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SUBTOTAL THYROIDECTOMY AND CERVICAL BLOCK DISSECTION: ITS EFFECT ON GRAVES' OPHTHALMOPATHY AND THYROID FUNCTION

By
Mosaad Soliman M.D
Mansoura University Hospital, Department of Surgery # 6
Mansoura, Egypt.

The thyroid gland and or cervical lymph nodes have been implicated as the major source of synthesis and secretion of TSAb responsible for the hyperthyroidism of Graves' disease (GD). Although an immunogenic pathogenesis of Graves' ophthalmopathy (GO) has been proposed, the actual mechanisms of retrobulbar involvement are not well defined. To determine whether cervical lymph nodes might have a role in the development of GO and whether these nodes participate in the activation of thyroid tissue remnant following subtotal thyroidectomy and hence recurrence of hyperthyroidism, we examined the effect of cervical lymphadenectomy on GO and thyroid function after subtotal thyroidectomy. A series of 30 patients who had GD with varying degrees of GO were included in this study. Subtotal thyroidectomy and excision of cervical lymph nodes as well as lymphatic trunks was carried out in 15 patients (group A). While subtotal thyroidectomy alone was done in the other 15 patients (group B). Exophthalmometry, TSAb level and magnetic resonance imaging (MRI) of the orbit were done before surgery and also 1 month, 6 months and yearly for 3 years thereafter. There was a statistically significant reduction in exophthalmometric measures, 6 months postoperatively in group A compared to group B. There was a further reduction at 1 year and was the same at subsequent periods. One month after surgery, TSAb levels decreased significantly in group A compared to group B. A further decrease of TSAb levels was observed at 6 months and almost normalized at 1 year in group A. Six months after surgery, TASb levels in group B were higher than those in group A, but still lower than the values before surgery. MRI of the orbit in the presurgical period showed extraocular muscle enlargement of all patients with GD even those with no clinical ophthalmopathy. Six months postoperatively, there was a significant reduction in extraocular muscle thickness as well as the individual muscle/optic nerve ratio in group A compared to group B. There was a further reduction at 1 year and remained unchanged thereafter. Recurrence of hyperthyroidism was observed in one patient of group B, 3 years after surgery but in none of group A. A larger size of lymphatic trunks and greater number of lymph nodes was excised from the side of the neck corresponding to higher grade of exophthalmopathy. Conclusions (1) The observed improvement of exophthalmos following cervical lymph node dissection, implies the potential role of these nodes in the initiation of retrobulbar immunological process responsible for GO. Support for this observation comes from the fact that the side with greater exophthalmos had a larger number of lymph nodes and lymphatic trunks in the neck than on the contralateral side. (2) The significant reduction of TSAb level following lymph node dissection points to these nodes as a major source of TSAb which when reaches a pathological level in the circulation it could lead to recurrence of hyperthyroidism. (3) Subtotal thyroidectomy and cervical lymphadenctomy seems to be a logic alternative to the standard thyroidectomy in concern of its ameliorating effect on GO, moreover, it can be used to prevent progression of the process in patients without clinical evidence of GO (4) This operation could be used to prevent the recurrence of hyperthyroidism especially in patients with high preoperative TSAb titer.

Keywords: Thyroidectomy, block dissection, Graves' & Thyroid Function.

INTRODUCTION

Graves' ophthalmopathy (GO) refers to the inflammatory response and its sequlae in and around the orbit in association with autoimmune thyroid disease [1]. GO and Graves' disease (GD) are closely related entities of autoimmune origin [2]. However, distinct process of initiation has been proposed [3]. Clinically evident ophthalmopathy occurs in 40% to 50% of patients with GD [4]. It is now generally accepted that GD results from the stimulation of the thyrotropin receptor (TSHR) on thyroid follicular cells by thyrotropin receptor antibodies (TSHR-Ab) [5]. The pathogenesis of GO is still controversial [6]. Some suggested the possible involvement of humoral immunity in the pathogenesis of GO because sera from patients with GO contain autoantibodies directed against crude preparations of eye muscle and orbital connective tissue [7]. The relation between GO and TSHR-Ab remains only partially defined. Some studies have shown a higher prevalence of TSHR-Ab positivity in patients with GO than in patients without clinical evidence of eye involvement [1]. On the other hand cell- mediated mechanism has been postulated based on the observation that extraocular muscle tissue from patients with GO contains B- and T-lymphocytes and abnormal HLA-DR expression on the perimysial fibroblasts [8]. Kriss [9] proposed the attractive hypothesis that a communicating lymphatics transmit immune complexes from the thyroid gland to retroorbital tissue.

The sites of antithyroid antibody production have not been directly demonstrated, but evidence suggests that the target organ and cervical lymph nodes are major sites of antibody synthesis in GD [10,11]. Whether cervical lymph nodes might have a role in the development of GO via supplying active lymphocytes or immune mediators to the retroorbital tissue through intercommunicating lymphatics and whether these nodes contribute to the activation of thyroid tissue remnant following subtotal thyroidectomy is not certain. This issue is studied here by comparing the effect of cervical block dissection, added to subtotal thyroidectomy, with the standard subtotal thyroidectomy on GO and the function of remaining thyroid tissue in patients with GD.

SUBJECTS AND METHODS

A total of 30 untreated patients with Graves' disease referred to Mansoura University Hospital were studied prospectively for 3 years.

Initially all patients were given antithyroid drugs as a preoperative preparation for 2-4 weeks and were euthyroid at the time of operation.

The diagnosis of GD was made on the basis of clinical presentation plus laboratory findings of elevated free T4 index (FTI) and /or T3 levels, suppressed TSH, and positive antibody assays in the presence of normal or increased thyroid radioiodine uptake and diffuse goiter. Patients were divided into two groups. Groups A, 15 patients (mean age 25 ± 7 years; 10 females and 5 males) underwent subtotal thyroidectomy together with bilateral excision of cervical lymph nodes and lmphatic trunks. Group B, 15 patients (mean age 36 ± 15 years, 12 females and 3 males) underwent standard subtotal thyoidectomy.

Operative technique in group A.

Following the standard subtotal thyroidectomy, using Kocher skin incision, devascularization of the gland and resection of the appropriate part leaving 4-6 grams on each side. All lymph nodes immediately adjacent to the thyroid gland and medial to the carotid sheath should be removed. The internal jagular vein is retracted medially and lateral venular tributaries are stapled & divided. All the fibrofatty tissue in the lateral neck is removed between the clavicle & the spinal accessory nerve high in the neck. The extreme ends of the dissected trunk are ligated to avoid lymphorrhoea and care should be taken to avoid injury of the thoracic duct on the left side. The whole process is completed without extension of the original incision.

Magnetic Resonance lmaging:

MRI of the orbit was performed in the axial and coronal planes using a 1.5 Tesla MR unit (Philips Gyroscan S-15, Holland) with a 5 inch surface coil. Plus sequences were as follows: spin echo technique for T1 weighted axial image (TR/TE 500/20 msec), for proton density and T2 coronal weighted images (TR/TE 2000/20 and 80 msec). Section thickness was 3 mm. The thickness of the superior and inferior rectus muscles of each eye was estimated at the sites of their greatest enlargement using the coronal section of T1 weighted image. Thickness of medial and lateral recti was measured in the axial section of the T1 weighted image. The degree of maximal EOM enlargement was determined by computing for the ratio of the maximal thickness of each muscle over the diameter of the optic nerve to minimize the interindividual difference in muscle thickness. EOM volume was calculated from the sum of volume of the 4 recti in ml. Acomputed digitizer [12] was used to measure the volume of each rectus muscle from coronal images of serial cross sections of MRI.

Ocular assessment

ocular examination, performed by an opthalmologist, consisted of visual acuity, lids (hyperemia, edema, retraction, lid lag), conjunctiva (injection, chemosis), cornea (keratitis, ulceration), extraocular muscle motility and retinoscopy. Thy proptosis of both eyes was measured with Hertel exophthalmometer. GO was scored according to the NOSPECS classification of the American thyroid Association.

Serology

Serum microsomal antibody and thyroglobulin antibody were measured by the tanned red cell hemagglutination technique. Serum TSAb activity was measured by assaying cAMP released into the culture medium of Chinese hamster ovary cells expressing human TSHR, using RIA (Amershan, UK).

Statistical analysis

Statistical comparisons were made by student's t test and x^2 test.

RESULTS

Clinical findings at 12 months based on the ATA classification showed improvement in all orbits in group A. Orbits of nine patients were improved in group B, no change in 6 and there was no instance of deterioration. The degree of proptosis estimated by Hertel exophthalmometry showed significant improvement, 6 months postoperatively in group A compared to group B (P<0.001). There was a further reduction at 1 year and was the same at subsequent periods (Fig 1).

These results were the confirmed in individual patients (Fig 2) MRI of the orbit in the presurgical period revealed increased orbital fat and/or muscle thickness in all patients, even those without clinical signs of eye disease. Six months postoperatively, there was a significant reduction in extraocular muscle thickness as well as individual muscle/ optic nerve ratio in group A (Fig 3a,b,c) compared to group B. There was a further reduction at 1 year and remained unchanged thereafter. (Table 1) lists the patients, in both groups and the corresponding number of enlarged eye muscles, the hormonal and TSAb measurements at the time MRI was done. There was no correlation between the number of EOM enlarged and the level of thyroid hormone or TSAb present in the patients sera. Most patients had bilateral EOM enlargement (70%). The least commonly involved eye muscle were the superior rectus and the most commonly involved muscle showing various degrees of enlargement for both groups was the inferior rectus muscle.

Group A had a total eye muscle volume mean of 3.25 ml and range of 1.8-5.3 ml, and group B had a total eye muscle volume mean of 2.8 ml, volume range: 1.8-5.2 ml. There was a significant reduction in EOM volume, 1 year postoperatively in-group A compared to group B (Fig 4). One month after surgery TSAb levels decreased significantly in group A compared to group B and compared to the preoperative values of both groups. A further decrease of TSAb levels was observed at 6 months and almost normalized at 1 year in group A. Six months after surgery, TSAb levels in group B were higher than those in group A, but still lower than the values before surgery (Table 1). Cervical block dissection in patients with symetrical exophthalmos revealed lymphatic trunks of comparable size and held almost equal number of lymph nodes (fig 5, a.b) On the other hand, a larger size of lymphatic trunks and greater number of lymph udes was excised from the side of the neck corresponding to higher grade of exophthalmopathy (Fig 6 a.b). Recurrence of hyperthyoridism was observed in one patient of group B, 3 years after surgery but in none) of group A. Interestingly, this patient with recurrent thyrotoxicosis reoperated upon and showed enlargement of the left thyroid lobe remnant, the same side of larger lymphatic trunk & greater ophthalmopathy (Fig 7 a,b).

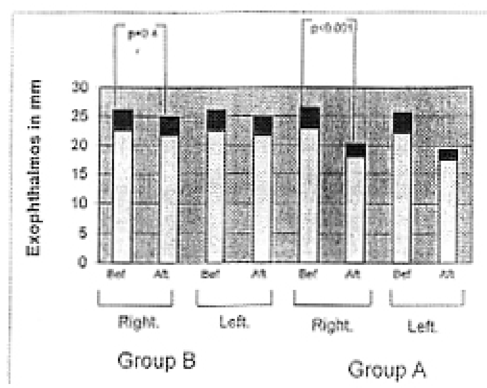


Fig.(1): The degree of proptosis estimated by Hertel exophthalmometer before and 6 months postoperatively

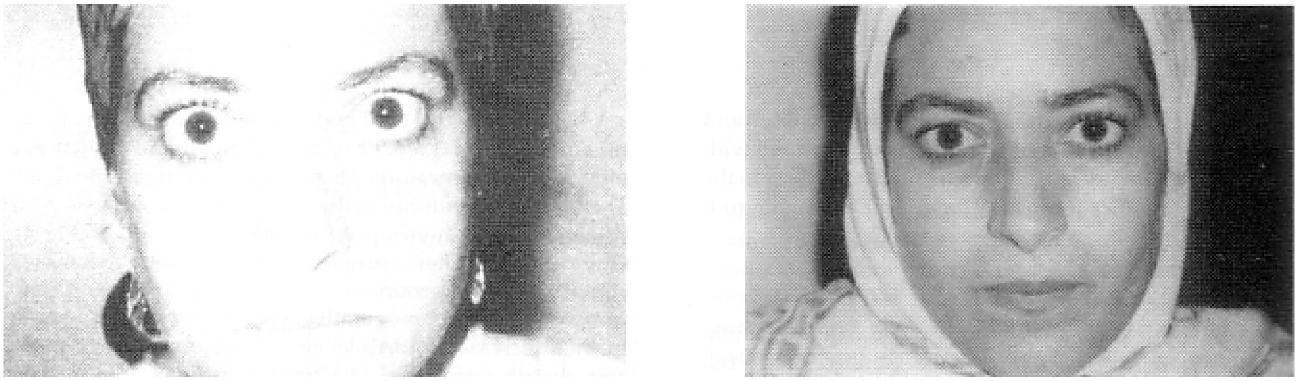
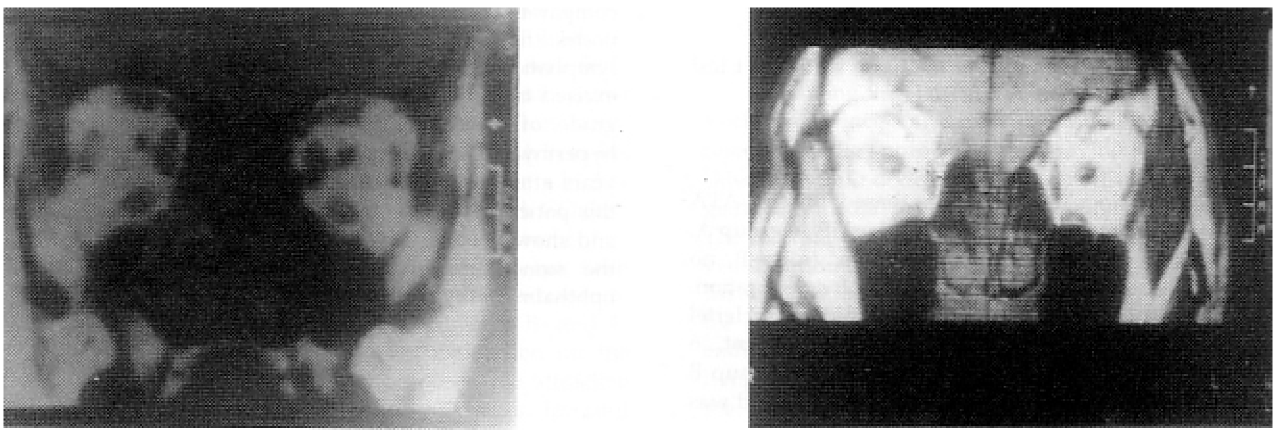


Fig. (2): Clinically evident proptosis before surgery and its amelioration after subtotal thyroidectomy & block dissection.



Before Surgery *Fig.(3a)* *After Surgery*

Before Surgery *Fig.(3b)* *After Surgery*

Before Surgery *Fig.(3c)* *After Surgery*

Fig.(3 a,b,c): MRI of the orbit in the presurgical period and 6 months postoperatively in coronal, sagittal and transverse planes. There was a significant reduction in extraocular muscle thickness and individual muscle/ optic nerve ratio in group A.

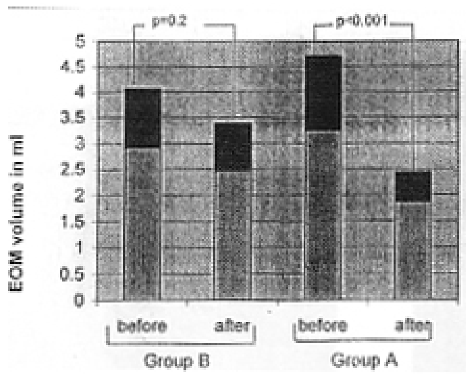
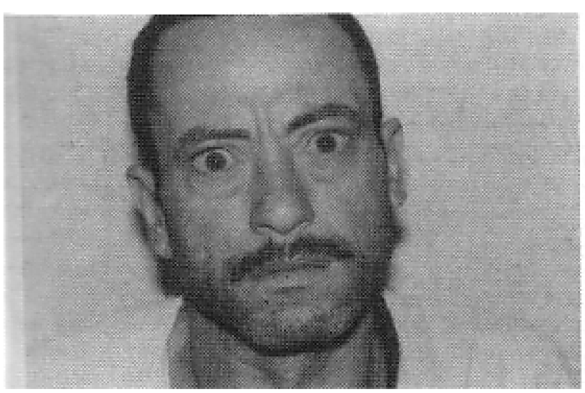


Fig.(4): The extraocular muscle volume in both groups before and after surgery are expressed as the mean of all patients in each group. There was a significant reduction in E O M Volume in group A following surgery but not in-group B.



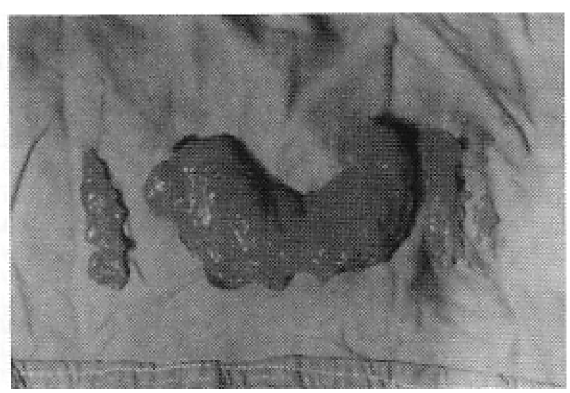


Fig.(5 a,b): Patients with symmetrical exophthalmos revealed lymphatic trunks of comparable size and almost equal number of lymph nodes

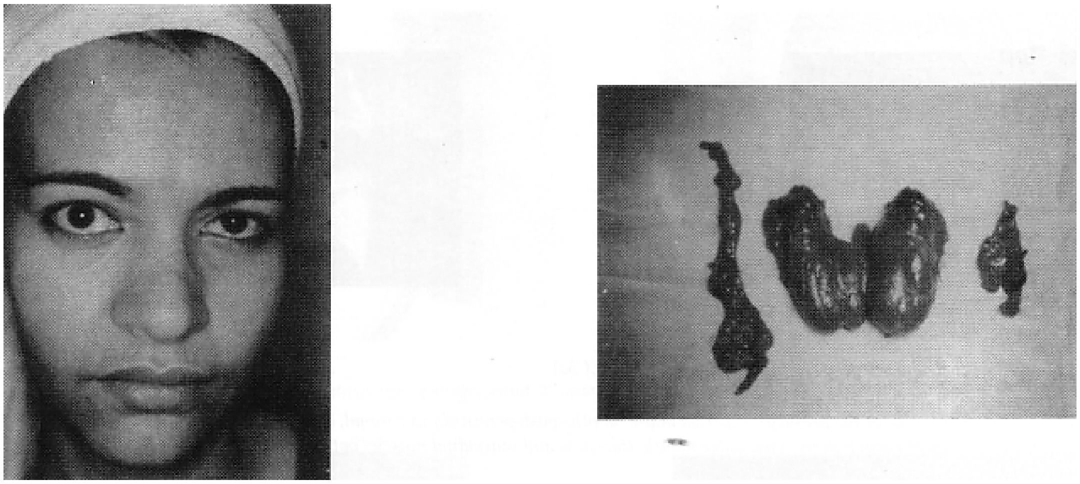


Fig.(6 a,b): Patents with asymmetrical exophthalmos had a larger size of lymphatic trunk and a greater number of lymph nodes on the side of the neck corresponding to higher grade of exophthalmopathy.

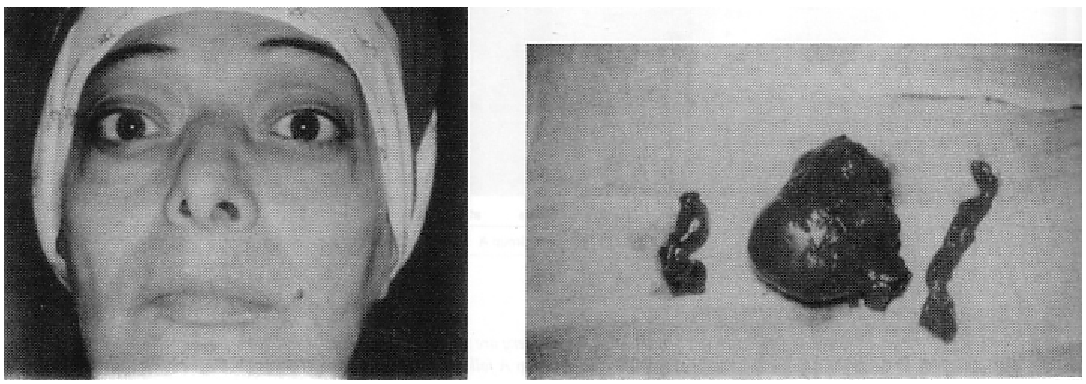


Fig.(7 a,b): Patient with recurrent hyperthyroidism in group B. Thyroidectomy and block dissection was done for this patient and revealed a larger size of lymphatic trunk on the side of greater exophthaloms.

Table (1) : *Levels of thyroid hormones, TSAb, number of enlarged extraocular muscles and degree of proposis in patients with GO before and after surgery.*
Group A

	T3		*T4*		***Exoph***				*TASb*		*No of EOM*			
					RT.		Lt.		Bef.	Aft.	RT.		Lt.	
	Bef.	Aft.	Bef.	Aft.	Bef.	Aft.	Bef.	Aft.			Bef.	Aft.	Bef.	Aft.
1.	3.9	1.6	21.6	7.2	23.0	21.0	23.0	20.0	282	178	4.0	3.0	3.0	2.0
2.	3.5	1.8	19.0	8.1	24.0	19.0	23.0	18.0	343	196	6.0	4.0	4.0	3.0
3.	3.8	0.75	18.0	5.4	26.0	14.0	24.0	19.0	238	156	2.0	2.0	2.0	1.0
4.	3.1	1.0	16.2	9.4	25.0	14.0	27.0	16.0	406	169	4.0	1.0	4.0	1.0
5.	1.8	1.6	25.5	7.2	22.0	18.0	21.0	16.0	613	207	0.0	0.0	1.0	0.0
6.	2.8	0.85	16.0	8.0	28.0	19.0	27.0	16.0	549	234	5.0	2.0	4.0	3.0
7.	3.0	0.9	17.0	7.3	24.0	17.0	24.0	17.0	497	149	3.0	3.0	5.0	2.0
8.	4.8	1.3	23.0	6.5	15.0	15.0	15.0	14.0	319	178	2.0	1.0	2.0	2.0
9.	3.3	0.8	22.0	5.8	18.0	18.0	18.0	16.0	563	271	1.0	0.0	1.0	1.0
10.	3.2	0.6	18.0	4.6	26.0	19.0	24.0	18.0	453	252	3.0	2.0	3.0	1.0
11.	1.9	0.7	8.5	5.2	24.0	21.0	25.0	21.0	417	219	4.0	2.0	3.0	2.0
12.	3.4	1.7	16.0	7.3	23.0	20.0	22.0	19.0	344	201	5.0	3.0	4.0	3.0
13.	2.7	0.93	12.1	8.0	18.0	18.0	18.0	17.0	394	163	1.0	1.0	1.0	0.0
14.	4.6	1.9	23.0	9.1	22.0	17.0	22.0	18.0	503	192	1.0	0.0	0.0	0.0
15.	3.2	1.1	15.2	6.0	16.0	20.0	20.0	16.0	283	167	2.0	1.0	3.0	1.0

Group B

	T3		*T4*		***Exoph***				*TASb*		*No of EOM*			
					RT.		Lt.		Bef.	Aft.	RT.		Lt.	
	Bef.	Aft.	Bef.	Aft.	Bef.	Aft.	Bef.	Aft.			Bef.	Aft.	Bef.	Aft.
1.	4.7	1.5	24.0	7.0	26.0	25.0	25.0	24.0	463	291	3.0	3.0	3.0	2.0
2.	3.2	0.9	23.0	6.1	23.0	23.0	22.0	22.0	516	319	5.0	3.0	4.0	3.0
3.	3.0	0.7	17.0	5.0	25.0	24.0	26.0	25.0	371	209	3.0	3.0	2.0	2.0
4.	2.0	0.6	8.0	4.1	24.0	23.0	24.0	22.0	284	203	3.0	2.0	2.0	2.0
5.	3.6	1.9	15.0	6.4	26.0	25.0	25.0	24.0	315	226	4.0	4.0	3.0	3.0
6.	3.9	2.1	16.0	8.1	15.0	15.0	15.0	15.0	378	198	1.0	0.0	2.0	2.0
7.	2.5	0.8	13.5	7.0	19.0	19.0	18.0	18.0	294	168	0.0	0.0	1.0	0.0
8.	3.9	2.0	19.0	5.6	27.0	26.0	26.0	24.0	641	482	2.0	1.0	2.0	2.0
9.	4.4	2.2	21.0	11.0	21.0	21.0	22.0	21.0	416	308	2.0	2.0	2.0	2.0
10.	3.6	1.4	20.0	6.5	25.0	24.0	26.0	25.0	236	173	3.0	1.0	3.0	2.0
11.	2.9	1.2	17.0	7.1	23.0	22.0	24.0	22.0	386	233	4.0	3.0	3.0	3.0
12.	3.4	0.5	18.0	6.0	17.0	17.0	18.0	18.0	477	309	1.0	0.0	1.0	0.0
13.	4.2	1.2	16.0	7.3	25.0	23.0	25.0	25.0	216	152	4.0	2.0	4.0	3.0
14.	1.9	1.5	17.0	4.2	22.0	19.0	23.0	22.0	541	177	3.0	2.0	2.0	2.0
15.	2.7	0.72	19.0	9.0	20.0	19.0	19.0	19.0	372	198	2.0	1.0	1.0	0.0

normal range of T3 = 0.75 – 2.00
normal range of T4 = 4.6 – 11.7
normal range of TSAb = 65 – 130
No. of EOM = number of enlarged extraocular muscles.
Exoph = degree of exophthalmos measured by Hertel exophthalmometer
Rt = right
Lt = left
Bef = before surgery
Aft = after surgery

DISCUSSION

Although the features of GO generally improves with the treatment of thyrotoxicosis, it has been claimed that the chosen therapy may affect the development or progression of GO, and contradictory results have been obtained with respect to the effects of different therapeutic procedures on GO [1]. In this prospective and controlled study we have shown clinical improvement in all patients of group A and in 9 of group B. Proptosis measured on MRI in our study, as a whole, were correlated to clinical measurement of proptosis by Hertel exophthalmometer. There is, however, a discrepancy in some degree between both measurements in some few cases, which may introduce the possibility of observer bias in the measurements, because MRI is more accurate and objective method for evaluation of proptosis than Hertel exopthalmomter [13]. The observed enlargement of extraocular muscle and/or orbital fat in all patients with GD even those without clinically apparent ophthalmopathy is consistent with the results of other studies [13]. The extraocular muscles were affected with varying frequency, the inferior rectus being the most commonly enlarged and the superior rectus was the least commonly enlarged. These observations were in line with those of Markl [14] who furthermore reported, that isolated involvement of lateral rectus was rare.

Over the years, efforts have been made to establish the correlation between ophthalmopathy and thyroid autoimmunity [6,15]. Some workers have demonstrated the presence of immunological cross-reactivity against eye muscle and thyroid shared autoantignes of 64 KDa [16]. Several different autoantibodies have been suggested to be present in the patient's sera because they have been shown to react with proteins of different molecular weight in human eye muscle as well as with other thyroid tissues [17]. Other studies have shown that although the extraocular muscles are generally enlarged, the extraocular muscle fibers themselves are usually normal [18]. The muscle enlargement is due to muscle fiber separation by edema, fibrosis, and aggregations of B- and T-lymphocytes, monocytes and macrophages [8]. Despite several hypotheses, the pathogenesis of GO remains controversial. Solomon [3] reported that orbital disease cannot easily be attributed to events going on in the thyroid gland or to circulating thyroid stimulating immunoglobulins and the pathogenesis of eye disease would probably be a separate retro-orbital autoimmune reaction [19] or an effect of circulating exophthalmogenic factors of immunologic or hypophyseal origin [20] rather than dependent upon transfer of antigen and sensitized lymphocytes from the thyroid gland to the retro-orbital tissues [21]. We believe that Graves' thyrotoxicosis and ophthalmopathy have a single basic pathogenic process, as suggested by Werner [22], rather than being two different autoimmune diseases. In the present study we found a significant reduction in exophthalmometric measurement and extraocular muscle volume following cervical block dissection compared to those underwent standard subtotal thyroidectomy which raises the possibility that cervical lymph nodes and lymphatic trunks are potentially involved in the pathogenesis of GO. We may consider several explanations for that role 1- possibly intercommunicating lymphatics exist between the cervical mph nodes and retro-orbital tissue. These lymphatics carry various cytokines as interlukin-1 and interferon gamma to the retro-orbital tissues and enhance glycosaminoglycan production by fibroblasts. Support for is possibility comes from the observation that hyaluronic acid synthesis by retro-ocular fibrolasts is regulated differently than is its synthesis by skin fibroblasts [23]. Synthesis by skin fibroblasts is markedly inhibited by triiodothyronine [24], whereas retro-ocular fibroblasts do not respond as vigorously to this hormone which indicates that a local mechanism involving the retro-orbital tissues, the thyroid gland and cervical lymph nodes is included rather than a systemic one.2- Cervical lymph nodes contain antigen-specific T lymphocytes that are carried through communicating lymphatics to the retro-orbital tissues provoking an immune reaction resulting in edema in the perimysial connective tissue stimulation of retro-orbital fibroblasts to release hyaluronic acid. Evidence indicates that most lymphocytes in the retro- orbital tissue were T cell and comprise a recently activated population within which memory cells are residing [25]. and that retro-ocular fibroblast cultures respond to human lymphocytes with an increase in glycosaminoglycan release and acceleration of glucose use [26]. T cells may be sensitized against the lymphatic endothelium in the neck then migrates and reacts with those in the retro-orbital space as evidenced by failure of extraocular muscle cells to express Ia antigens in contrary to fibroblasts and endothelial cells which were Ia-positive [25]. Support for this possibility comes from the observation that the side with greater exophthalmos had a larger number of lymph nodes and lymphatic trunks in the neck than on the contralateral side. The relation between GO and TSAb remains only partially defined. Some clinical studies have shown a higher prevalence of TSAb positivity in patients with GO than in patients without clinical evidence of eye involvement [1]. Nishikawa et al [27] have suggested a close relation between orbital muscle changes evaluated by MRI and TSAb in patients with GO. In the present study we did not find a correlation between GO and TSAb level. We have previously reported a significant reduction of TSAb level following standard subtotal thyroidectomy [28]. However, in the present study, the reduction in TSAb level was more dramatic & more statistically significant in patients for whom block dissection was done. This raises the possibility that cervical lymph nodes are major source of TSAb which when reaches a pathological level in the circulation it could lead to stimulation of the thyroid tissue remnant, in case of standard subtotal thyroidectomy, eventually ending with recurrence of hyperthyroidism. This, in turn, can be prevented by cervical block dissection especially in patients with high preoperative TSAb titer.

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