

# Perioperative Management of Thyroid Dysfunction

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Health Services Insights

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DOI: 10.1177/1178632916689677



**ABSTRACT:** Due to the manifold effects of thyroid hormone across virtually all organ systems, the complications associated with thyroid dysfunction are numerous and diverse. The stresses encountered during the perioperative period may exacerbate underlying thyroid disorders, potentially precipitating decompensation and even death. Thus, it is of the utmost importance for the clinician to comprehend the mechanisms by which thyroid disease may complicate surgery and postoperative recovery and to be cognizant of the most effective means of optimizing the status of thyrotoxic and hypothyroid patients perioperatively. This article describes the adverse effects of thyroid dysfunction as they relate to the patient undergoing both thyroid and nonthyroid surgery and recommends treatment approaches aimed at decreasing perioperative risk.

**KEYWORDS:** perioperative management, hypothyroid, hyperthyroid, thyrotoxicosis

**RECEIVED:** August 29, 2016. **ACCEPTED:** December 19, 2016.

**PEER REVIEW:** Five peer reviewers contributed to the peer review report. Reviewers' reports totaled 827 words, excluding any confidential comments to the academic editor.

**TYPE:** Review

**FUNDING:** The author(s) received no financial support for the research, authorship, and/or publication of this article.

**DECLARATION OF CONFLICTING INTERESTS:** The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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## Introduction

Patients with thyroid dysfunction are well represented in the general population. Studies report the prevalence of abnormal thyrotropin values to be as high as 21% in women and 3% in men.<sup>1</sup> Due to the myriad effects of thyroid hormone throughout the body, the effects of thyroid dysfunction are manifold and may complicate surgical procedures and postoperative recovery. Thus, although routine screening to detect thyroid disease is not indicated in patients where there is no index of suspicion for the same, the recognition, diagnosis, and optimization of preexisting thyroid conditions in patients undergoing surgery are important perioperative considerations. This article will address the issues concerning the perioperative management of thyroid disease in patients with hypothyroidism and hyperthyroidism who are undergoing nonthyroid surgery, as well as specific concerns related to the management of patients undergoing thyroid surgery for thyrotoxicosis.

## Preoperative Screening

Routine preoperative thyroid function testing is not recommended for patients with no history of thyroid dysfunction. In such patients, it would be appropriate to check the thyrotropin (TSH) level if there is a reason to suspect thyroid disease based on symptoms such as unexplained weight changes, palpitations, tremor or changes in bowel habits, skin, hair, or eyes that suggest thyroid dysfunction. Furthermore, when the physical examination or other investigation confirms the presence of exophthalmos, goiter, abnormal reflexes, hair or skin abnormalities, or tachycardia or bradycardia, a TSH test would be appropriately included in a preoperative evaluation.

In patients with known hypothyroidism or hypothyroidism who have been undergoing treatment, a TSH test should be included in the preoperative assessment to determine the

adequacy of treatment and to ensure that thyroid therapy is optimized before surgery.

## Complications of Hypothyroidism

Thyroid hormones play a crucial role in homeostasis due to their effects on the cardiovascular, respiratory, renal, gastrointestinal, hematologic, and central nervous systems. The cardiovascular concerns are among the most relevant in perioperative situations. Patients with hypothyroidism are at increased risk of coronary events<sup>2</sup> possibly due to increased cholesterol levels,<sup>3</sup> prolonged half-life of multiple coagulation factors,<sup>4</sup> and anemia.<sup>5</sup> Nonspecific ST changes and low voltage on electrocardiogram are observed and, less commonly, “torsade de pointes” ventricular tachycardia has been described.<sup>6</sup>

Hypothyroidism has been associated with a diminished cardiac output of 30% to 50%, with both slowing of the pulse and decreased contractility.<sup>7</sup> Furthermore, deficiency of thyroid hormones causes an increase in peripheral vascular resistance resulting in increased cardiac afterload, leading to a decreased pulse pressure via an increase in diastolic pressure and a decrease in systolic blood pressure.<sup>8</sup> Even though catecholamine levels are increased in these patients, hypothyroid patients have a predisposition to develop hypotension under anesthesia, likely due to downregulation of  $\beta$ -adrenergic receptors.<sup>9</sup>

In addition to the cardiovascular concerns, hypothyroid patients face additional challenges due to the ventilatory dysfunction and renal manifestations associated with this condition. Pleural effusions and respiratory muscle weakness, along with impaired hypoxic and hypercapnic respiratory drive and increased prevalence of obstructive sleep apnea, may complicate their perioperative management, as may a predisposition to pneumonia and atelectasis.<sup>8</sup> Increased antidiuretic hormone



leads to hyponatremia.<sup>10</sup> Increased capillary permeability and resultant shifts of fluid into the extravascular space decrease intravascular volume and renal perfusion leading to decreased clearance of medications.<sup>11</sup> These pulmonary and renal factors contribute to the increased susceptibility of hypothyroid patients to anesthetics, tranquilizers, and narcotics.<sup>12,13</sup>

Decreased gastrointestinal motility, which is most commonly manifested as constipation in hypothyroid patients, increases the tendency for postoperative ileus.<sup>14</sup> This is of increased concern considering that postoperative pain management regimens commonly use opioids which independently promote constipation.

Hypothyroidism is associated with several hematologic effects. Most commonly described is a normochromic, normocytic anemia. However, because of the increased prevalence of pernicious anemia among patients with hypothyroidism, concomitant autoimmune-mediated vitamin B12 deficiency may cause macrocytosis. Furthermore, in premenopausal women, menorrhagia secondary to hypothyroidism results in microcytic anemia secondary to iron deficiency.<sup>8</sup> Other hematologic manifestations of hypothyroidism include a decrease in factor VIII activity, prolonged partial thromboplastin time,<sup>15</sup> and acquired von Willebrand disease.<sup>16</sup>

A rare, yet most dreaded complication of surgery in hypothyroid patients is myxedema coma, a condition that has been associated with mortality as high as 80%.<sup>17</sup> Myxedema coma is characterized by altered mental status, which may manifest as coma or seizure, and hypothermia, bradycardia, hyponatremia, heart failure, and hypopnea. It is commonly associated with a precipitant such as surgery, infection, cold exposure, and administration of sedatives.

### Preoperative Considerations in the Hypothyroid Patient

The pathophysiologic changes associated with hypothyroidism are generally reversible with replacement of thyroid hormone. Thus, rather than face the risk of acute decompensation, it is preferable to postpone elective surgery until adequate treatment with thyroid hormone has achieved euthyroidism. A full replacement dose of levothyroxine is usually 1.6 µg/kg/day. However, in the elderly or those with known coronary artery disease, the initial dose is usually 25 µg daily, with a planned increase every 2 to 6 weeks until a euthyroid state is attained. Once TSH values normalize, surgery can be performed. If the patient is to fast on the day of surgery, the patient may miss the dose of levothyroxine that day, as it has a long half-life of approximately 7 days. If oral medications cannot be given postoperatively, the dose may be missed for several days. However, if there is still no ability to administer the drug enterally after 5 days, intravenous (IV) levothyroxine should be administered at a dose between 60% and 80% of the oral dose.<sup>8</sup>

In cases where surgery is not elective, the risk of proceeding with surgery must be weighed against the risks detailed above. Unfortunately, there are no large randomized studies

comparing surgical outcomes in hypothyroid versus euthyroid patients.

In a prospective study comparing postoperative outcomes in patients with subclinical hypothyroidism, defined as elevated thyroid-stimulating hormone with normal free thyroxine, to euthyroid patients undergoing coronary artery bypass grafting, no increase in major adverse cardiovascular events, wound problems, mediastinitis, leg infection, respiratory complications, delirium, or reoperation during the same hospitalization was noted. However, there was an increase in the rate of postoperative atrial fibrillation in the subclinical hypothyroidism group.<sup>18</sup>

One retrospective study analyzed the outcome of anesthesia and surgery in 59 hypothyroid patients compared with 50 euthyroid patients. There were no differences in duration of surgery or anesthesia, lowest temperature and blood pressure recorded during surgery, need for vasopressors, time to extubation, fluid and electrolyte imbalances, incidence of arrhythmias, pulmonary or myocardial infarction, sepsis, need for postoperative respiratory assistance, bleeding complications, or time to hospital discharge. Analysis of subsets of patients divided based on their thyroxine levels (thyroxine level < 1.0 µg/dL, 1.0 to <3.0 µg/dL, and ≥3.0 µg/dL) revealed no differences in outcomes. Because there were only 7 patients in the group with the lowest T4 concentration, the authors concluded that in mild to moderate hypothyroidism, there is no evidence to justify postponing surgery that is needed, but in severe hypothyroidism, there is insufficient evidence to make a recommendation.<sup>19</sup>

In another retrospective study, 40 hypothyroid surgical patients, most of whom had mild to moderate severe hypothyroidism, were compared with 80 euthyroid surgical patients who served as controls. Among those undergoing noncardiac surgery, intraoperative hypotension occurred at a higher rate in the hypothyroid group. For those undergoing cardiac surgery, the development of heart failure was more prevalent in the hypothyroid group. In addition, the hypothyroid group had a higher rate of gastrointestinal and neuropsychiatric complications. Furthermore, even though there was a similar rate of postoperative infection in both groups, the hypothyroid patients were less likely to be febrile. No differences were noted in perioperative blood loss, duration of hospitalization, rates of arrhythmia, hypothermia, hyponatremia, delayed recovery from anesthesia, tissue integrity, wound healing, pulmonary complications, or death. Of note, applicability of conclusions drawn from these data may be limited as only 2 of the patients studied were categorized as having severe hypothyroidism.<sup>20</sup>

### Recommendations for Hypothyroid Patients

Although the definitions of mild, moderate, and severe hypothyroidism are somewhat subject to interpretation and vary between studies, and the number of studies is quite limited, the following conclusions are reasonable based on the literature. Although elective surgery is best postponed until a euthyroid state is achieved, patients requiring urgent or emergent surgery

may proceed with surgery if they have mild or moderate hypothyroidism. Levothyroxine should be started preoperatively and there should be increased awareness of the possibility of minor postoperative complications such as those mentioned above.

In general, the classification of “severely hypothyroid” includes those patients with myxedema coma or severe complications such as altered mentation, pericardial effusions or heart failure, or very low levels of thyroxine ( $<1 \mu\text{g/dL}$ ). Based on the lack of outcomes data and an understanding of the risks outlined above, nonemergent surgery should be postponed until the hypothyroidism has been treated. If emergent surgery is required, thyroid hormone levels should be normalized as rapidly as possible, using IV levothyroxine in a loading dose of 200 to 500  $\mu\text{g}$  followed by 50 to 100  $\mu\text{g}$  IV daily.<sup>21</sup> Simultaneous administration of IV liothyronine should be considered if there is suspicion for myxedema coma. If there is any suspicion for concurrent adrenal insufficiency, glucocorticoids should be administered in stress doses prior to or together with thyroid hormone.

Patients who require cardiac revascularization comprise the only subset of patients who may not benefit from preoperative replacement of thyroid hormone. Although one may intuit from the above discussion that preoperative optimization of thyroid hormone status would benefit all patients, in cardiac patients with angina, there is a real possibility of worsening cardiac ischemia by replacing thyroid hormone and consequently increasing myocardial oxygen demand. In fact, as retrospective and prospective studies of cardiac patients undergoing cardiac surgery or catheterization found no increase in the rate of adverse events in those patients whose hypothyroidism had not been treated,<sup>22,23</sup> it is reasonable to proceed with the revascularization procedure before repleting thyroid hormone.

### Complications of Hyperthyroidism

As in hypothyroidism, the manifestations of abnormally elevated thyroid hormone levels seen in thyrotoxicosis are numerous and pervade multiple organ systems. The most salient features are the cardiovascular ones, namely, the positive inotropic and chronotropic effects of thyroid hormone on the heart, the vasodilation and decrease in systemic vascular resistance, and the consequent increase in sodium and water retention mediated by the renin-angiotensin-aldosterone system, all of which culminate in an increase in cardiac output by 50% to 300%.<sup>24</sup> Atrial fibrillation occurs in 10% to 15% of patients with overt hyperthyroidism and in a similar percentage of those with subclinical hyperthyroidism, ie, decreased TSH with normal thyroxine and triiodothyronine.<sup>25</sup> The prevalence of atrial fibrillation increases with age.<sup>26</sup>

### Optimization of Cardiovascular Status Before Surgery in Hyperthyroid Patients

There are no published studies evaluating the perioperative outcomes of hyperthyroid patients compared with euthyroid patients. Because of the risk of precipitating thyroid storm, a

scenario characterized by tachycardia, confusion, fever, gastrointestinal complaints, and potentially leading to cardiovascular collapse, elective surgeries should always be postponed in patients with overt hyperthyroidism. In those with mild or subclinical disease, preoperative  $\beta$ -blockade is considered sufficient. This is supported by a prospective randomized trial showing that in hyperthyroid patients undergoing thyroidectomy who were treated with just 5 weeks of metoprolol preoperatively, there were no serious intra- or postoperative complications, compared with patients who were pretreated for 12 weeks with a combination of methimazole and levothyroxine to render them euthyroid.<sup>27</sup>

For patients with overt hyperthyroidism requiring urgent or emergent surgery, cardiac status must be closely monitored. Perioperative placement of an arterial line or central venous pressure monitor is appropriate if there is evidence of cardiopulmonary disease or the patient is not hemodynamically stable. Cardiac status should be optimized and  $\beta$ -blockers are most commonly used for this purpose. Although no particular  $\beta$ -blocker has established superiority over others, atenolol may be preferred in some cases. Like metoprolol, it is a beta-1-selective agent which may be tolerated better in patients with reactive airway disease. In addition, its long half-life facilitates once-daily dosing. However, because its metabolism is accelerated in thyrotoxicosis, the total daily dose may still need to be divided into 2 doses.<sup>28</sup> Although an initial dose of 25 mg daily may be used, often higher doses, such as 50 mg up to more than 200 mg daily, may be required. Although propranolol is a nonselective beta-1 and beta-2-blocker with a shorter half-life necessitating the administration of multiple daily doses, it may have additional benefit because it inhibits the monodeiodinase type I enzyme which converts T4 to the more biologically active T3 hormone.<sup>29</sup> It can be used intravenously to control pulse and blood pressure and even decrease fever intraoperatively.<sup>30</sup>

Calcium channel blockers should be used in patients who cannot tolerate  $\beta$ -blockers. These drugs should be titrated to achieve a heart rate under 80 beats per minute. Because they decrease sympathetic activity, both reserpine and guanethidine may be considered for those in whom  $\beta$ -blockers and calcium channel blockers are contraindicated.<sup>31</sup>

### Recommendations for Treatment of Thyrotoxicosis

In cases where thyrotoxicosis is due to the increased synthesis of thyroid hormone, ie, in the Graves disease and toxic nodular disease, but not in cases of exogenous thyroid hormone intoxication or thyroiditis, antithyroid drugs (ATDs) should be used as soon as possible to decrease thyroid hormone levels. Thionamides, including propylthiouracil (PTU) and methimazole, which are available in the United States, and carbimazole, which is available elsewhere, inhibit de novo production of thyroid hormone but do not actually affect the release of preformed hormone. Thus, their effects may not be apparent for several days. Methimazole may achieve a euthyroid state

faster than PTU but is still expected to take between 3 and 8 weeks. It is preferred because of its decreased potential for hepatotoxicity and its longer half-life which facilitates dosing once or twice daily. Propylthiouracil, in contrast, is administered every 6 to 8 hours.<sup>32</sup> Furthermore, methimazole may be started in doses of 20 to 30 mg daily and is available in 5, 10, and 20 mg tablets, whereas PTU would generally be administered in doses of 100 to 150 mg every 6 to 8 hours and is only available in 50 mg tablets. For patients who are unable to take oral medications, both drugs can be administered rectally.

Propylthiouracil offers the additional benefit of reducing conversion of thyroxine to the more biologically potent triiodothyronine. In addition, it is generally preferred in the first trimester of pregnancy because of its decreased teratogenicity relative to methimazole. However, both drugs have similar toxicities. Urticaria, rash, arthralgia, and fever occur in 1% to 5% of patients. Both agents may cause agranulocytosis at a rate between 1 in 200 and 1 in 5 patients. This effect is dose related in methimazole and rarely occurs at doses below 40 mg daily.<sup>28</sup> In contrast, regarding PTU, these toxicities are idiosyncratic and not dose related. It is prudent to avoid both drugs in a patient who has experienced an adverse effect secondary to one of them because cross-sensitivity can occur.

Concomitant use of  $\beta$ -blockers and thionamides should adequately prepare most patients for surgery within a few weeks. These agents should be continued throughout the postoperative period to prevent thyroid storm and possibly longer unless the patient is treated with thyroid resection or I<sup>131</sup> ablation and is no longer hyperthyroid. Obviously, in patients undergoing thyroidectomy, thionamides should be stopped postoperatively. However, because the half-life of levothyroxine is so long, it may still be necessary to continue  $\beta$ -blockers for about a week, possibly longer, after thyroidectomy. In patients who have undergone thyroidectomy, thyroid hormone therapy will be necessary once hormone levels have declined below normal.

Another medication which decreases thyroid hormone release but it is generally avoided due to its other unfavorable systemic effects is Lithium.<sup>31</sup>

When there is an urgent need to stabilize the thyrotoxicosis rapidly, inorganic iodide should be given as an adjunct to thionamides because its administration blocks the organification of iodine, decreasing the synthesis of thyroid hormones by the gland. This transient phenomenon, known as the Wolff-Chaikoff effect,<sup>33</sup> is apparent within 24 hours. However, in patients with toxic thyroid nodules, it is imperative that administration of a thionamide precedes that of iodide because of the potential for precipitating an iodine-induced increase in thyroid hormone production via the Jod-Basedow effect. The Jod-Basedow effect is not relevant in patients with the Graves disease, and those patients, if unable to take thionamides, may even be treated with just iodine and  $\beta$ -blockade. However, as escape from the Wolff-Chaikoff effect is anticipated to occur

after approximately 10 days, treatment with iodine should not be started more than 10 days preoperatively.

Iodine may be administered orally, rectally, or intravenously.<sup>34</sup> Commonly administered doses and formulations include 1 drop 3 times daily of saturated solution of potassium iodide or a dose of 3 to 5 drops of Lugol's solution thrice daily.<sup>35</sup> In addition, iopodate, an oral cholecystographic agent which contains a large iodine load, was used in the past to decrease hormone production and reduce the peripheral conversion of thyroxine to triiodothyronine. However, this agent is no longer available and another iodine-containing product known as iopanoic acid, when administered in a dose of 500 mg twice daily, reduces triiodothyronine levels even faster than the other iodine preparations mentioned above.<sup>28</sup>

Glucocorticoids decrease the conversion of thyroxine to triiodothyronine within a matter of hours, so they may be added preoperatively and tapered over 3 days postoperatively. Suggested regimens include hydrocortisone 100 mg orally or IV every 8 hours, dexamethasone 2 mg orally or IV every 6 hours, or betamethasone 0.5 mg orally, intramuscular, or IV every 6 hours.<sup>28</sup>

Cholestyramine is an additional modality that may be used to rapidly lower thyroid hormone levels in thyrotoxic patients. Studied in a dose of 4 g four times daily, cholestyramine decreases circulating hormone levels by binding thyroid hormone in the intestine and decreasing its reabsorption.<sup>36</sup> As the enterohepatic circulation of thyroid hormone is increased in thyrotoxic individuals, this binding resin is quite effective.<sup>36</sup> In fact, the American Thyroid Association, in its recently published Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis, specifically recommended that those undergoing thyroidectomy for the Graves should be rendered euthyroid prior to the procedure with ATD pretreatment, with or without  $\beta$ -adrenergic blockade, and potassium iodide should be given in the immediate preoperative period. When it is not possible to render the patient euthyroid prior to thyroidectomy or when the patient is allergic to ATDs, the patient should be treated with  $\beta$ -blockade, potassium iodide, glucocorticoids, and "potentially cholestyramine" in the immediate preoperative period.<sup>37</sup>

In cases of thyrotoxicosis, due to exogenous thyroid hormone intoxication, no specific targeted therapy is indicated other than  $\beta$ -blockade or calcium channel blockade, as needed, to stabilize cardiovascular status, as the passage of time will permit metabolism of excess hormone within a matter of days to weeks. In cases where the etiology of the thyrotoxicosis is thyroiditis, and elevated thyroid hormone levels are attributable to increased release of thyroid hormone rather than overproduction, there is, similarly, no role for ATDs. Nonsteroidal anti-inflammatory medications are advised for those patients. For all patients with thyrotoxicosis, regardless of cause, corticosteroids, iopanoic acid, and cholestyramine may be considered, as their functionality is independent of thyroid hormone production. Steroids and iopanoic acid will decrease T4 to T3 conversion regardless of



the source of T<sub>4</sub>, and cholestyramine will decrease thyroid hormone absorption from the intestines regardless of whether it was endogenously produced or exogenously administered.

There is another strong recommendation made by the American Thyroid Association in its recently published guidelines which relates specifically to those undergoing thyroidectomy. The guidelines suggest the supplementation of oral calcium, vitamin D, or both preoperatively to reduce the risk of postoperative hypocalcemia due to parathyroid injury or increased bone turnover.<sup>37</sup> The authors reference a meta-analysis of risk factors for postoperative hypocalcemia which determined that both preoperative vitamin D deficiency and the Graves disease increased the likelihood of this complication.<sup>38</sup>

## Conclusions

Although hypothyroidism and hyperthyroidism represent opposite ends of a disease spectrum, the ubiquitous effects of both thyroid hormone deficiency and thyroid hormone excess throughout multiple organ systems predispose patients with either conditions to specific perioperative complications, some of which can be severe or even fatal. Apart from the dreaded complication of myxedema coma which involves the central nervous system, hypothyroid patients undergoing surgery are predisposed to anemia, electrophysiologic disturbances, and hypotension, all of which can precipitate cardiovascular collapse. Renal and pulmonary changes can lead to fluid and electrolyte disturbances and respiratory failure, and decreased gastrointestinal motility can promote development of an ileus. Similarly grave are the complications of thyrotoxicosis which may trigger arrhythmias, fever, gastrointestinal disturbances, and even progress to the mental status changes and cardiovascular decompensation associated with the calamitous state of thyroid storm. Thus, the goal of therapy in the perioperative patient with thyroid dysfunction centers around the attempt to normalize hormone levels prior to surgical intervention whenever possible and, when that is not feasible, to use other measures that will maximize hemodynamic stability and prevent decompensation.

## Author Contributions

MRP reviewed and approved the final manuscript.

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