Effect of thyroidectomy on thyroid eye disease in patients with Grave's disease

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Aims: To compare the effectiveness of thyroidectomy to other forms of treatment in treating Grave's ophthalmopathy patients' ocular manifestations.

Methods: In this research conducted at Alexandria University Hospital, Faculty of Medicine, Alexandria University, fifty patients have been selected (between January 2020 and December 2020) to undergo thyroidectomy to treat their thyroid-associated eye condition. The surgical procedures performed included total thyroidectomy in 35 patients (70%), 7 patients (14%) underwent Dunhill procedures including complete lobectomy and subtotal resection of the opposite lobe, and subtotal thyroidectomy in 8 patients (16%).

Results: Preoperative thyroid stimulating hormone receptor antibody (TRAb) levels showed frequent markedly elevation (>2 IU/L). Following surgery, TRAb levels in 33 individuals returned to normal(1 IU/L – absent; p: 0.001). Significant statistical difference was found between groups. The ophthalmopathy index decreased statistically significantly from 6.1±2.32 before treatment to 3.31±2.09 after surgery (p: 0.001), indicating that the index's value were successfully reduced across the board in the group under investigation. The degree of the surgery's impact on postoperative complications is provided.

Conclusions: According to this study, surgery helps patients with Graves' illness by lowering their TRAb levels and alleviating their ocular symptoms. To better understand the long-term consequences of thyroidectomy and to develop treatment plans that will increase visual improvement and reduce problems, further investigation and long-term studies are required.

Keywords: Graves's Disease; Thyroid Eye Disease; Thyroidectomy; Grave's ophthalmopathy

INTRODUCTION

The most common Graves' disease (GD) non-thyroidal consequence is thyroid eye disease (TED). With a reported incidence of 16/100,000 women and 2.9/100,000 males and calculated prevalence of 0.25%. TED is an autoimmune disorder. The immunological reactions between lymphocytes and cells that express the thyroid-stimulating hormone (TSH) are what cause the non-thyroidal symptoms of GD. (1) Female gender and cigarette smoking are the two primary risk factors for Thyroid Eye Disease (TED) in people with Graves' disease (GD). TED is 2.5 times more likely to affect women than men, which is consistent with the higher prevalence of autoimmune illnesses in females. (2) Initially, TED was associated exclusively with the Graves' triad, which includes hyperthyroidism, pretibial myxedema, and eye disease. Recently, though, TED has been observed in people with Hashimoto's thyroiditis and even in those who don't have any thyroid abnormalities. Even though TED symptoms frequently include both eyes, they frequently exhibit asymmetry. Swelling around the eyes and in the surrounding areas, raised eyelids, delayed eyelid movement during downward gaze, restricted eye movement due to muscle stiffness, optic nerve compression, and corneal damage resulting in symptoms like eye irritation and dryness are the most typical early warning signs of TED. (3)

The severity of TED is typically assessed based on overall evaluation using parameters such as proptosis (bulging of the eyes), diplopia (double vision), and optic neuropathy (damage to the optic nerve). However, individual parameters may not necessarily indicate severe disease. TED activity, on the other hand, relates to the disease's progression and regressive stages, where it passes through an active period, a partly regressive phase, and a static, inactive phase. It is essential to remember that TED activity does not necessarily correspond to TED severity, since a patient may still experience severe residual ocular symptoms even when the condition is dormant. (3) A protein called the thyroid stimulating hormone receptor (TSHR) is present in immune cells, fat cells, and thyroid cells. Levels of TSHR antibodies are correlated with the degree and activity of TED. The tissues surrounding the eyes and thyroid are invaded by special cells called fibrocytes which originate from the bone marrow. These fibrocytes express TSHR and are more prevalent in TED patients than in healthy people, pointing to a role for TSHR in the development of TED. (5,6) The relationship between thyroid medication and TED is not fully understood. Although some research has suggested that having greater amounts of T3 hormone may raise the chance of the beginning or progression of TED, the results have been contradictory. On the other hand, evidence indicates that the presence of hypothyroidism (low thyroid function) and increased TSH levels are linked with TED regardless of the kind of medication used. (5,6) The fundamental objective of treating TED patients is to restore normal thyroid function since severe TED is associated with abnormal thyroid function. To safely restore normal thyroid function without making TED worse, the best method for treating hyperthyroidism is yet unknown. Antithyroid medications (ATDs), radioactive iodine (RAI), and surgical thyroid removal are the most used forms of therapy (7)

In the current study, our focus is on testing the effect of thyroidectomy, which involves the surgical removal of the thyroid gland, on TED. This differs from the surgical treatment of TED, as thyroidectomy aims to address the underlying thyroid dysfunction that may contribute to the development or progression of TED. (8)

AIM OF THE WORK

We aim to compare the effectiveness of thyroidectomy to other forms of treatment in treating Grave's ophthalmopathy patients' ocular manifestations.

MATERIAL & METHODS

1. Study Design

In a retrospective cohort analysis, a total of 50 Graves' disease patients received surgical management between January 2020 and December 2020. Ethical approval has been obtained from the Alexandria Faculty of Medicine Institutional Review Board.

2. Patients Criteria

Patients who were eligible for surgical therapy and had Graves' disease symptoms along with ocular symptoms of varying degrees of severity received conservative care. This involves administering thyreostatic medications, beta-blockers, and steroids while carefully observing their clinical state and laboratory findings.

3. Preoperative Assessment

Additionally, all patients with Graves' illness got two doses of 10 drops each of 5% Lugol's iodine for 14 days (about 2 weeks) before the planned surgery. The purpose of these preparations was to ensure the patients were in a balanced state, both clinically and biochemically, prior to the operation. This approach is commonly followed as a standard procedure before surgery.

4. Indications for surgery

Severe and moderate orbitopathy with concurrent goiter, large goiters that cause compression-related symptoms, when located retrosternally or in the mediastinum, recurrent hyperthyroidism after thyreostatic therapy, and cosmetic complains. It should be underlined that for a specific patient, the reasons for surgery may have been represented by two or more criteria.

5. Ocular Evaluation

Due to the patients' ocular symptoms, such as swelling and inflammation of the eyelids and conjunctiva, limited eye movement causing double vision, reduced vision clarity, and bulging of the eyeballs beyond the eye sockets (exophthalmos), which could potentially damage the cornea, all patients underwent thorough eye examinations and assessments. These assessments involved evaluating the extent of symptoms, including eyelid retraction, condition of the tissues around the eyes, mobility of the eye muscles, transparency of the cornea and lens, visual clarity, to estimate the degree of ocular protrusion we used Hertl's exophthalmometer, through the Donaldson-developed ophthalmopathy index and the NO SPECS classification, the disease's severity was assessed. Prior to starting therapy as well as three, six, and twelve months after having a thyroidectomy, ocular symptoms were evaluated. (9,10)

6. Follow-Up

All patients had their TSH, free T4, and thyroid stimulating hormone receptor antibody (TRAb) measured both before and 12 months after surgery. Radioimmunoassay was used in the current experiments to measure TRAb levels. All the patients had pre- and postoperative indirect laryngoscopy for laryngological evaluation, and their postoperative calcium levels were assessed. Following hospitalization, tests included ophthalmologic evaluation, blood calcium levels, antithyroid antibody TRAb, TSH, and free T4 readings.

7. Statistical Data Analysis

Data Analysis will be done using SPSS ® software version 28.0.1. Statistical data analysis will be done using mean, SD, median, IQR, frequency, percentage, and proportion with a 95% Confidence interval and using various statistical tests such as the Chi-Square test, t-test, and ANOVA.

RESULTS

Each of the 50 patients received surgical care. Total thyroidectomies were done in 35 individuals (or 70%), Dunhill surgeries in 7 patients (14%), and subtotal thyroidectomies in 8 patients (16%). All 50 patients had their levels of TRAb checked before surgery, and 44 (88%) of them had their postoperative measures obtained. A specific group's TRAb findings analysis supported the diagnosis of Graves' illness. Prior to surgery, a sizable proportion of patients in this research exhibited high

TRAb levels (>2 IU/L). As a result of the whole group's altered TRAb levels, the ophthalmopathy index decreased statistically significantly from 6.1±2.32 before treatment to 3.31±2.09 after the surgery ($p<0.001$, t-test), showing improvement in ocular manifestations. The relationship between the extent of surgery and postoperative complications was investigated. The study examined how the overall eye condition, as evaluated by the ophthalmopathy index and confirmed by ophthalmologists, worsened in 5 patients. Three patients also expressed subjective concerns about eyesight decline. Postoperative ocular complications were noted. These included exophthalmos in 18 cases (36%), conjunctival injection In 9 cases (18%), restrictive squint in 14 cases (28%), and upper eyelid lag in 9 cases (18%).

Table (1): Preoperative, Indication and Opthalamogical Index

Preoperative Management	
Beta-blocker (propranolol) and antithyroid medicines (thiamazole, propylthiouracil)	40 (100%)
Beta-blockers (propranolol) and antithyroid drugs (thiamazole and propylthiouracil) combined with steroids (methylprednisolone)	7 (14%)
Antithyroid medications (thiamazole, propylthiouracil)	3 (6%)
Indication for surgical treatment	
Large goiter (weighing more than 250 g) with compression symptoms retrosternal mediastinal	9 (18%) 8 1
Recurrent hyperthyroidism after thyreostatic medication therapy (surgery in euthyreotic individuals)	11 (22%)
Thyroid enlargement with orbitopathy, including severe (ophthalmopathy > 9) and intermediate (ophthalmopathy >4 to £ 8) cases.	27 (54%) 7 20
Cosmetic considerations	3 (6%)
Ophthalmology Index	
Group (1) o.I >9	9 (18%)
Group (2) o.I > 4 / < or = 8	38 (76%)
Group (3) < or = 3	3 (6%)

Table (2): Postoperative Outcome

TRAb Levels		**Preoperative**	**Postoperative**	
Group (1)				
> 2 IU/L Present		33 (66%)		
1-2 IU/L Doubtful		2	8	
< 1 IU/L Absent			28	
Group (2)				
> 2 IU/L Present		6 (12%)		
[1:2] IU/L Doubtful		1	4	
< 1 IU/L Absent			5	
Group (3)				
> 2 IU/L Present		6 (12%)	1	
[1:2] IU/L Doubtful		2	6	
< 1 IU/L Absent			5	
Exophthalmos Intensity Changes				
Group (1) o.I >9	[9 (18%)]	10.70	5.85	
Group (2) o.I > 4 / < or = 8	[38 (76%)]	5.80	2.90	
Group (3) < or = 3	[4 (6%)]	3	2	
Ophthalmopathy Index				
Group (1)		6.50	3.50	> 0.631
Group (2)		4.90	2.50	> 0.510
Group (3)		5.70	2.70	< 0.001

Table (3): Postoperative Complication

	Patients	Group1	Group2	Group3
Laryngeal nerve palsy that is bilaterally recurrent Transient Fixed	2 (4%)	2 (4%)		
Recurrent Laryngeal Nerve Palsy on One Side Transient Fixed	5 (10%)	3 (6%)	1 (2%)	1 (2%)
Hypocalcemia Fixed Bleeding	4 (8%) 1 (2%)	4 (8%) 1 (2%)		
Exophthalmos	18 (36%)	14 (28%)	3(6%)	1 (2%)
Conjunctival injection Moderate Marked	7 (14%) 2 (4%)	5 (10%) 2 (4%)	1 (2%)	1 (2%)
Restrictive squint	14 (28%)	10 (20%)	3 (6%)	1 (2%)
Upper eyelid lag	9 (18%)	4 (8%)	2 (4%)	3 (6%)

DISCUSSION

The development of autoimmune illnesses, such as Graves' disease, is known to be significantly influenced by antigen-presenting cells [7]. The ideal course of treatment for individuals with Graves' disease, particularly those showing high TRAb levels and concomitant compression symptoms, is complete thyroidectomy, which is supported by the outcomes of our study and is based on this concept. In line with Lewirski et al. (11), a substantial elevation of antireceptor TSH-R antibodies at the time of hyperthyroidism diagnosis, which persists throughout thyreostatics and radioiodine therapy, indicates the necessity of considering an alternative, more radical treatment approach. Moreover, according to Marcocci et al. (12), the majority of patients who get surgical intervention had a considerable decrease in TRAb levels. However, there is yet no conclusive link between antibody titer and surgical extent. We did not uncover any instances of recurrent hyperthyroidism, independent of the surgical treatment strategy used, when we compared the results of our investigation to the existing literature. It is generally acknowledged that a rise in antibody titer following surgery is a bad prognostic sign for recurrent hyperthyroidism. This rise may be explained by the existence of remaining glandular tissue, which is immunologically active. This can induce or affect the autoimmune process, develop a recurrent goiter after resection, and cause greater exophthalmos. An improvement in ocular state was achieved by the thyroid tissue being removed, as shown by the statistically significant drop in the ophthalmopathy index for the entire study group after the procedure ($p < 0.001$, t-test). Patients who received complete thyroidectomies showed

more dramatic effects and statistically significant differences. In a randomized control study conducted by allstedt et al. (14), the ophthalmopathy improvement according to the extent of resection was not statistically significant. Weetman (15) on the other hand noted a decrease in the state of the eyes in individuals who had subtotal thyroidectomies. Regardless of the results, it is crucial to remember that thyroid disorders can significantly affect the condition of the eyes. This is because the TSH receptor is active regardless of whether a person has hyperthyroidism or hypothyroidism. Increased surface antigen expression and autoimmune responses are caused by this activation. According to Michelangeli et al. (16), this activation is caused by the thyreotropic impact of TSH itself in hypothyroidism and by anti-receptor antibodies (anti-TSHR) in hyperthyroidism. In the randomized study conducted by Janowska et al. (17), as well as in other studies by Winsa et al. (8), Perzik (18), and Mori et al. (19). Patients who underwent thyroid resection (16%) and those who got RAI (33%), respectively, experienced the advancement of ophthalmopathy. Our findings of notable postoperative ocular complications are in line with these reports. The increase happened in patients who did not get postoperative thyroxin replacement treatment or regular steroid hormone therapy. No correlation between the levels of TRAb antibodies and the severity of ocular manifestations was found in this study. This conclusion is consistent with those made by Aizwa et al. (20), who likewise noted no relationship between the amount of TRAb antibody and the severity of ocular symptoms. Among the postoperative complications observed in this study, one patient had bilateral transient recurrent laryngeal nerve palsy, whereas five other patients had unilateral transitory palsy. Four people showed signs of hypocalcemia, and one woman needed further surgery because of bleeding. These results agree with the data from previous literature. It is essential to note that both postoperative hypothyroidism and recurrent laryngeal nerve palsy were of a temporary character in our dataset, and their occurrence did not differ from that which has been documented in the literature.

CONCLUSION

According to the study, surgery helps patients with Graves' illness by lowering their TRAb levels and alleviating their ocular symptoms. To better understand the long-term consequences of thyroidectomy and to develop treatment plans that will increase visual improvement and reduce problems, further investigation and long-term studies are required.

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