



Correlation between parathyroid function and serum levels of 1,25(OH)2D3, serum phosphorus, and parathyroid hormone after surgery for papillary thyroid carcinoma

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ABSTRACT

The objective of this work was to investigate the factors influencing parathyroid function (PTF) after surgery for papillary thyroid carcinoma (PTC) and the relationship of serum 1,25(OH)2D3 and serum phosphorus to parathyroid hormone (PTH) levels. 113 patients with papillary thyroid carcinoma (PTC) were enrolled, including 75 patients with lowered PTF (70 patients with temporary (temporary reduction group) and 5 patients with permanent (permanent reduction group)) and 38 patients with normal PTF (normal group). The results of detection indexes showed that the serum PTH levels were decreased to different degrees compared with those before surgery. Serum 1,25(OH)2D3 levels decreased less in the normal group before and after surgery but decreased more in the temporary and permanent reduction groups. The change range of blood phosphorus before and after the surgery was small in the normal group, and the increase ranges in the temporary and permanent reduction groups were larger. The lowered PTF was negatively correlated with age and blood phosphorus ($P < 0.01$) but positively correlated with serum PTH ($P < 0.05$) and serum 1,25(OH)2D3 ($P < 0.01$). In conclusion, lowered PTF after surgery for PTC was negatively correlated with blood phosphorus, which can indicate a decrease in PTH levels in patients. Meanwhile, the lowered PTF was positively correlated with serum PTH and serum 1,25(OH)2D3 levels.

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Introduction

Papillary thyroid carcinoma (PTC) is a malignant and life-threatening cancer, the incidence of which has increased sharply in recent years. Most patients have significant prognostic effects after surgical treatment, with a 10-year survival rate of more than 90%, but the prevention and treatment of PTC remains an important challenge (1). In the past few years, the American Thyroid Association (ATA) has recommended total thyroidectomy as the primary treatment for PTC larger than 1 cm (2). However, recent studies have found that for PTC patients with diameters between 1 and 4cm, there is no significant difference in long-term survival between total thyroidectomy and unilateral lobectomy, and the incidence of complications after unilateral lobectomy is lower (3). According to the most recent clinical practice guidelines, adenolobectomy is a safe and effective PTC procedure with diameters between 1 and 4 cm (4). Compared with other surgical procedures, adenolobectomy is more conservative and can effectively reduce the incidence of postoperative complications. According to the latest reports, the prevalence rate of related complications after thyroid surgery is still high, ranging from 16.4% to 37.9% (5,6).

The parathyroid gland (PG) is closely related to the thyroid in anatomical position. PG is mainly located in the fibrous sac between the dorsal membrane of the thyroid

propria and the surgical dorsal membrane on the dorsal side of the gland lobe on both sides of the thyroid. Most of the upper PGS were located at the level of the inferior thyroid Angle, and the position of the lower PGS was relatively fixed, while the anatomical position of the lower PGS was more variable. It is difficult to accurately distinguish PG, fat granules and lymph nodes with the naked eye. In addition, the blood supply of PG is fragile, which makes it easy to destroy its blood supply and damage PG during the operation, or even accidentally remove PG (7). Although central lymph node dissection is effective in reducing the risk of postoperative tumor recurrence, it is closely associated with recurrent laryngeal nerve, PG, and thyroid gland. Therefore, when the central lymph node lesions are completely removed, the possibility of PG damage will also be increased, thus resulting in postoperative adrenal dysfunction (8,9). Adrenal dysfunction is a typical postoperative disease, that can lead to hypocalcemia, manifested as perioral paralysis, quadriplegia, severe cases can occur quadriplegia and respiratory muscle spasm symptoms. To reduce the symptoms, blood calcium levels can be improved with intravenous calcium supplements or oral calcium supplements, but this treatment may increase the patient's hospital stay and recovery time after surgery. Therefore, the selection of treatment methods should take into account the patient's body and postoperative rehabilitation status, so as to restore normal life as soon as possible (10).

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Patients with permanently lowered parathyroid function (PTF) may develop hypocalcemia after surgery, which may result in laryngeal muscle and diaphragm spasms or even death. To maintain blood calcium levels, these patients need to have their blood calcium levels tested regularly and take oral or intravenous calcium supplements. However, long-term calcium supplements may bring side effects, such as ectopic calcification, kidney stones and other diseases, which will not only aggravate patients' pain but also increase their burden on economy and life (11,12). Therefore, to reduce these loads, patients should try to avoid long-term calcium supplements and take other effective methods to reduce the patient's pain and economic load. The quality of life (QOL) of patients after surgery has been seriously affected, which encourages surgeons to pay more attention to the protection of PG. Therefore, how to effectively prevent and mitigate the decline of post-operative PTFS remains an important challenge for head and neck physicians and thyroid specialists.

At present, domestic studies on the risk factors of PTF decline after thyroidectomy combined with bilateral central lymph node dissection are still relatively few, and no consistent conclusions have been reached. Therefore, it is necessary to further explore this problem. Some studies have speculated that thyroid hyperplasia is related to parathyroid hyperthyroidism, while some studies have suggested that hyperPTF may lead to lowered PTF and high concentrations of parathyroid hormone (PTH). In this work, the influencing factors of PTF after PTC operation and the correlation between serum 1,25(OH)₂D₃, serum phosphorus level, and PTH level were investigated, so as to detect abnormal PTF in patients earlier and take effective interference protection measures as soon as possible, thus improving the QOL of patients.

Materials and Methods

Research objects

113 patients who received surgery for thyroid nodules in the Department of Endocrinology, Yangpu Hospital, School of Medicine, Tongji University from January 1, 2019, to January 1, 2022, were selected. The criteria for enrolling and excluding the patients were listed in Table 1 and Table 2, respectively. This work was approved by Yan-

gpu Hospital, the School of Medicine, Tongji University Ethics Committee, and all patients signed relevant informed consent.

Surgery modes

A total thyroidectomy was performed by a professional surgical team, including all visible thyroid tissue, a local adenolobectomy, the affected glandular lobe and the isthmus of the thyroid, a small amount of tissue from the recurrent laryngeal nerve into the larynx, and many more tissues for optimal treatment. Before the surgeon performed a dissection of the cervical lymph nodes, he or she would undergo preoperative supplementary examinations and frozen sections to determine whether the operation could be performed. During the surgery, the doctor would try to find and retain PGs and their blood supply vessels in Situ near the thyroid gland and perform a score for Parathyroid Glands Remaining in Situ to determine whether glands needed to be removed. If unavoidable, the doctor would cut the parathyroid gland and control its fragment size to about 0.5 mm to ensure the safety and accuracy of the surgery. The drug was injected into the sternocleidomastoid muscle using a syringe.

Data collection

Medical data were collected, including sex, age, B-ultrasound and CT data, and cTNM staging. During the surgery, it was necessary to observe whether nano carbon was applied, whether cancer cells invaded the trachea, whether lateral cervical scanning was carried out, and whether PG autologous transplantation was carried out. Postoperatively, the staging of pTNM, the presence of associated Hashimoto's thyroiditis, the presence of extra-capsular invasion of cancer cells, the maximum diameter of cancer cells, and the presence of unintentional PG removal (a disease with PG tissue in the pathological examination is defined as "unintentional PG removal") were collected.

The PTH level was within the normal range before the surgery but was sharply lower than the normal guideline value after the surgery, accompanied by symptoms of hypocalcemia. PTF recovery definition was given as follows: PTH \geq 6.5 pg/mL without the need for therapeutic calcium supplementation or active vitamin D to prevent hypocalcemia. Using the Profound a10 Ultrasound Treatment

Table 1. Criteria for enrolling the patients.

No.	Criteria for enrolling the patients
1	Postoperative pathological diagnosis was PTC
2	The first operation was performed by a senior head and neck surgeon
3	Preoperative thyroid function, serum PTH and blood calcium levels were normal
4	Case data were complete and informed consent was signed before operation
5	Pathological specimens were dissected by experienced pathologists

Table 2. Criteria for excluding the patients.

No.	Criteria for excluding the patients
1	Complicated with heart, kidney, liver and other important organ diseases
2	Patients with systemic infections
3	Patients with abnormal metabolism of vitamin D levels
4	Multiple endocrine adenomas, Graves' disease, parathyroid adenomas, lowered PTF or hyperplasia
5	Take medications that cause changes in blood calcium concentration, such as calcium and vitamin D, before surgery

Management System manufactured by Alocca, the sonologists performed preoperative thyroid ultrasound screening, which included locating the thyroid and PGs and measuring the nodule duct diameter. In addition, nodule composition, echo reflexes, tumor boundaries, calcification, and blood flow were also evaluated. Serum 1,25-(OH)D3 was detected by electrochemiluminescence immunoassay using Germany's Roche cobase411 automatic immune analyzer.

Methods for statistics

Excel database was established and imported into the IBM SPSS Statistics 26 for data analysis. Qualitative data was expressed by percentage, quantitative data with normal distribution was expressed by mean \pm standard deviation, comparison between groups was performed by T-test, and correlation analysis was performed by Person method. Quantitative data with non-normal distribution were expressed as M (P25, P75), comparison between groups was performed by Wilcoxon rank sum test, and correlation analysis was performed by the Spearman method. Logistic regression analysis was employed to analyze the adenoma diameter influencing factors. The receiver operating characteristic (ROC) curve was utilized to analyze the value of preoperative indicators in predicting the maximum diameter of tumors, and the area under the ROC curve (AUC) comparison was performed by Z-test. The test level was set as $\alpha = 0.05$.

Results

Basic clinical data

As shown in Table 3 and Table 4, clinical data of 113 patients with PTC were collected in this work, including 37 males and 76 females. They were (40.12 ± 13.26) years old on average. Of the 113 patients, 75 were lowered (70 temporarily and 5 permanently), and 38 were normal.

Effects of PTF on PTH level

As illustrated in Figure 1, serum PTH levels in the lowered PTF normal group ($n = 38$), temporary reduction group ($n = 70$), and permanent reduction group ($n = 5$) were lowered to varying degrees compared with those before surgery. The decrease in serum PTH level was the most obvious on the first day after surgery and was the lightest in the PTF normal group. The decreases in the temporary reduction group and permanent reduction group were basically the same. The serum PTH level in the 3 groups showed the lowest value on the first day after surgery, while it in the PTF normal group was still within the normal range and gradually recovered to the preoperative normal level within 6 months after the surgery.

Effects of PTF on serum 1,25(OH)2D3 levels

As demonstrated in Figure 2, the serum 1,25(OH)2D3 levels were lowered before and after surgery in both the PTF normal group and the lowered PTF groups. The decrease in the normal group was small, while that in the temporary reduction group and permanent reduction group was large.

Effects of PTF on serum phosphorus level

As illustrated in Figure 3, the serum phosphorus levels in the PTF normal group and lowered PTF groups

increased after the surgery. The serum phosphorus in the normal group changed less, while that in the temporary reduction group and permanent reduction group increased more. Within postoperative 1 – 3 d, the PTH level was greatly decreased, and the increase in serum phosphorus level suggested that the patients had insufficient PTH.

Correlation analysis

The purpose of this work was to investigate the correlation between PTF and other related indicators after surgery for PTC. It was found that lowered PTF was negatively correlated with age and serum phosphorus ($P < 0.01$) and positively correlated with serum PTH ($P < 0.05$) and 1,25(OH)2D3 ($P < 0.01$) (Table 5).

Discussion

At present, most of the treatment methods for PTC are surgical, but people have different opinions on the choice of surgical methods. For patients with c N+, some doctors suggest that the removal of the ipsilateral central region should be carried out at the same time as the removal of

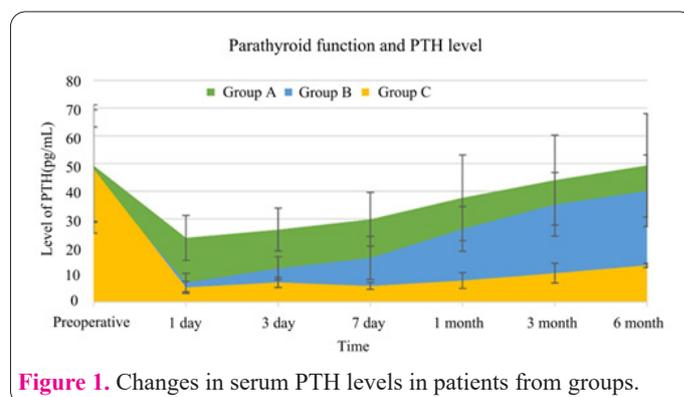


Figure 1. Changes in serum PTH levels in patients from groups.

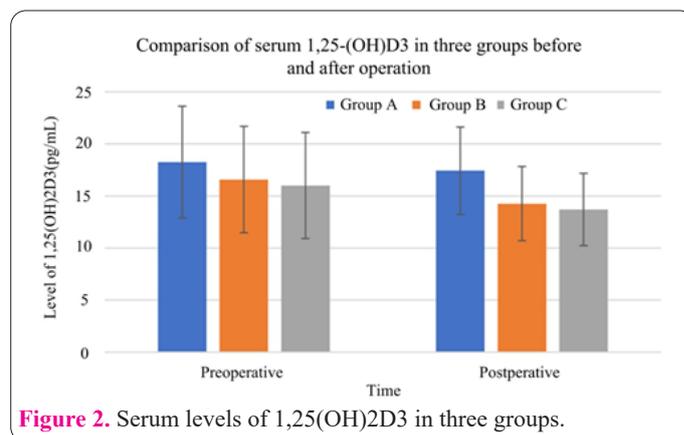


Figure 2. Serum levels of 1,25(OH)2D3 in three groups.

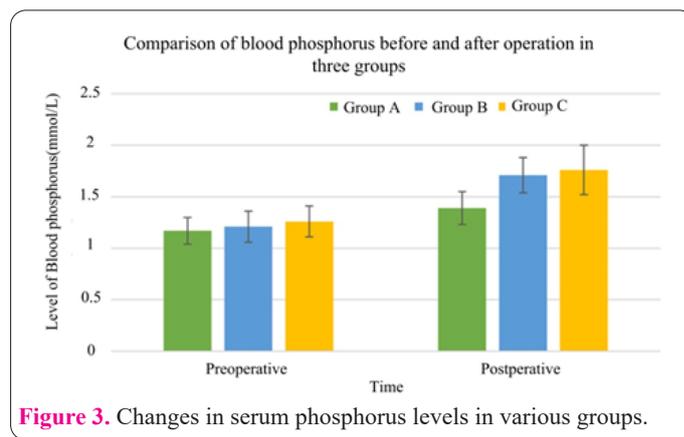


Figure 3. Changes in serum phosphorus levels in various groups.

Table 3. Basic data of patients.

Item		PTF normal group (n = 38)	Lowered PTF group (n = 75)
Gender	Males	13	16
	Females	25	59
Age (years old)	< 55	30	66
	≥ 55	8	9
Tumor invasion of trachea	Yes	1	2
	No	37	73
Hashimoto's thyroiditis	Yes	7	17
	No	31	58
Cervical region was dissected	Yes	2	17
	No	36	58
Carbon nanoscale	Yes	18	39
	No	20	36
Autogenous parathyroid transplantation	Yes	29	40
	No	9	35
Accidental removal of parathyroid glands	Yes	6	33
	No	32	42
cTNM	I	25	59
	II	10	14
	III	2	2
	IV	0	0
cT	T1	10	29
	T2	21	35
	T3	5	9
	T4	2	2
cN	cN0	9	17
	cN1a	29	58
cTNM	I	32	66
	II	3	7
	III	1	2
	IV	1	0
cT	T1	17	29
	T2	13	27
	T3	7	8
	T4	1	12
cN	cN0	12	24
	cN1a	26	51

Table 4. Main preoperative indexes of patients.

Clinical factors	Normal group (n = 38)	Reduction Group (n = 75)
Maximum tumor diameter (mm, $\bar{x}\pm s$)	2.011 ± 0.915	2.034 ± 0.879
Preoperative PTH (pg/mL, $\bar{x}\pm s$)	49.28 ± 20.13	46.22 ± 19.11
Preoperative serum 1,25-(OH)D3 (pg/mL, $\bar{x}\pm s$)	18.26 ± 5.37	16.12 ± 5.42
Preoperative serum phosphorus (mmol/L, $\bar{x}\pm s$)	1.82 ± 0.33	1.87 ± 0.29

the affected glandular lobe, while for patients with cN0, whether the removal of the ipsilateral central lymph node is necessary is still debated (13,14). In developed countries in Europe and the United States, in order to prevent intraoperative damage to PG and recurrent laryngeal nerves, adenolobectomy rather than central lymph node removal

is preferred. However, in China, the surgical methods for cN0 PTC patients are more radical. In order to prevent postoperative tumor recurrence and regional lymph node regeneration, preventive lymph node removal in the central region is recommended after ipsilateral glandular lobe and isthmus resection (15). With the application of

Table 5. Correlation between lowered PTF and other indicators.

Other indicators	Correlation coefficient	P value
Age	-0.142	0.621
PTH	0.149*	0.041
Serum 1,25(OH)2D3	0.212**	<0.01
Serum phosphorus	-0.268**	<0.01

recurrent laryngeal nerve detectors, the accuracy and safety of thyroid surgery have been significantly improved. It can quickly identify recurrent laryngeal nerve and its direction, and effectively reduce the intraoperative injury to recurrent laryngeal nerve. However, how to correctly identify PG and how to effectively guarantee its blood supply remains a major challenge in thyroid surgery (16,17).

Scientific studies have shown that the occurrence of HPT is related to many reasons, among which the intact PTH (iPTH) is the most sensitive technical index to measure parathyroid function. Early detection can effectively find patients with HPT, so as to take early treatment measures (18,19). It is believed that iPTH measured within 4 months after surgery and its reduction rate can accurately determine not only early postoperative hypocalcemia but also persistent postoperative hypocalcemia (HPT). Its sensitivity and specificity reached 100% and 80.4% respectively, while the latter reached 94.7% and 84.8% respectively. The decrease of iPTH can be regarded as an important technical index reflecting the damage of PTF during surgery, which can effectively predict early postoperative hypocalcemia and is closely related to persistent HPT (20). However, whether perioperative vitamin D deficiency increases the risk of postoperative PTF reduction remains controversial. Some scientific studies have shown that a lack of vitamin D will increase the risk of postoperative hypocalcemia and affect the length of hospital stay of patients (21,22). However, some studies have found that even severe vitamin D deficiency (< 10 ng/mL) only indicates an increased risk of PTF reduction in the short term, and does not predict a long-term risk of PTF reduction (23). Therefore, vitamin D supplementation prior to thyroidectomy may help improve patient outcomes. However, due to the diversity of subjects in the current literature, we need to conduct a large number of randomized controlled trials to better demonstrate the association between vitamin D deficiency and low PTF.

113 patients were included in this work, including 96 patients < 55 years of age, among whom 66 patients had lowered PTF after surgery, with an incidence of 68.8%. After ≥ 55 years, 17 patients had lowered PTF after surgery, among which 9 patients had lowered PTF after surgery, the incidence was 52.9%. The comparison of the two differences was not statistically obvious. Based on the results of this study, age cannot be considered independent of lowered PTF after surgery. At present, there is no clear conclusion on the relationship between age and lowered PTF after surgery. The analysis of clinical data of patients undergoing thyroid surgery found that the older the patients were, the lower the likelihood of lowered PTF (24). Some studies have found that the risk of lowered PTF after surgery increases with age. Atherosclerosis is prone to occur in older patients with hypertension (25). Domestic studies have found that patients with hypertension are prone to postoperative lowered PTF (26). In this work, lowered

PTH levels in patients with PTF had a relatively stable recovery compared with normal patients, while lowered serum PTH level in the reduction group was lower than those in the normal group. This result keeps in line with the results of most studies (27), and the decrease of PTF was positively correlated with serum PTH level. Studies have found that the value of PTA mass is positively correlated with the preoperative serum PTH content, while the serum phosphorus content is negatively correlated with it (28). In the results of this study, serum phosphorus levels increased with the decrease of PTF, showing a negative correlation, which is consistent with some research results.

In conclusion, PTF is lowered after surgery, which is jointly influenced by several clinical factors. In clinical work, multiple clinical factors should be combined to predict whether PTFs will be lowered after surgery, and appropriate preventive measures should be taken in advance. This work was a non-big data retrospective analysis, and the possible errors in the research results were affected by the research methods and small sample size. Therefore, in future studies, big data and multi-center analysis should be carried out as far as possible to further explore the influence of papillary PTC on PTF after operation.

Conclusion

In this work, the correlation between PTF and serum levels of 1,25(OH)2D3, serum phosphorus and PTH after papillary PTC operation was investigated. It was found that lowered PTF after PTC operation was negatively correlated with serum phosphorus, which could indicate the decrease in PTH level in PTC patients. Lowered PTF was positively correlated with serum PTH and serum 1,25(OH)2D3 levels. In addition, the PTH level could affect the PTF and other indicators, which will be further discussed in the following research. On the other hand, it is suggested in the work that clinicians should conduct long-term follow-up for the diagnosis and treatment of PTA patients after surgery, so as to formulate reasonable treatment plans and help patients improve their QOL.

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