotoxicosis occurs, strengthen hemodialysis was effective measures to eliminate the excessive thyroid hormones, a beta blocker to control the symptoms and signs, bile acid sequestrants may also be of benefit in severe cases to decrease enterohepatic recycling of thyroid hormones, and glucocorticoids can be used to reduce T4-to-T3 conversion and promote vasomotor stability[18]. All the principles are based upon clinical experience and case studies since there are no prospective studies.

Although the sample size is the largest in Asia, it is still small. A larger sample size is needed in the future to assess the incidence of thyrotoxicosis after surgery for SHPT with ESRD and normal thyroid function. The incidence of thyrotoxicosis may still be underestimated. One of the most important reasons is that we have predictive dialysis to improve patient prognosis and reduce serum thyroid hormone levels indirectly.

In conclusion, most of the SHPT patients with ESRD and normal thyroid function are likely to suffer thyrotoxicosis after parathyroidectomy. Clinicians should pay attention to this common complication, and evaluate the thyroid function and the related symptoms in these patients during postoperative period to make early diagnosis and appropriate prevention and treatment of thyrotoxicosis.

# Declarations

# Ethics approval and consent to participate

The study was approved and registered by the local ethics committee of the First Affiliated Hospital of Chongqing Medical University (Reg. No. 2018–005), no informed consent had to be obtained because of retrospective data collection.

# Consent for publication

Not applicable

# Availability of data and material

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 interests.

# Funding

There were no sources of funding for this study.

# Authors' contributions

BZ/JL/HL/HL participated in the study design, data collection and drafted the manuscript. ZX/HL/KW/LK (Hongyuan Li) assisted in literature search and provided critical revision of the manuscript for important intellectual content. All authors read and approved the final manuscript.

# Acknowledgements

This study was performed using data provided by the Department of Endocrine and Breast Surgery, Chongqing Medical University, China. The opinions, results, and conclusions reported in this article are those of the authors.

## References

*1.*Jha V, Garcia-Garcia G, Iseki K, et al. Chronic kidney disease: global dimension and perspectives. *The Lancet.* 2013;382(9888):260–272.

*2.*Mills KT, Xu Y, Zhang W, et al. A systematic analysis of worldwide population-based data on the global burden of chronic kidney disease in 2010. *Kidney international.* Nov 2015;88(5):950–957.

*3.*Barsoum RS. Chronic kidney disease in the developing world. *The New England journal of medicine.* Mar 9 2006;354(10):997–999.

*4.*Li W, Zhang M, Du S, et al. Impact of parathyroidectomy on survival among haemodialysis patients: A prospective cohort study. *Nephrology.* Feb 2016;21(2):133–138.

*5.*Komaba H, Kakuta T, Fukagawa M. Management of secondary hyperparathyroidism: how and why? *Clinical and experimental nephrology.* Mar 2017;21(Suppl 1):37–45.

*6.*Cunningham J, Locatelli F, Rodriguez M. Secondary hyperparathyroidism: pathogenesis, disease progression, and therapeutic options. *Clinical journal of the American Society of Nephrology: CJASN.* Apr 2011;6(4):913–921.

*7.*Moorthi RN, Moe SM. CKD-mineral and bone disorder: core curriculum 2011. *American journal of kidney diseases: the official journal of the National Kidney Foundation.* Dec 2011;58(6):1022–1036.

*8.*Foley RN, Li S, Liu J, Gilbertson DT, Chen SC, Collins AJ. The fall and rise of parathyroidectomy in U.S. hemodialysis patients, 1992 to 2002. *Journal of the American Society of Nephrology: JASN.* Jan 2005;16(1):210–218.

*9.*Koshkelashvili N, Lai JY. IMAGES IN CLINICAL MEDICINE. Hyperkalemia after Missed Hemodialysis. *The New England journal of medicine.* Jun 9 2016;374(23):2268.

*10.*De Leo S, Lee SY, Braverman LE. Hyperthyroidism. *The Lancet.* 2016;388(10047):906–918.

*11.*Siu CW, Yeung CY, Lau CP, Kung AW, Tse HF. Incidence, clinical characteristics and outcome of congestive heart failure as the initial presentation in patients with primary hyperthyroidism. *Heart (British Cardiac Society).* Apr 2007;93(4):483–487.

*12.*Sato H, Miyamoto Y, Inagaki M, et al. Atrial Fibrillation Induced by Post-Parathyroidectomy Transient Thyrotoxicosis. *Internal Medicine.* 2008;47(20):1807–1811.

*13.*Xu Z, Wu YT, Li X, et al. Thyrotoxicosis Occurring in Secondary Hyperparathyroidism Patients Undergoing Dialysis after Total Parathyroidectomy with Autotransplantation. *Chinese medical journal.* Aug 20 2017;130(16):1995–1996.

*14.*Franklyn JA, Boelaert K. Thyrotoxicosis. *Lancet (London, England).* Mar 24 2012;379(9821):1155–1166.

*15.*Rudofsky G, Tsioga M, Reismann P, et al. Transient hyperthyroidism after surgery for secondary hyperparathyroidism: a common problem. *European journal of medical research.* Aug 8 2011;16(8):375–380.

*16.*Lindblom P, Valdemarsson S, Westerdahl J, Tennvall J, Bergenfelz A. Hyperthyroidism after surgery for primary hyperparathyroidism. *Langenbeck's archives of surgery.* Dec 1999;384(6):568–575.

*17.*Stang MT, Yim JH, Challinor SM, Bahl S, Carty SE. Hyperthyroidism after parathyroid exploration. *Surgery.* Dec 2005;138(6):1058–1064; discussion 1064–1055.

*18.*Ross DS, Burch HB, Cooper DS, et al. 2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis. *Thyroid: official journal of the American Thyroid Association.* Oct 2016;26(10):1343–1421.

*19.*Trzepacz PT, McCue M, Klein I, Levey GS, Greenhouse J. A psychiatric and neuropsychological study of patients with untreated Graves' disease. *General hospital psychiatry.* Jan 1988;10(1):49–55.

*20.*Klein I, Danzi S. Thyroid disease and the heart. *Circulation.* Oct 9 2007;116(15):1725–1735.

# Tables

Table 1. Characteristics of all patients (n=36) undergoing parathyroidectomy plus auto-transplantation.

| Characteristics | Values |
|---|---|
| Number (Female/Male) | 15/21 |
| Age（year） | 46.3±10.6 |
| Duration of dialysis（year） | 8.0±4.2 |
| Operation time（min） | 98.5±26.9 |
| Preoperative PTH(Pg/ml) | 2133.6±900.1 |
| Postoperative PTH(Pg/ml) | 36.9±58.2 |

PTH: parathyroid hormone

Table 2. Frequency of biochemical thyrotoxicosis (sTSH below normal level and FT4 above normal level) in all patients (n=36), of which 24 patients with complete Tg data.

| | First day after surgery | Third day after surgery | Fifth day after surgery |
|---|---|---|---|
| T3↑ | 20（55.6） | 9（25） | 2（5.6） |
| FT3↑ | 30（83.3） | 26（72） | 20（55.6） |
| T4↑ | 19（52.8） | 18（50） | 10（27.8） |
| FT4↑ | 21（58.3） | 28（77.8） | 19（52.8） |
| sTSH↓ | 4（11.1） | 17（47.2） | 24（66.7） |
| sTSH↓and FT4↑ | 3（8.3） | 14（38.9） | 24（66.7） |
| Tg↑ | 29 (90.6) | 25 (78.1) | 612(38.7) |

T3: triiodothyronine, T4: thyroxine, fT3: free triiodothyronine, fT4: free thyroxine, sTSH: high sensitivity thyrotropin stimulating hormone. ↑: Biochemical parameter above normal maximum. ↓: Biochemical parameter below normal minimum. Frequency (percent).

Table 3. Patients' characteristics of thyroid function of all patients (n=36) before and the days from surgery are displayed. Mean values and their standard deviation are given.

| variables | Before surgery | First day after surgery | Third day after surgery | Fifth day after surgery |
|---|---|---|---|---|
| T3(0.66-1.61ng/ml) | 1.03±0.21 | 1.66±0.69** | 2.09±4.97 | 1.05±0.39 |
| T4(5.44-11.85ug/dl) | 6.42±1.72 | 11.67±3.52** | 12.41±4.40†† | 9.96±2.90§§ |
| fT3(2.14-4.21pg/ml) | 3.01±0.38 | 10.93±7.05** | 7.62±4.97†† | 5.15±2.72§§ |
| fT4(0.59-1.25ng/dl) | 0.66±0.14 | 1.53±0.69** | 2.13±2.16†† | 1.40±0.59§§ |
| sTSH(0.49-4.91uIU/ml) | 2.09±1.14 | 1.51±0.95* | 0.88±1.20†† | 1.12±2.25 |
| Tg(0.00-50.03ng/ml) | 8.43±6.26 | 213.07±157.69** | 138.18±124.56†† | 67.70±97.43§ |

T3: triiodothyronine, T4: thyroxine, fT3: free triiodothyronine, fT4: free thyroxine, sTSH: high sensitivity thyrotropin stimulating hormone, Tg: thyroglobulin. *: significant statistic difference between before surgery and one day from surgery (P value<0.05), ** indicates P<0.001; †: significant statistic difference between before surgery and three days from surgery (P<0.05), †† indicates P<0.001; §: statistic difference between before surgery and five days from surgery (P<0.05) (P value <0.05), §§ indicates P<0.001.

# Figures

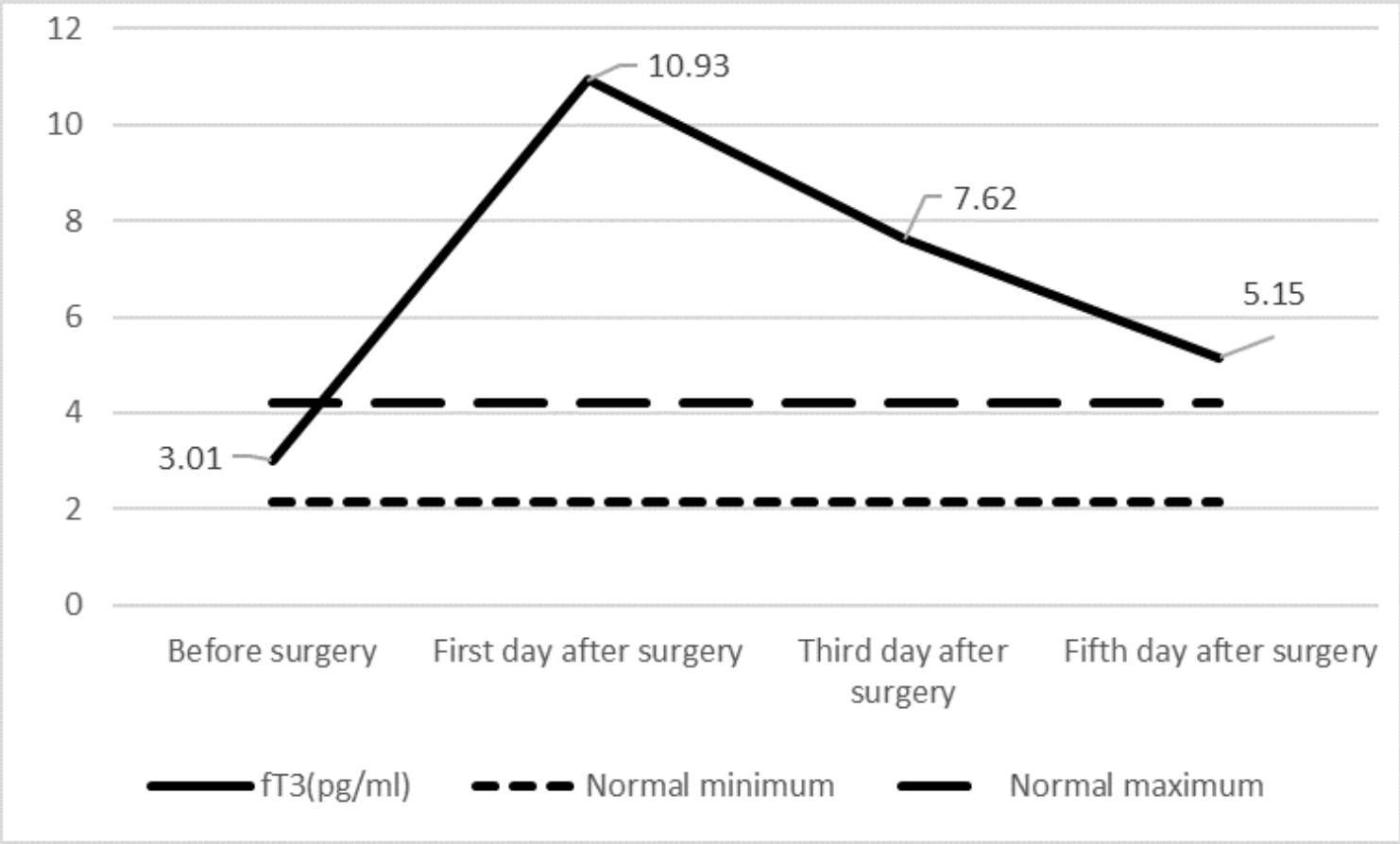
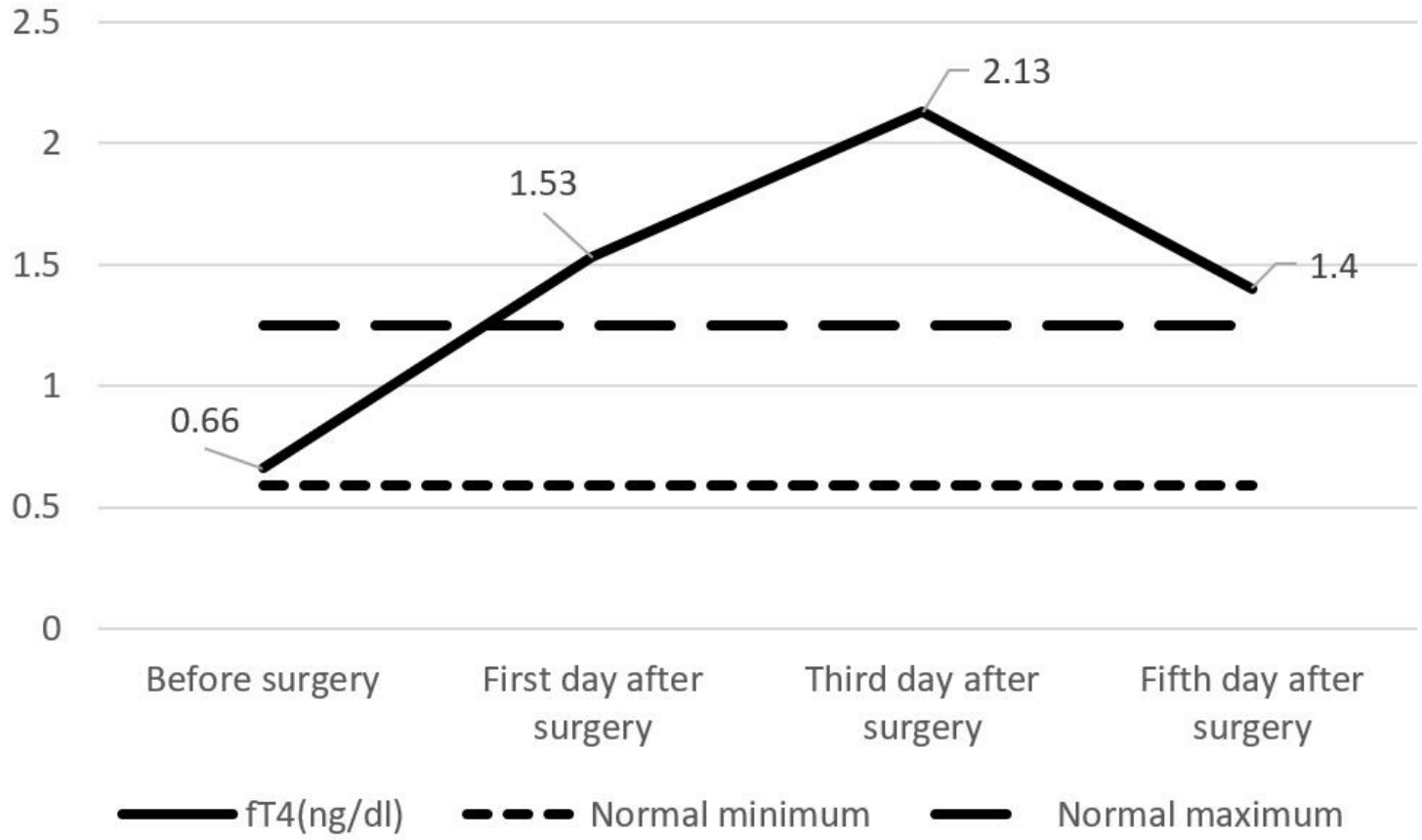



**Figure 1**

Fluctuation of mean value of fT3 in all patients (n=36) before and on day 1, 3 and 5 after surgery. fT3: free triiodothyronine.




## Figure 2

Fluctuation of mean value of fT4 in all patients (n=36) before and on day 1, 3 and 5 after surgery. fT4: free thyroxine.

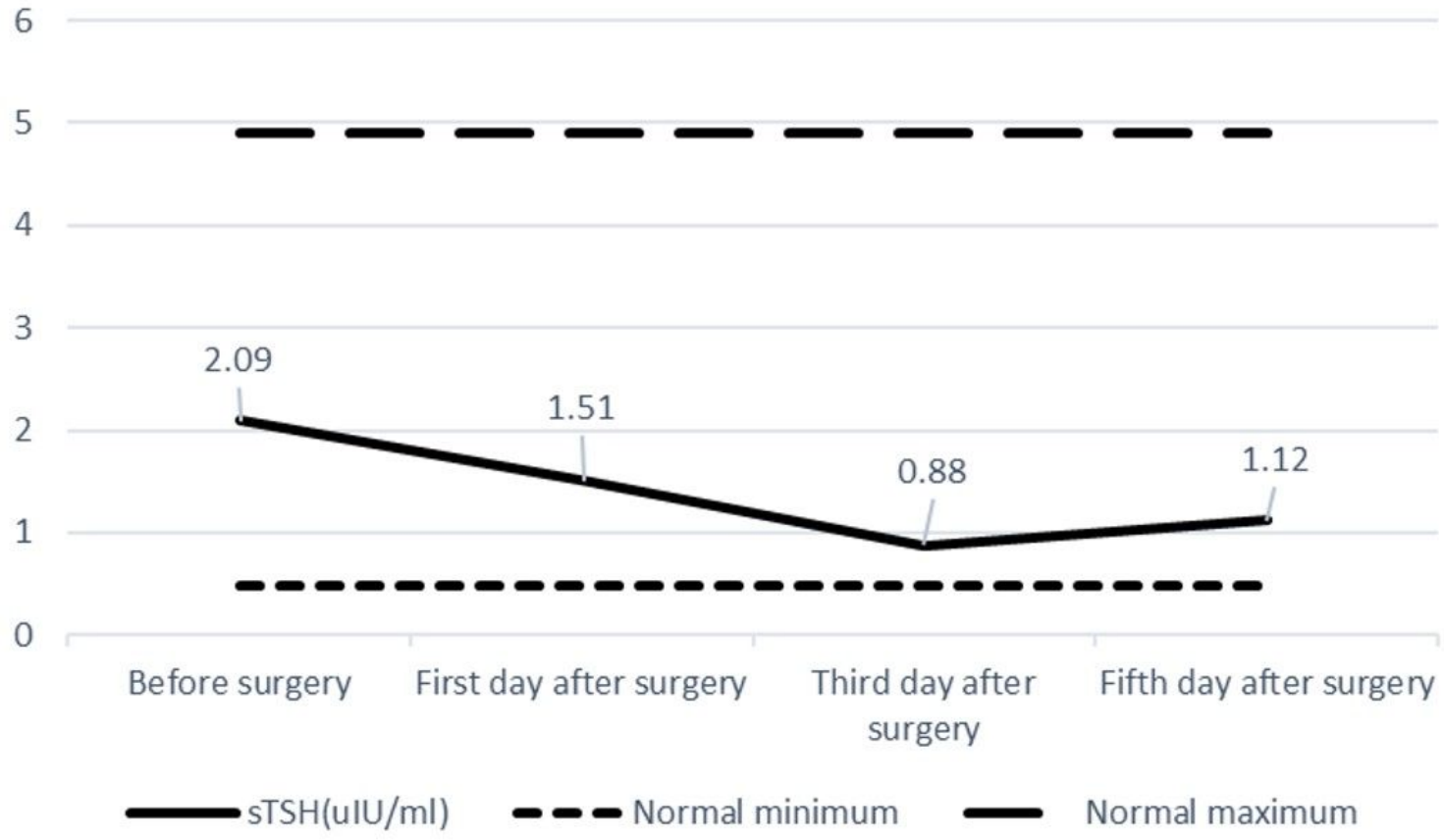



**Figure 3**

Fluctuation of mean value of sTSH in all patients (n=36) before and on day 1, 3 and 5 after surgery. sTSH: high sensitivity thyrotropin stimulating hormone.

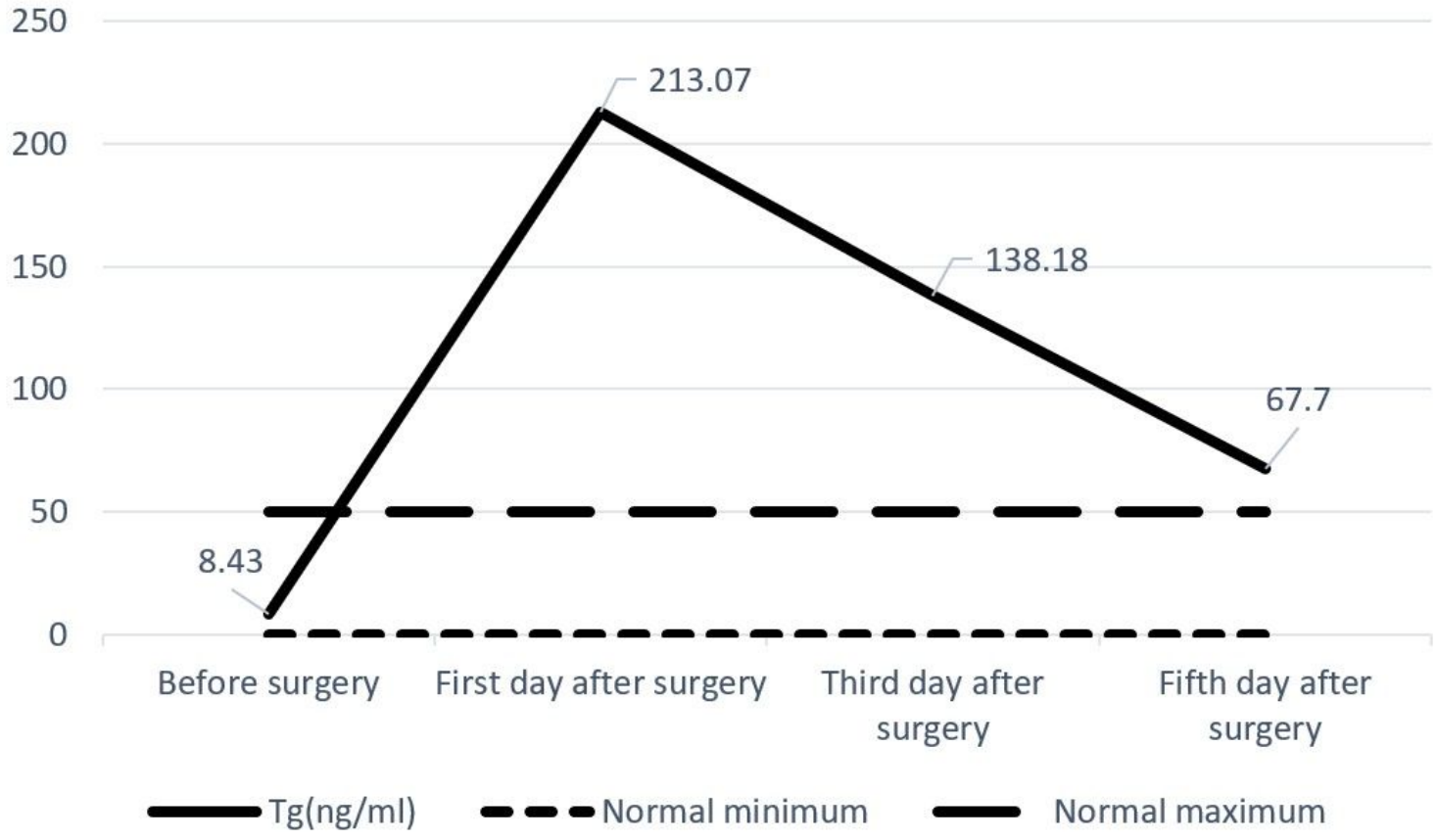



**Figure 4**

Fluctuation of mean value of Tg in patients (n=24) before and on day 1, 3 and 5 after surgery. Tg: thyroglobulin.