Review Article

Post-thyroidectomy hypothyroidism and thyroid hormone supplementation: a narrative review of the history, treatment, and patient experience

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Background and Objective: Surgical management of thyroid disease bears risk of need for lifelong thyroid hormone supplementation in patients undergoing partial thyroidectomy, with a guarantee in those undergoing total or subtotal thyroidectomy. The aim of this study is to review the evidence-based management of thyroid hormone supplementation in the post-surgical setting, and to better understand quality of life (QoL) considerations in the post-thyroidectomy population. Specific emphasis is placed on management of the patient with differentiated thyroid cancer (DTC), both from management and QoL perspectives.

Methods: Review of English language studies on history, diagnosis and management of hypothyroidism following thyroidectomy, as well as relevant QoL assessment, conducted by authors February to May of 2022.

Key Content and Findings: Treatment of primary hypothyroidism following thyroidectomy may warrant a multidisciplinary and nuanced approach. QoL may be significantly impacted in certain post-surgical cohorts, including patients with DTC and autoimmune thyroiditis, with special consideration and treatment algorithms warranted in managing these patients.

Conclusions: Optimizing treatment algorithms for initiation and adjustment of thyroid hormone supplementation is crucial to elevate patient outcomes with respect to both physiology and QoL. Regular assessment of QoL may guide providers toward new treatment methods and optimize patient experience in the setting of post-operative hypothyroidism.

Keywords: Thyroidectomy; thyroid hormone supplementation; levothyroxine; quality of life (QoL); hypothyroidism

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Introduction

Background

Surgical management of benign and malignant thyroid disease is well-tolerated by patients, with low morbidity when performed by current standards, especially while in the hands of high-volume providers (1). A keen focus on and meticulous care of the recurrent laryngeal nerve as well as the external branch of superior laryngeal nerve enable preservation of full vocal fold function

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and excellent voice quality in most patients (2). Careful visualization and delicate handling of the parathyroid glands translates to low rates of permanent or clinically significant hypoparathyroidism and hypocalcemia (3). Fastidious hemostasis achieved intraoperatively allows for safe avoidance of drains and low rates of hematoma, further improving patient outcomes and the quality of the perioperative experience following thyroidectomy (4). Yet, despite scrupulous and multiply reiterated surgical technique, the reality of post-thyroidectomy hypothyroidism persists; we can do everything right and patients will inevitably become hypothyroid after removal of the thyroid gland.

Rationale and knowledge gap

While all aspects of potential surgical morbidity are progressively optimized, postoperative patients inevitably face the transition to synthetic hormone supplementation, a transition that is calculated yet nuanced, and one that may prove very impactful in a certain subset of patients (5).

Objective

The aim of this study is to review the evidence-based management of thyroid hormone supplementation in the post-surgical setting, and to better understand quality of life (QoL) considerations in the post-thyroidectomy population. We present this article in accordance with the Narrative Review reporting checklist (available at https://aot.amegroups.com/article/view/10.21037/aot-22-17/rc).

Methods

This study includes a review of evaluation and management of iatrogenic, post-thyroidectomy hypothyroidism. There is no patient information reviewed and thus institutional review board approval was not indicated. Search inclusion parameters were English language studies of adult populations, with review articles including historical reviews, systematic reviews, and cohort studies. Exclusion criteria included those not in English, and those exclusively reviewing pediatric data; there may have been some pediatric patient data embedded within adult studies. Literature search was conducted by multiple authors between February and May 2022 (*Table 1*).

Key content and findings

History of thyroid surgery and thyroid hormone supplementation

The earliest depictions and mentions of goiter and thyroidectomy date back thousands of years. It was not until the mid-1800s when Theodore Kocher made significant strides in reducing the unacceptably high mortality of this procedure that the surgical technique became well-described (6). In parallel, descriptions of the condition of cretinism trace back hundreds of years, and it was not until 1850 when the first link between stunting of growth, skin changes, and intellectual disability, namely, "change of features a cretinous type", and depletion of the thyroid was first observed (7). Theodore Kocher, amongst other important figures, was integral in this crucial discovery, remarking on the significant difference in the appearance and condition of his patients who had undergone total *vs.* partial thyroidectomy, the former displaying many classic features of cretinism and myxedema (7). The first recorded postulation relating what we now consider hypothyroidism to the function of the thyroid gland was made at the Clinical Society of London meeting in 1883. The initial documentation of this finding in the medical literature was made in the *British Medical Journal* in 1885 by Victor Horsley, who stated: "*Various as have been surmises as to the function of the thyroid gland, it is not a little surprising that, although arrest of it had been vaguely known for hundreds of years to be connected with the cretinous state... Cretinism, as is well known, has been attributed to every cause except the destruction of the thyroid… I am prepared, in my first two lectures, to support the dictum (first completely enunciated by my friend, Dr. Felix Semon) that cretinism, congenital or acquired myxoedema, and cachexia strumipriva, are merely phases of one and the same state, and due to the same cause, namely, arrest of the function of the thyroid gland.*" (7).

It would be several years still until any treatment of the declared postsurgical hypothyroid state was developed. The origins of thyroid hormone supplementation include implantation of animal thyroid glands into the abdominal cavity of hypothyroid patients, and later organotherapy, or injection and treatment of patients with thyroid extract or consumption of desiccated thyroid tissue; desiccated thyroid hormone extract remained the dominant treatment of hypothyroidism until the 1970's (7,8). The advent of synthetic thyroid hormone use occurred in the mid-1900s; while synthetic thyroxine was isolated as early as 1914 by Kendall, and its biochemical structure was defined in 1926,

Table 1 Literature search methodology

Items	Specification
Date of search	2/01/2022–05/30/2022
Databases and other sources searched	PubMed
Search terms used	"Hypothyroidism", "Thyroid hormone supplementation", "Hypothyroidism" AND "History", "Hypothyroidism" AND "thyroid hormone supplementation", "Thyroidectomy" AND "hypothyroidism", "Thyroidectomy" AND "History", "Thyroidectomy" AND "iatrogenic hypothyroidism", "Hashimoto's thyroiditis" AND "Thyroidectomy", "Thyroidectomy" AND "Quality-of-life"
Timeframe	1988–2022
Inclusion and exclusion criteria	Inclusion criteria: research articles and reviews in English about hypothyroidism diagnosis, management, and treatment, with specific search of articles assessing hypothyroidism following thyroidectomy. Historical articles on the discovery and evolution of hypothyroidism diagnosis and management were also included
	Exclusion criteria: research articles and reviews not in English, or those exclusively evaluating pediatric patients
Selection process	Jennifer A. Brooks conducted the literature review, all authors concurred on literature selection
Any additional considerations, if applicable	Some papers were identified by reviewing reference lists of relevant publications

it was not made commercially available until 1949. Concerns about the ability of monotherapy with thyroxine to fully normalize thyroid function were quelled by the discovery of peripheral conversion of thyroxine (T4) to tri-iodothyronine (T3). Emergence of the thyroid stimulating hormone (TSH) radioimmunoassay enabled more accurate determination of thyroid hormone status as compared to prior use of protein-bound iodine or basal metabolic rate. The decreasing cost of levothyroxine coupled with the recognition that desiccated extract formulations exhibited variable potency and thyrotoxic symptoms allowed synthetic thyroxine monotherapy to become the norm in treating hypothyroidism (8-10).

Etiologies of hypothyroidism

Hypothyroidism is a common concern, with incidence of overt hypothyroidism afflicting approximately 4% of the general population; this figure is much higher (15%) when accounting for subclinical hypothyroidism (11). Hypothyroidism may be primary in nature, due to insult to, dysfunction or removal of the thyroid gland, or secondary, related to disruption of the hypothalamic-pituitary-thyroid axis. The most common cause of primary hypothyroidism in regions of adequate dietary iodine is chronic lymphocytic thyroiditis or Hashimoto's thyroiditis (HT), associated with a defect in immune surveillance of the thyroid gland, demarcated by high levels of anti-thyroid peroxidase (anti-TPO) antibodies, and leading to gradual destruction of the thyroid parenchyma (12). Thyroidectomy, either partial or total, is a primary iatrogenic cause of hypothyroidism (13). Secondary hypothyroidism may be due to pituitary gland dysfunction, trauma, tumors, or infarcts. For the purposes of this review, we will focus on primary hypothyroidism, particularly iatrogenic post-operative hypothyroidism.

Symptoms of hypothyroidism

The most common symptoms of hypothyroidism can be vague and non-specific, and include fatigue, weight gain, cold intolerance, voice change, and dry skin. Severe hypothyroidism may additionally present with voice change, carpal tunnel syndrome, and sleep apnea (10). Long-term sequelae of untreated hypothyroidism include dyslipidemia and progression of cardiovascular disease, as well as a reversible form of cardiomyopathy in severe cases (5).

Initiation of L-thyroxine (LT4) in hypothyroid patients

Levothyroxine, or LT4 remains the mainstay of treatment for symptomatic hypothyroidism, with a strong recommendation for monotherapeutic use per the 2014 American Thyroid Association (ATA) guidelines:

"*Levothyroxine is recommended as the preparation of choice for the treatment of hypothyroidism due to its efficacy in resolving the symptoms of hypothyroidism*, *long-term experience of its benefits*, *favorable side effect profile*, *ease of administration*, *good intestinal absorption*, *long serum half- life*, *and low cost*" (5).

The goals of LT4 administration are threefold: to reduce symptomatology associated with a hypothyroid state, to normalize TSH and thyroid hormone levels, and to avoid iatrogenic hyperthyroidism. The daily dose is dependent on several factors, including age, gender, and weight. The standard weight-based dosing is 1.6 mcg/kg in patients with little residual thyroid function. This rate may be higher in patients after total thyroidectomy, secondary to lack of any residual functioning thyroid tissue (10,12). Initial dosage in full therapeutic range is associated with more rapid achievement of a euthyroid state, however, time to symptom improvement is similar when lower doses are initiated, and certain symptoms, such as perceived skin changes, may take several months to improve once the TSH level has normalized (10).

Repeat serum testing is recommended to assess thyroid hormone levels 4–6 weeks after initiation of treatment, dose adjustment, or transition to new formulation of LT4. Given the long half-life of thyroxine (~1 week), the recommended 4–6-week interval allows for passage of 6 half-lives, achievement of a new steady hormone state, and more accurate assessment of the effect of the current dosage. Following partial thyroidectomy, TSH and thyroid hormone levels are also checked along this timeline, to allow adequate time for a decrease in thyroid hormone levels to be biochemically detectable as well as potentially clinically appreciated (12).

Administration of calcium salts (e.g., carbonate or citrate) can alter the absorption of LT4, an important consideration in our postoperative patients following thyroidectomy who may warrant treatment for transient hypocalcemia, with more potential interference and difficulty in ensuring proper LT4 dosing in patients with severe or permanent hypocalcemia (12). The ATA guidelines suggest a 4-hour separation of interfering supplements and levothyroxine, although the 4-hour interval is based mostly on common practice, logic, and indirect evidence.

Thyroid hormone replacement following thyroidectomy

Assessment of thyroid function is an important aspect of postoperative care following partial or total thyroidectomy. As mentioned, evaluation of TSH level 4–6 weeks postoperatively is considered standard to screen for iatrogenic hypothyroidism following hemithyroidectomy, as well as to assess appropriateness of initial dose of LT4 following total thyroidectomy (5,14). Rates of hypothyroidism following thyroid lobectomy are historically cited around 20%. However, certain studies demonstrate elevated rates following hemithyroidectomy for benign disease (47%), and even higher rates (73%) for patients being treated via partial surgery in the setting of small, non-aggressive differentiated thyroid cancers (DTCs), given the goal of low-normal TSH levels in these patients (14). Increased rates of hypothyroidism and need for thyroid hormone replacement have also been demonstrated in patients with higher preoperative TSH levels, anti-TPO antibodies, and smaller thyroid volume or glandular heterogeneity (14-16).

Nuances in thyroid hormone replacement therapy

Normalization of serum TSH most often correlates with symptomatic improvement for patients being treated with LT4 for hypothyroidism. Yet, a small subset of patients experiences persistent symptoms along the spectrum of symptomatic hypothyroidism despite being deemed biochemically euthyroid, highlighting the nuance and challenge of managing this condition (5,10). It is not entirely clear why this discrepancy exists for some patients. True allergy to LT4 is rare and may be related to color additives, as the synthetic version of thyroid hormone is a precise biochemical replica of our native form (10). Reported intolerance to LT4 is thus often difficult to classify and navigating toward symptomatic improvement in patients with normal TSH values on monotherapy poses challenges to treating providers, with a potential impact on QoL in patients as well.

Some studies suggest that the presence of TPO antibodies in otherwise euthyroid patients may be associated with more symptoms and mood issues, chronic fatigue and overall poorer QoL compared to euthyroid patients without thyroid autoimmunity (5,10,17,18). However, thyroid dysfunction appears to be disproportionately diagnosed in patients with psychological distress, despite no clear associated between TSH and General Health Questionnaire-12 (GHQ-12) scores. There is also evidence to suggest that postoperative patients with a residual thyroid lobe may exhibit better QoL, specifically less chronic fatigue, than those treated with total thyroidectomy, despite the need for thyroid hormone replacement therapy (14). These findings are important to continually assess as our

surgical landscape evolves to include higher adoption of partial surgery for well-behaved DTC and are crucial to include in the risk benefit analysis and discussion regarding associated treatment options (15).

Guidelines from professional societies largely agree that levothyroxine should be standard of care for most individuals with hypothyroidism, irrespective of the cause. However, recognition that a subset of patients remain symptomatic on levothyroxine monotherapy has been variably acknowledged, and there has been disagreement on whether thyroid gland extract or combination levothyroxine and liothyronine should be recommended on a trial basis. Several guidelines emphasize the importance of optimizing levothyroxine dose in patients with residual symptoms, and in excluding diagnoses other than hypothyroidism that can cause non-specific symptoms, such as concomitant autoimmune disease, iron deficiency, menopause, etc. A recent consensus document authored by the ATA, European Thyroid Association (ETA), and British Thyroid Association (BTA), summarized the controversy surrounding levothyroxine and liothyronine combination therapy, including a summary of prior clinical trials and suggestions for future studies, a review of patient-reported outcomes, QoL metrics, and discussion of patient satisfaction, as well as a guide on "in whom" and "how" clinicians might prescribe "non-standard" therapy (5,19,20). However, all but monotherapy for treatment of hypothyroidism is considered innovative therapy, and it remains emphasized that other treatment approaches should be continually studied for treatment effect and safety. It bears mention that treatment with thyroid hormone replacement is explicitly not recommended in patients who are biochemically euthyroid, given the lack of benefit in symptoms, coupled with risks of overtreatment and resultant thyrotoxicosis (5,10).

Assessing QoL in hypothyroidism following thyroidectomy

As in all areas of medical and surgical practice, regular assessment of patient experience and QoL as it relates to the treatment of post-thyroidectomy hypothyroidism is imperative. An early case-control study by Saravanan *et al.* in 2002 assessed wellness of patients on LT4 using the GHQ-12 and found that patients on thyroid hormone replacement therapy with normal TSH levels demonstrated "*significant differences in their psychological well-being compared to age- and sex-matched controls*" (21). This was one of the first studies to assess patient QoL as it relates to treatment for hypothyroidism, highlighting the importance of assessing more than objective outcome measures.

As mentioned, patients with HT, particularly those with severely elevated TPO antibodies (>1,000 IU/mL), represent a cohort of patients who may remain symptomatic despite medical therapy and normalization of serum biomarkers for hypothyroidism (22). Various studies have been undertaken to assess the role of T3 assessment and possible combination medical therapy in these patients, as well as for surgical candidacy. A prospective, open-label trial from Norway in 2019 randomized patients with HT and high TPO antibody titer and reported persistent symptoms despite biochemical euthyroidism to total thyroidectomy *vs.* medical management and demonstrated improved Short-Form-36 (SF-36) Health Survey scores in those who underwent surgery (23). The SF-36 Health Survey evaluates QoL measures including social functioning, pain scores, role-emotional and mental health on a 100-point scale. In a similar vein, a 2020 retrospective cohort study out of Stanford demonstrated postoperative QoL scores on par with a healthy control population in a small subset of patients undergoing thyroidectomy for refractory, non-compressive symptoms in the setting of HT (18). A similar study by Promberger *et al.* in 2014 had not demonstrated this benefit and concluded that surgery should be targeted only in patients with HT and compressive symptoms. Of course, the role of surgery here must be heavily scrutinized, as complications of surgery can certainly, independently depress QoL and are cited to be higher at baseline for patients with HT due to the possibility of challenging intraoperative dissection (17,18).

Patients with a diagnosis of DTC have also been the subject of recent QoL evaluation. DTC is generally associated with excellent long-term survival and low mortality rates, and as such, maximizing QoL in this patient population is essential. A 2020 cross-sectional study by Li *et al.* demonstrated significantly reduced QoL in patients with DTC compared to healthy controls, again per the validated SF-36 health survey. Health-related QoL (HRQOL) was further reduced in patients with one or more comorbid conditions, including diabetes, depression and hypertension, or in the setting of surgical complications (24). In parallel, studies assessing post-thyroidectomy QoL, such as a 2021 study by Luddy *et al.*, found significantly higher rates of asthenia, or chronic fatigue, in the postoperative population compared to patients undergoing thyroid lobectomy [42% after total thyroidectomy *vs.* 4% after thyroid lobectomy, with an odds ratio 10.4; 95% confidence interval (CI), 3.86–28.16], including significantly higher

Table 2 Summary of QoL studies in thyroidectomy patients

Author	Year	No. of patients, gender	Disease process	QoL metric	Main findings
Ott *et al.*	2011	426, female	Benign and malignant nodules	SF-36	In women undergoing thyroid surgery for benign conditions, patients with histologic identification of HT and high TPO-antibody load had poorer QoL despite being biochemically euthyroid
Promberger *et al.*	2014	248, female	HT, benign nodules	SF-36	In women with benign euthyroid goiter, thyroid surgery does not lead to an overall improvement in HRQOL. Patients with histologically confirmed HT might benefit in terms of QoL
Guldvog *et al.*	2019	150	HT	SF-36	Patients with high TPO antibody titer and reported persistent symptoms despite biochemical euthyroidism randomized to total thyroidectomy demonstrated improved SF-36 Health Survey scores compared to those patients medically managed
Thatipamala *et al.*	2022	19	HT	SF-36	Postoperative QoL scores were on par with a healthy control population in a small subset of patients undergoing thyroidectomy for refractory, non-compressive symptoms in the setting of HT
Bongers *et al.*	2020	270	Low risk DTC	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire 3.0, supplementary Thyroid Cancer specific questionnaire module version 2.0, ASC questionnaires	Long-term QoL was not significantly different between low-risk DTC patients treated with total thyroidectomy compared with hemithyroidectomy
Luddy *et al.*	2021	182	Benign and malignant nodules	SF-36, BFI	Significantly higher rates of asthenia, or chronic fatigue, found in the total thyroidectomy postoperative population compared to patients undergoing thyroid lobectomy, with significantly higher rates of fatigue in patients with malignant diagnoses
Chen *et al.*	2022	1,060	Low or intermediate risk DTC	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire 3.0, Hospital Anxiety and Depression Scale, THYCA-QoL	Results of this study suggest that HRQOL of patients with DTC with low to intermediate risk of recurrence is not associated with the extent of surgery
Lan *et al.*	2021	69	PTMC	SF-36, THYCA-QoL	In patients with PTMC, thyroid lobectomy offers an advantage over total thyroidectomy in terms of HRQOL

QoL, quality of life; SF-36, Short Form-36; HT, Hashimoto's thyroiditis; TPO, thyroid peroxidase; HRQOL, health-related quality of life; DTC, differentiated thyroid cancer; ASC, Assessment of Survivor Concerns; BFI, Brief Fatigue Inventory; THYCA-QoL, Thyroid Cancer Quality of Life; PTMC, papillary thyroid microcarcinoma.

rates of fatigue in patients with malignant diagnoses. Interestingly, there was no correlation detected between degree of asthenia and hypothyroidism (25). Another 2022 study by Chen *et al.* identified significantly with poorer HRQOL in the total thyroidectomy cohort at 1 and 3 months in patients with low and intermediate risk DTC compared to those undergoing partial surgery, although all quality-of-life measures did appear to equilibrate by the 6- and 12-month postoperative assessments (26,27). Still, other studies have shown no difference in QoL in patients with DTC based on total or partial thyroidectomy status (28) (*Table 2*).

In sum, the relationship between decreased post-thyroidectomy QoL and hypothyroidism, TSH level, or thyroid autoimmunity is complex, and not yet clearly elucidated. Importantly, as our surgical landscape evolves to accept more conservative treatment for low-risk DTC, it is crucial to continually reweigh the risks and benefits of various treatment options, including any shifts in QoL for patients between various management approaches.

Novel strategies in LT4 management immediately following thyroidectomy

With a wealth of study and information regarding the impact of thyroid surgery and associated hypothyroidism on patient QoL, providers may turn their attention to proactive, preventive strategies: what action can we take to improve QoL for patients with post-operative hypothyroidism? Further study is certainly warranted, in order to better clarify what aspects of this disease and treatment are most impactful on patient QoL. An area of interest and possible clinical practice is the role of proactive initiation of low dose LT4 in patients following hemithyroidectomy and pending completion surgery. The prior practice of utilizing thyroxine suppression to shrink or stabilize benign thyroid nodules is mostly defunct, due to clear evidence of effect failure as well as risk of ill effects of long-term TSH suppression (29). However, the role of earlier initiation of LT4 when iatrogenic hypothyroidism is looming, namely in the setting of pending completion surgery, may warrant further consideration. Recent, small studies have also investigated novel schema for determining LT4 dosing following total or completion thyroidectomy, suggesting that the incorporation of multiple, clinical factors in addition to standard weight-based algorithm for initial LT4 dose may contribute to more accurate dosing and less overdosing in the post-surgical patient cohort (30). Whether these varied approaches translate to improved QoL in our patients is yet to be determined. Of course, these studies will also require synthesis and broader comparison to more concretely advance our understanding of any strategies that deviate from our current, sound treatment guidelines for post-operative hypothyroidism.

Conclusions

Primary hypothyroidism in the post-operative setting poses challenging and multi-faceted issues with management. Consideration of and sensitivity to patient experience and QoL remain crucial elements of a well-rounded treatment strategy, particularly as related to patients with complex conditions such as HT and DTC. The role of innovative therapy for the most challenging clinical scenarios needs to be further elucidated, such that medical and surgical providers alike may optimize treatment options and quality outcomes for our patients.

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Footnote

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