

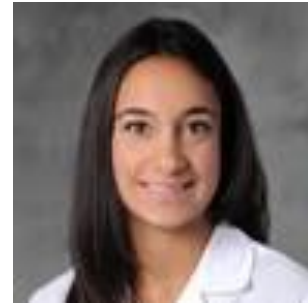
Endocrine Surgery Review

Thyroidectomy Versus Medical Management for Euthyroid Patients with Hashimoto Disease and Persisting Symptoms: A Randomized Trial

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In Brief

Traditionally, surgical therapy for Hashimoto's disease (HD) has been reserved for patients who have findings suspicious for thyroid cancer or in patients exhibiting neck pain or compressive symptoms.^{1,2} However, a subset of patients with HD who achieve a euthyroid state with medical management have persistent symptoms. This has been hypothesized to be secondary to the autoimmune response to antigenic thyroid tissue, and can be quantified using anti-TPO levels.³ The present study, the Norwegian Trial on Surgery for Hashimoto's Disease, sought to compare outcomes of total thyroidectomy plus standard medical therapy with standard medical therapy alone.³ Patients were included in the trial if they had HD, were medically fit for surgery, over the age of 18, and could consent to participation. Lab criteria for inclusion consisted of serum anti-TPO antibody level >1000 IU/mL (normal <100 IU/mL) and serum TSH >3.5 mIU/L (normal range 0.2-3.5 mIU/L) prior to medical therapy.

The study enrolled 150 patients who were then randomized to receive medical therapy alone (control group) or medical therapy plus operative management. The patients who underwent medical therapy alone received levothyroxine to achieve a euthyroid state before collecting data. Every third month, patients were seen and TSH, fT4, and fT3 levels were drawn, with medications subsequently adjusted to maintain a euthyroid state (defined as TSH, fT3, and fT4 within normal range and the absence of hyper- or hypothyroid symptoms). The surgical group underwent total thyroidectomy. Patient reported outcome measures (PROMs) were recorded at baseline, 6, 12, and 18 months. Measures included the Short Form-36 Health Survey (SF-36) and the Fatigue Questionnaire. Surgical complications were tracked at follow-up visits.

Outcomes

Patients who underwent total thyroidectomy had an improvement in SF-36 survey scores, with an increase in mean score from 38 at baseline to 64 at 18 months (increase of 26 points with 95% CI, 21 to 31 points). Decreased mean SF-36 scores were observed (from 38 to 35 at 18 months decrease of 3 points with 95% CI, -8 to 2 points) in patients who underwent medical therapy alone. Compared to the control group, patients who underwent thyroidectomy reported significantly higher mean SF-36 scores at both 6 (57 points versus 37 points, $p < 0.001$) and 18 months (64 points versus 35 points, $p < 0.001$).

At 18 months, the mean total fatigue score decreased from 23 to 14 points (decrease of 9 points with 95% CI, 7 to 10 points) in the surgery group but remained unchanged in the control group (23 to 24 points with CI, -1 to 2 points). Additionally, the proportion of patients reporting chronic fatigue decreased in the surgery group (82% to 35%), while there was no significant change in the control group (84% at baseline to 74% at 18 months). The mean difference in

patients reporting fatigue between groups was statistically significant at 39 percentage points ($p < 0.001$).

Median levels of anti-TPO antibodies in the surgical group decreased to near-normal levels by 18 months post-operatively (median of 152 IU/mL at 18 months from 2232 IU/ml at baseline), while it remained elevated in the control group (median of 1300 IU/mL at 18 months from 2052 IU/mL at baseline). The estimated difference in the means between the groups was 1148 IU/mL (CI, 1080 to 1304 IU/mL).

Thyroidectomy resulted in a surgical infection in three (4.1%) of patients, long-standing hypocalcemia which required calcium and vitamin D supplementation for over a year in three patients (4.1%), and permanent unilateral recurrent laryngeal nerve palsy in four (5.5%) of patients.

The authors conclude that the improvement in SF-36 score and fatigue symptoms in the surgery group is related to the near normalization of anti-TPO antibodies. They do address that there may be a placebo effect in these patients, but note this effect is believed to diminish after six months.

Critique and Future Directions

This study suggests that traditional medical management of HD may be inadequate for symptomatic control in a subset of patients. The authors acknowledge that the results of this study may be due to placebo effect despite persistent improvement at 18 months, calling for longer-term follow-up at 5 and 10-years.

Thyroidectomy for HD has traditionally been performed for patients with compressive symptoms and with findings suspicious for thyroid cancer. Previous studies have demonstrated the improvement of compressive symptoms in patients with HD after thyroidectomy.⁴⁻⁶ However, the concern that the chronic inflammatory process associated with HD makes surgical dissection challenging and increases the risk of postoperative complications with thyroidectomy has tempered enthusiasm for surgical intervention. Previous retrospective reviews of surgical outcomes for thyroidectomy in HD demonstrated rates of permanent hypocalcemia from 0-1.2% and permanent recurrent laryngeal nerve palsy of 0-1.2%.^{7,8} Postoperative outcomes in the present study demonstrated a relatively high rate of complications, with wound infections in 4.1%, permanent hypocalcemia in 4.1%, and permanent recurrent laryngeal nerve palsy in 5.5%. The authors attribute previously low-reported rates to publication bias and under-reporting of complications, but may additionally be due to the small sample-size ($n=73$) in the surgical group. Further large-scale evaluation of postoperative complication rates for thyroidectomy in HD is warranted to determine the true risk of thyroidectomy in Hashimoto's disease and to further define the relationship between thyroidectomy and reduction of anti-TPO levels. The present study performed thyroidectomy in patients with anti-TPO levels >1000 , but additional studies are necessary to determine the optimal threshold at which patients derive benefit without excess risk of complications.

Lastly, HD occurs with an additional concomitant autoimmune disease in about 14% of cases, which may confound results in broadly-applied quality of life measures.⁹ Accounting for the presence of additional autoimmune processes with subgroup analysis may aid in delineating which patients would benefit from thyroidectomy in the long-term. Additionally, utilization of a specific thyroid-related quality of life instrument would strengthen the claim that the normalization of anti-TPO antibody after thyroidectomy results in improvement of quality of life for patients with Hashimoto's disease.

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