

# Investigating the Predictive Factors of Hypoparathyroidism after Thyroidectomy: A Systematic Review

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## Abstract

**Introduction:** One of the most common surgeries performed worldwide is thyroidectomy, the most common of which is hypoparathyroidism. Hypoparathyroidism can be transient or permanent. Parathyroid Hormone (PTH) is a major factor in regulating calcium, and small changes in PTH levels alter calcium levels within minutes. Therefore, hypocalcemia may occur after thyroidectomy. This study looked at the predictive factors of hypoparathyroidism after thyroidectomy.

**Methods:** In the present systematic review study, all quantitative articles related to the purposes of the study and published from 2015 to 2019 were reviewed. Searches of PubMed, Google Scholar, and Science Direct databases were performed using keywords for predictive factors, hypoparathyroidism, and thyroidectomy and their synonyms. In total, 3811 titles were initially identified with the described search strategy. From among these articles, 20 articles were selected, and by removing poor quality articles, eight articles were finally studied in terms of content.

**Results:** Hypoparathyroidism is common after thyroidectomy. The main role of PTHs is in the regulation of calcium. Calcium deficiency at the blood level is threatening and can lead to chronic kidney disease, kidney stones and myocardial dysfunction. Therefore, measuring serum PTH immediately after thyroidectomy and the identification of patients at risk can reduce the risk of hypocalcemia by prescribing calcium and active vitamin D.

**Conclusion:** predictive factors of hypoparathyroidism after thyroidectomy are important because of the role of PTHs. According to findings, measuring serum calcium, iPTH, and phosphorus the day after surgery, reducing the duration of surgery and female gender are among the predictive factors of hypoparathyroidism after thyroidectomy.

**Keywords:** Predictive Factors, Hypoparathyroidism, Thyroidectomy

## Introduction

One of the most common surgeries performed worldwide with the occurrence of complications that do not occur frequently but are disabling is thyroidectomy.<sup>1</sup> Thyroidectomy is used to treat benign thyroid diseases such as endometrial goiter, Graves' disease, and diffuse goiter. The nerves of the larynx and parathyroid glands are at risk during thyroidectomy.<sup>2</sup> The most common side effects of thyroidectomy are damage to the larynx, which can lead to dysphonia and shortness of breath, as well as hypoparathyroidism, which can lead to hypocalcemia.<sup>1</sup> Despite ongoing advances and the improvement of surgical techniques, hypoparathyroidism is still an unresolved problem in thyroidectomy.<sup>3</sup>

Hypoparathyroidism is a hereditary or adventitious disease that leads to hypocalcemia and a slight increase in phosphate levels by lowering the level of hypo

PTHs in the blood. The most common cause of hypoparathyroidism is the destruction of the vessels of the parathyroid glands, which may be secondary to trauma or thyroid surgery.<sup>4</sup> Hypoparathyroidism is one of the most important and annoying complications after thyroidectomy.<sup>5</sup> Hypoparathyroidism can be transient or permanent.<sup>6</sup> Some sources consider six months after thyroidectomy as a time interval for distinguishing between transient and permanent hypoparathyroidism,<sup>7,8</sup> but some sources say up to a year.<sup>9,10</sup> PTH is the main factor to regulating calcium, and small changes in PTH levels alter calcium levels within minutes.<sup>1</sup> Treatment of hypoparathyroidism with the goal of achieving normal calcium levels and reduce the symptoms of hypocalcemia using active vitamin D and calcium.<sup>4</sup>

Hypocalcemia is the most common complication

after thyroidectomy. The disease is mostly caused by hypoparathyroidism. Hypocalcemia after thyroidectomy requires repeated measurements of calcium and vitamin D in the blood and management of their levels in the blood, which increases the patients discomfort and care costs<sup>9</sup> and may also increase the length of hospital stay.<sup>11</sup> Symptoms associated with hypocalcemia appear about 24 to 48 h after surgery.<sup>1</sup> One of the symptoms of hypocalcemia is paraesthesia, which is very common.<sup>4</sup> Hypocalcemia can lead to serious and threatening diseases such as chronic kidney disease, kidney stones and myocardial dysfunction.<sup>6</sup> Measurement of serum PTH above post-thyroidectomy is a sensitive method for identifying patients at risk for hypocalcemia, which, despite low PTH levels, administration of calcium and active vitamin D can reduce the incidence of symptomatic hypocalcemia.<sup>12</sup>

There are many studies on the predictive factors of hypoparathyroidism after thyroidectomy, however the results are scattered. The aim of this review study is to investigate the predisposing factors for hypoparathyroidism after thyroidectomy. Due to the lack of study in this field and the importance of timely detection and treatment of hypoparathyroidism in the after thyroidectomy period to reduce its incidence, this study seeks to investigate the predictive factors of hypoparathyroidism after thyroidectomy.

The results of this review study are important to encourage the implementation of planning for early detection of hypoparathyroidism after thyroidectomy, as well as appropriate and timely treatment measures to prevent the complications of hypoparathyroidism.

## Materials and Methods

The present study is a review study based on the PRISMA model, which reviews the predictive factors of hypoparathyroidism after thyroidectomy, based on quantitative and analytical articles published in English journals. The study was conducted in six stages:

The first step of research was the question design. What are the predictors of hypoparathyroidism after thyroidectomy? To address this question, the PICO strategy was used. P (Population) of patients undergoing thyroidectomy surgery, I (Intervention) Thyroidectomy surgery, O (Outcome) Factors predicting hypoparathyroidism. It should be noted that C (Comparison) was not used due to the type of review study.

The second step was to select keywords related to the research topic and search phrases and planning to determine the search strategies. It should be noted that according to experts, descriptive terms and keywords were defined based on MeSH. Keywords include predictive factors, hypoparathyroidism, and thyroidectomy. PubMed search strategies are listed in Table 1.

In the third step, the entry and exit criteria were determined by the members of the research team. The criteria for entering the study were: 1) Studies in the period from January 1, 2015 to December 31, 2019. The choice of this five-year course is due to the use of new studies. 2) Studies with keywords and their synonyms, 3) Studies published in English academic journals, 4) Studies that were quantitative and analytical. Books and articles that were reported as case studies and hypoparathyroidism without thyroidectomy which were not relevant to the research purposes were excluded from the study.

**Table 1.** Search Strategy in PubMed (Date: 2015/01/01:2019/12/31)

Search Round	Syntax
1	((“Factors”[Title/Abstract]) OR (“Agents”[Title/Abstract]) OR (“Effects”[Title/Abstract])) AND ((English[Language]))
2	((“predictive”[Title/Abstract]) OR (“Foretaste”[Title/Abstract]) OR (“Dope”[Title/Abstract]) OR (“Anticipate”[Title/Abstract]) OR (“Prognosticate”[Title/Abstract]) OR (“Augur”[Title/Abstract]) OR (“Foresee”[Title/Abstract])) AND ((English[Language]))
3	1+2
4	((“Hypoparathyroidism”[Title/Abstract])) AND ((English[Language]))
5	3+4
6	((“Thyroidectomy”[Title/Abstract])) AND ((English[Language]))
7	5+6

**Table 2.** Results of Comprehensive Search in Databases

PubMed	Google Scholar	Science Direct	Total
36	3500	275	3811

The fourth step was the systematic search of electronic databases. PubMed, Google Scholar, and Science Direct databases, which represent the vast majority of published journals and studies, were searched between January 1, 2015, and December 31, 2019, by two researchers separately based on keywords and pre-determined strategies. (Table 2).

The fifth stage was the selection of qualified research studies. The summary of articles was reviewed by two people (first and second authors) and the screening of studies, extraction of results and also evaluation of quality control of articles were evaluated by two researchers independently. Related articles were separated and their full text was extracted. In total,

3811 articles were found, and after deleting duplicate articles, 756 articles entered the review stage in terms of title and abstract. After reviewing the titles and abstracts of the articles, 107 articles entered the next stage, in which the full text of the articles was reviewed by two article researchers based on the entry and exit criteria. From among these manuscripts, 53 articles were not published in the period from January 1, 2015 to December 31, 2019, six articles were not quantitative and analytical, 12 articles were not in the field of factors predicting hypoparathyroidism after thyroidectomy, and 16 articles were not in line with the study objective. Finally, 20 articles entered the final analysis (Figure 1).

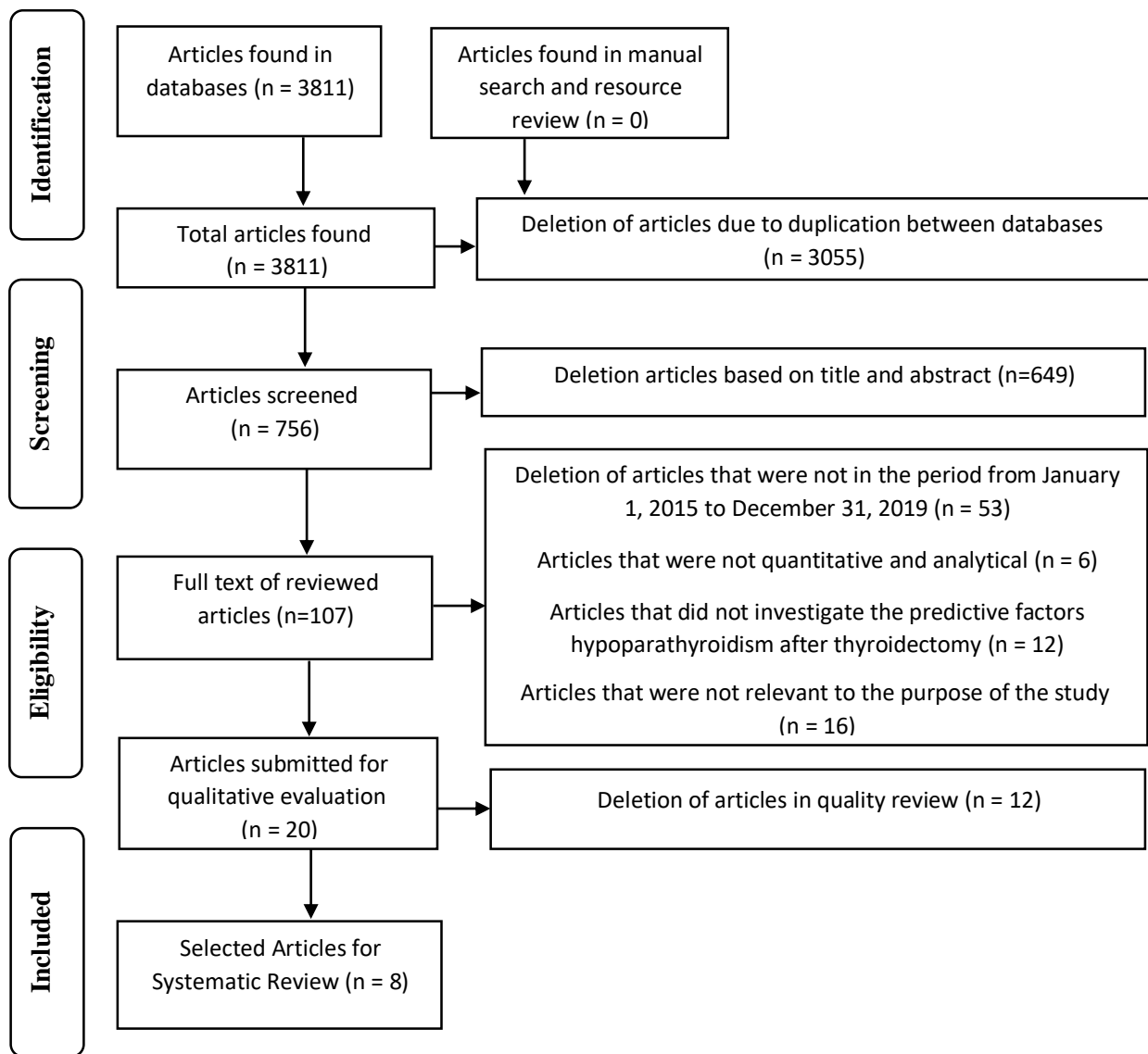


Figure 1. PRISMA Flow Diagram

In the sixth step, the quality of the articles in question was examined independently by two researchers separately. In order to check the quality of the articles, the PRISMA statement checklist was used. This checklist includes 27 items that are divided into non-executable, unreported and reported. The purpose of this checklist is to evaluate the quality of studies and ways to achieve and detect errors in studies, design, implementation and data analysis. Thus, 12 articles were excluded due to poor quality. Finally, eight articles were reviewed systematically. In order to control the blur, a search strategy was used for each database with controlled keywords, and the studies were selected according to the entry and exit criteria. For example, the keywords used in the PubMed database included: Factors, Agents, Effects, Predictive, Foretaste, Dope, Anticipate, Prognosticate, Augur, Foresee, Hypoparathyroidism, Thyroidectomy. To answer systematic review questions, the data extracted from the review of the texts were combined.<sup>13</sup> In this study, the six recommended steps of Moher et al. were used for composition.<sup>14</sup> The extraction form was used to collect the data needed to answer the systematic data review questions. The

composition of the data and their analysis were descriptive. All data collected from quantitative and analytical studies after extraction were transcribed into a word document, and the two researchers analyzed the data separately. Then, the main and sub fields were identified and coded, and the codes were compared, discussed and interpreted.

## Results

The results of these studies indicate hypoparathyroidism after thyroidectomy. Hypoparathyroidism after a thyroidectomy can be transient or permanent. The main role of PTH is in the regulation of calcium. Lack of calcium in the blood level can be life-threatening and can lead to chronic kidney disease, kidney stones and myocardial dysfunction. Therefore, serum PTH measurement immediately after thyroidectomy and identification of patients at risk can reduce the risk of hypocalcemia by prescribing calcium and active vitamin D. In Table 3, a summary of the characteristics of the reviewed articles, including the names of the authors, the year of publication, the place of study, journal name, number of samples, type of quantitative and analytical study, and the results of the study have been presented.

**Table 1.** Predictive Factors of Hypoparathyroidism after Thyroidectomy

Author	Year	Country	Journal Name	Results
Sala et al. <sup>(15)</sup>	2019	Romania	Endocrine Care	In this prospective analytical study, 134 patients with thyroidectomy were selected, most of whom (118) were women with a mean age of 51.8 years. Patients were divided into two groups with iPTH levels below 12 and above 12. By measuring serum calcium and iPTH levels 24 h after surgery, it was found that severe hypocalcemia ( $Ca < 7.9$ mg/dl) was observed in the iPTH group below 12 with $P = 0.001$ , and 17 patients in this group had low iPTH one month after thyroidectomy, and eight of these patients had low calcium levels six months after surgery. In contrast, in the iPTH group above 12, calcium levels were normal one month after surgery and no decrease was observed.
Suwannasarn et al. <sup>(16)</sup>	2017	Thailand	Asian Journal of Surgery	In this prospective analytical study, 65 patients with thyroidectomy were selected. Hypocalcemia was observed in 42 patients (70%) and 25 patients (38.5%) had symptomatic hypocalcemia. In patients with symptomatic and persistent hypocalcemia, longer surgical time, female gender, and a significant drop in iPTH levels were observed 4 h after surgery.
Cho et al. <sup>(17)</sup>	2016	Korea	International Journal of Surgery	In this prospective analytical study, 1,030 patients with thyroidectomy were selected. Among them, 28.2% of patients had transient hypocalcemia and 2.6% of patients had persistent hypocalcemia. Effective factors that increased the risk of transient hypocalcemia were young people ( $P = 0.001$ ), female gender ( $P < 0/001$ ), increased time-surgery ( $P = 0.009$ ), and the presence of parathyroid glandular tissue ( $P < 0/001$ ) and no factor had a significant relationship with permanent hypocalcemia. Also, patients with a relative decrease in calcium and a relative increase in serum phosphorus on the first and second day after surgery were hypocalcemic.

Selberherr et al. <sup>(18)</sup>	2015	Austria	Surgery	In this prospective analytical study, 237 patients with thyroidectomy were selected. Patients were divided into three groups based on postoperative iPTH. 170 patients were in the first group with an iPTH above 15 pig/ml and were not given calcium and vitamin D supplements. 26 patients in the second group with iPTH were between 10 and 15 and received calcium and vitamin D supplements regardless of clinical symptoms. 33 people in the third group with an iPTH below 10, received calcium and vitamin D supplements, regardless of clinical symptoms. On the second day, the iPTH test was repeated. In the first group, the normal iPTH level, in the second group 10 of the 26 patients increased their iPTH level and did not receive the supplement, and in the third group the results did not change and supplement continued. The iPTH test was repeated one month after surgery. Calcium and vitamin D supplements were discontinued in all 16 patients in group 2 and in 20 of 33 patients in group 3. The iPTH test was repeated six months after surgery, and in 11 of the 13 patients, calcium and vitamin D supplements were discontinued.
Wang et al. <sup>(19)</sup>	2018	China	American Journal of Otolaryngology	In this analytical study, 110 medical records of patients with thyroidectomy were selected. Among the patients, there were 42 cases with normal parathyroid function, 58 cases with transient hypoparathyroidism and 10 cases with persistent hypoparathyroidism. In this study, it was found that lateral incision during thyroidectomy in the neck and reduction of blood calcium concentration 24 h after thyroidectomy is a risk factor for persistent hypoparathyroidism after thyroidectomy.
Su et al. <sup>(20)</sup>	2017	China	Medicine	In this analytical study, 903 medical records of patients with thyroidectomy were selected. 44.2% of patients had transient hypoparathyroidism and 1.1% had persistent hypoparathyroidism. Factors that increased transient hypoparathyroidism were female gender ( $P < 0.001$ ), non-use of carbon nanoparticles ( $P = 0.38$ ), and accidental removal of the parathyroid glands ( $P = 0.04$ ). Lack of use of carbon nanoparticles ( $P = 0.41$ ) and tumor presence in the upper thyroid gland ( $P = 0.31$ ) were factors in the development of persistent hypoparathyroidism. They found that the use of carbon nanoparticles in patients with thyroid cancer, especially in women with high blood pressure and tumors in the upper pole of the thyroid gland, could reduce hypoparathyroidism after thyroidectomy.
Sonne-Holm et al. <sup>(21)</sup>	2017	Denmark	European Thyroid Journal	In this analytical study, 582 medical records of patients with thyroidectomy were selected. Serum levels of parathyroid and calcium hormones were measured before and after surgery and after 3 and 12 months. The prevalence of transient hypoparathyroidism in the first 24 h and 3 months after surgery respectively was 47.8% and 17.8%. Also, the incidence of persistent hypoparathyroidism one year after surgery was 10.7%. Studies have shown that increased surgical duration was significantly associated with hypoparathyroidism.
Rosa et al. <sup>(22)</sup>	2015	Brazil	Archives of Endocrinology and Metabolism	In this analytical study, 140 medical records of patients with thyroidectomy were selected. Parathyroid hormone levels immediately after surgery were compared with ionized calcium in the morning after surgery. Patients with high ionized calcium levels had high PTH levels immediately after the first day surgery. Therefore, the amount of ionized calcium on the first day after surgery is a diagnostic measure of hypoparathyroidism.

## Discussion

The aim of this study was to investigate the predictive factors of hypoparathyroidism after thyroidectomy. Hypoparathyroidism is the most common complication of total thyroidectomy<sup>22</sup> that biological, clinical and surgical complications may be affected by total thyroidectomy due to hypoparathyroidism<sup>17</sup> and in addition to causing very unpleasant symptoms, patients

have a longer hospitalization and thus increase hospitalization costs for the patient and the treatment system.<sup>22</sup> Patients with persistent hypoparathyroidism which is one of the most serious postoperative complications, often experience paresthesia of the face and hands. In very severe cases, tetany and even suffocation due to Laryngospasm occur, which is currently not an effective treatment. In these patients,

due to long-term consumption of oral calcium and calcitriol, medical and therapeutic costs increase and as a result the quality of life of these patients is both physically and mentally effected.<sup>19</sup> According to the study, half of the patients developed hypoparathyroidism in the first 24 h after the thyroidectomy, indicating a high prevalence of the disease.<sup>21</sup> According to a study by Su et al., about half of the patients developed transient hypoparathyroidism and a very small number of patients developed persistent hypoparathyroidism.<sup>20</sup> Wang et al., further described the incidence of persistent hypoparathyroidism.<sup>19</sup> Hypoparathyroidism may be asymptomatic and self-limiting, but can lead to hypocalcemia with symptoms of paraesthesia and muscle spasms that appear in the first 24 h after surgery.<sup>21</sup>

Hypocalcemia is caused by a disturbance in the metabolism of parathyroid, which can also be developed as a side effect after a thyroidectomy.<sup>21</sup> Many surgeons regularly prescribe calcium and vitamin D to all patients who have had total thyroidectomy. Although it is effective in reducing the number of symptomatic patients, but it can be unpleasant because it is expensive and difficult for some patients to tolerate. In addition, this treatment is not 100% effective, and patients with severe hypocalcemia may experience tetanic contractions despite treatment. However, many patients receive medication unnecessarily. Also, calcium and vitamin D intake in normal patients can lead to the following: 1) inhibits the function of the parathyroid glands, 2) overestimating patients who need calcium and magnesium replacement and 3) in the event of definitive hypoparathyroidism, it can obscure the hypoparathyroidism that this prevents the surgeons from creating the optimal treatment. Another solution is to treat only symptomatic patients, but this requires a longer hospital stay, which is very difficult. The best solution is to have a reliable way to predict the factors that cause hypoparathyroidism after thyroidectomy so that only those who really need treatment can be treated.<sup>22</sup>

Many studies have assessed the potential risk factors for hypoparathyroidism-causing factors after thyroidectomy, some of which have been generally accepted. However, there is no reliable way to predict the factors that cause hypoparathyroidism after thyroidectomy and it is still a challenge. Previous studies have described measuring iPTH using a blood sample on the morning after surgery as an affordable way to diagnose hypoparathyroidism after thyroidectomy. As a result, the

need for calcium and vitamin D supplementation for patients using iPTH measurement is identified.<sup>18,19</sup> Suwannasarn et al., also confirmed that an iPTH measurement 4 h after surgery and its reduction could identify patients at risk for persistent hypoparathyroidism and hypocalcemia after thyroidectomy. This method is immediate and cost-effective in detecting hypocalcemia after thyroidectomy.<sup>16</sup> However, in a previous analytical study Rosa et al., mentioned that ionized blood calcium levels in the morning after thyroidectomy can be considered as an alternative to iPTH levels in the prevention of hypoparathyroidism after thyroidectomy surgery. The iPTH and calcium levels are directly related on the first day after surgery, but none are superior. However, as iPTH is not available in most centers and is also expensive, serum calcium levels, due to their availability in most centers and affordability, are a good diagnostic factor for preventing hypoparathyroidism after thyroidectomy.<sup>22</sup>

By using the ROC curve, Sala et al., proved that the most reliable predictor of permanent hypoparathyroidism is serum calcium measurement the day after thyroidectomy. Postoperative monitoring of total serum calcium is available in many hospitals as it is cheap and easy to measure. Serum calcium can be checked 4-6 h after a thyroidectomy or the next morning to predict patients' need for calcium supplements. However, due to the hospital conditions at the study site, they were unable to perform the iPTH dose in all thyroidectomy patients, especially a few hours after thyroidectomy.<sup>15</sup> The results of Wang et al.'s study also showed that lateral incision during thyroidectomy in the neck and reduction of blood calcium concentration 24 h after thyroidectomy is a risk factor for persistent hypoparathyroidism after thyroidectomy. Performing this test facilitates early diagnosis and prevents the pain of repeated blood tests resulting in economic burden.<sup>19</sup>

Cho et al. in their study, stated that hypocalcemia is significantly more common in female patients. Although the gender ratio in their study group was disproportionate (865 females versus 165 males), but the female gender factor showed the greatest risk for hypocalcemia after thyroidectomy (95% confidence interval). They believed the reason for the report was that women were more likely to have a hormone-related illness, such as menopausal syndrome or osteoporosis, which could be linked to calcium or vitamin D because these factors can be disruptive. In

addition, they did not control these possible disruptive factors, which could explain some of the conflicting results.<sup>17</sup> In addition, Su et al. identified the female gender as an important factor for transient hypoparathyroidism after thyroidectomy.<sup>20</sup> However, in the study of Suwannasarn et al. the incidence of persistent hypoparathyroidism in women was lower than in men.<sup>16</sup>

In a retrospective analytical study conducted by Sonne-Holm et al., long-term surgery and youthful age were identified as risk factors for hypoparathyroidism after thyroidectomy. They stated that surgery lasting more than 120 min, due to reduced blood flow, causes ischemia in the parathyroid glands, which increases the risk of hypoparathyroidism, which is a very important factor. Their study also found that the surgeon's experience had no role in the development of hypoparathyroidism.<sup>21</sup> Cho et al., also revealed that the time of surgery is usually longer in patients with hypocalcemia.<sup>17</sup>

In a previous analytical study, Su et al., showed that carbon nanoparticles were not used as an important factor in transient hypoparathyroidism after thyroidectomy. The non-use of carbon nanoparticles is a significant risk factor in the development of persistent hypoparathyroidism after thyroidectomy. In this study, it was found that women were almost twice as likely as men to develop transient hypoparathyroidism after thyroid surgery. Therefore, women may take calcium supplements earlier and possibly before surgery to reduce the symptoms of hypocalcemia. Carbon nanoparticles can pass through lymphatic capillaries instead of blood capillaries due to differences in permeability. There are many vessels and nodes lymph in the thyroid gland, while almost none in the parathyroid glands. As a result, the use of carbon nanoparticles can cause the thyroid gland and surrounding lymph nodes to turn black, but the parathyroid glands do not change color, making it easier to cut the lymph nodes and parathyroid glands. Therefore, the use of carbon nanoparticles to reduce the incidence of hypoparathyroidism after thyroidectomy is considered helpful.<sup>20</sup>

In another analytical study, Cho et al. showed that a relative decrease in calcium and an increase in serum phosphorus appeared to be a predictor of hypocalcemia after total thyroidectomy. The ROC curve for these changes was relatively accurate in predicting the progression of hypocalcemia on the day after surgery.<sup>17</sup>

A study by Suwannasarn et al. described preoperative vitamin D deficiency as a good predictor of postoperative hypocalcemia as calcium is critical for homeostasis.<sup>16</sup>

## Conclusion

Due to the role of PTHs in the body's function, it is important to predict the factors that cause hypoparathyroidism after thyroidectomy. According to studies, measuring serum calcium, iPTH and phosphorus the day after surgery, reducing the duration of surgery and female gender are among the predictive factors of hypoparathyroidism after thyroidectomy.

## Conflict of Interest

The authors declare no conflicts of interest.

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