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Changes in intraocular pressure and corneal and retinal nerve fiber layer thicknesses in hypothyroidism

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PURPOSE. To evaluate the changes in intraocular pressure (IOP), corneal thickness (CT), and retinal nerve fiber layer thickness (RNFLT) in patients with hypothyroidism before and after treatment.

METHODS. A complete ophthalmic examination including visual acuity, IOP, anterior segment, and fundus examination together with CT and RNFLT measurements were performed for each patient with newly diagnosed hypothyroidism, at the initial diagnosis and the third and ninth months of the L-thyroxine treatment. Wilcoxon signed rank test and Spearman's correlation test were used for statistical evaluation of the results.

RESULTS. A total of 56 eyes of 28 patients were included in the study. The mean IOP and CT values were found to decrease with medical treatment ($p=0.000$). There was no significant change in any of the RNFLT parameters measured with scanning laser polarimeter after L-thyroxine treatment (Wilcoxon, $p>0.05$). The change in IOP levels was not correlated with the change in thyroid hormone levels (Spearman's correlation test, $p>0.05$). The mean increase in serum free T_3 and serum free T_4 levels and the mean decrease in serum TSH levels at the ninth month of the therapy were found to be correlated with the decrease in CT in the left eyes (Spearman's correlation test, $R>0.4$ and $p<0.05$).

CONCLUSIONS. Hypothyroidism seems to cause a reversible increase in CT and IOP. IOP changes may be secondary to CT changes. RNFLT parameters measured with scanning laser polarimeter do not seem to be affected by hypothyroidism. When the CT is taken into account and the IOPs corrected for CT, the prevalence of glaucoma in hypothyroidism may not be as high as previously reported. This issue should be taken into account while assessing glaucoma in patients with hypothyroidism. (Eur J Ophthalmol 2005; 15: 556-61)

KEY WORDS. Hypothyroidism, Corneal thickness, Intraocular pressure, Retinal nerve fiber layer thickness

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INTRODUCTION

The prevalence of glaucoma among hypothyroid individuals was reported to be higher than normal in some previous studies (1-3). Contradictory effects of hypothyroidism on intraocular pressure (IOP) were exerted. Although some of the previous studies had demonstrated an increased IOP in hypothyroid state (2, 4, 5), others failed to show such an association (3, 6). Centanni et al reported reversible IOP increases even in subclinical hypothyroidism (4).

In hypothyroid patients, hydrophilic mucopolysaccharides accumulate in the ground substance of dermis and other tissues, leading to thickening of the facial features and doughy indurations of skin, named myxoedema (7). Chemosis, periorbital edema, and ble-

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pharoptosis are common ocular findings accompanying the clinical state (2, 8). A possible suggestion made by some authors for the relationship between hypothyroidism and glaucoma was a deposition of glycosaminoglycan in trabecular meshwork preventing outflow of aqueous humor, which may consequently result in glaucoma (2).

In this study, we aimed to evaluate the alterations in intraocular pressure (IOP), corneal thickness, and retinal nerve fiber layer thickness (RNFLT) with the establishment of euthyroidic state in patients with newly diagnosed hypothyroidism.

METHODS

Patients with newly detected hypothyroidism in the endocrinology department were assessed for inclusion in the study before the L-thyroxine replacement therapy was begun. Informed consent was obtained from all of the patients. Patients with any corneal pathology and retinal vascular disease such as diabetic or hypertensive retinopathy were excluded from the study. A complete ophthalmic examination including visual acuity, IOP measurement (with Goldmann applanation tonometer), anterior segment and fundus examinations together with visual field examination, corneal thickness, and RNFLT measurements were performed for each patient. L-thyroxine replacement treatment was then initiated. After the achievement of euthyroidism, serum free T_3, free T_4, and thyroid stimulating hormone (TSH) levels together with ophthalmic examination including corneal thickness and RNFLT assessments were repeated in the third and ninth months of euthyroidism. All of the IOP measurements during the follow-up were performed at the same hour of the day as the initial examination for each patient to avoid the misinterpretation that may be caused by diurnal IOP variation. The visual field was tested at the first visit by automated perimetry (Humphrey 30-2 program, Humphrey-Zeiss) and was repeated at the following visits in patients with any visual field loss. Corneal thickness measurements were performed by using Mentor Q&Q Advent Pachymeter. The mean of three consecutive measurements from the central cornea was used for the assessment. RNFLT measurements were done by using a scanning laser polarimeter (NFA-GDx; Laser Diagnostic Technologies, San Diego, CA). The

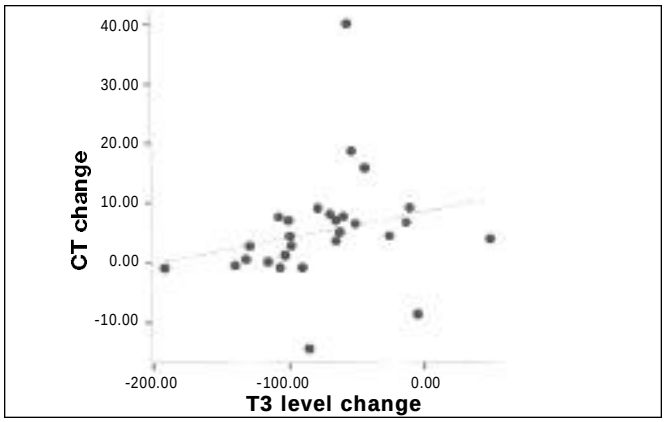

Fig. 1 - Correlation between the changes in corneal thickness and the changes in serum thyroid stimulating hormone levels at the ninth month of L-thyroxine therapy in the left eyes (R=0.463 and p=0.023).

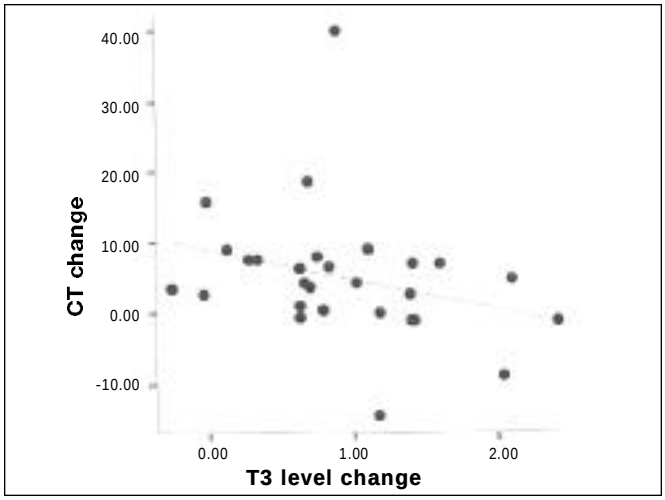

Fig. 2 - Correlation between the changes in corneal thickness and the changes in serum free T_4 levels at the ninth month of L-thyroxine therapy in the left eyes (R=-0.468 and p=0.028).

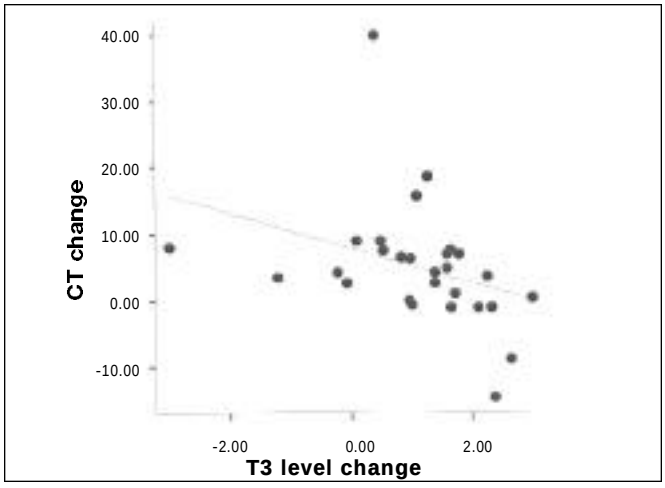

Fig. 3 - Correlation between the changes in corneal thickness and the changes in serum free T_3 levels at the ninth month of L-thyroxine therapy in the left eyes (R=-0.593 and p=0.003).

mean of three good quality images was used for the assessment of RNFLT for each eye.

Although the measurements were performed in both eyes, we assessed right eyes and left eyes separately as independent variables to avoid any statistical misinterpretation. Wilcoxon signed ranks test was used to compare the changes in IOP, corneal thickness, and RNFLT before and after hypothyroidism treatment. Spearman's correlation test was used to investigate a possible correlation between the changes in IOP, corneal thickness, RNFLT, and serum free T_3, T_4, and TSH levels after medical treatment.

RESULTS

The power of the study was found to be 87% and the necessary sample size was found to be 19 eyes when alpha (p value) is accepted as 0.05. Fifty-six eyes of 28 patients, 25 women and 3 men, ranging between 21 and 73 years of age (mean 43.6±13.7 years) were involved in the study. All of the patients completed the ninth month visits after the initiation of medical treatment. Pigmentary glaucoma was detected in right and left eyes of one patient at the first visit and a topical antiglaucomatous treatment was initiated.

TABLE I - INTRAOCULAR PRESSURE (IOP) AND CORNEAL THICKNESS VALUES AT THE BEGINNING, THIRD, AND NINTH MONTHS OF MEDICAL TREATMENT

	Beginning		**Third month**		**Ninth month**	
	IOP (mmHg)	**Corneal thickness (µm)**	**IOP (mmHg)**	**Corneal thickness (µm)**	**IOP (mmHg)**	**Corneal thickness (µm)**
Right eye	17.75±2.25	551.63±34.27	16.11±2.27	547.85±30.61	15.26±3.26	551.16±31.47
Range	13-22	482.60-634.60	10-19	471.60-604.00	9-20	474.00-616.30
p value *			p=0.002	p=0.000	p=0.000	p=0.209
Left eye	16.89±2.81	553.53±33.76	15.29±2.77	548.35±32.33	14.88±3.77	549.10±29.69
Range	12-21	483.00-628.00	10-20	456.60-602.30	9-20	482.66±610.60
p value*			p=0.004	p=0.000	p=0.000	p=0.023

Values are mean±SD.
*Wilcoxon signed rank test

TABLE II - SERUM FREE T_3, FREE T_4, AND TSH LEVELS AT THE BEGINNING, THIRD, AND NINTH MONTHS OF TREATMENT

	Free T_3 (2-4.2 mU/L)	**Free T_4 (0.8-1.7 mU/L)**	**TSH (0.35-5 mU/L)**
Pretreatment	2.10±0.85	0.68±0.63	80.24±43.29
Third month	3.07±0.54	1.33±0.35	7.05±8.66
Ninth month	3.19±0.57	1.40±0.52	1.84±2.17

Free T3, T4 and TSH hormone levels mentioned in header parentheses present the normal range
Values are mean±SD. All p=0.000
TSH = Thyroid stimulating hormone

The IOP was 30 mmHg with Krukenberg spindle, cup/disk ratio was 0.4, and the angles were widely open and hyperpigmented bilaterally without any visual field loss in this patient. Corneal pachymetry revealed a corneal thickness of 504 µm in the right eye and 517 µm in the left. After topical Xalatan treatment was initiated, IOP returned to normal levels (15 mmHg in the right eye and 13 mmHg in the left). This patient was excluded from the study since an antiglaucomatous drug had to be started.

The mean IOP was 17.7±2.2 mmHg in the right eyes and 16.8±2.8 mmHg in the left at the time of diagnosis, which decreased to 16.1±2.2 mmHg with a mean decrease of 1.62±2.13 mmHg in the right eyes and to 15.2±2.7 mmHg with a mean decrease of 1.59±2.85 mmHg in the left at the third month of the euthyroid state (Tab. I, $p<0.05$). At the ninth month of treatment, the mean IOP further declined to 15.26±3.26 mmHg in the right eyes and 14.88±3.77 mmHg in the left with a mean decrease of 2.53±2.67 mmHg in the right eyes and 2.03±2.53 mmHg in the left from baseline ($p=0.000$). IOP levels decreased in 24 right eyes (82.7%) and 21 left eyes (72.4%); increased in 4 right eyes (13.7%) and 3 left eyes (10.3%); and did not change in 1 right eye (3.4%) and 5 left eyes (17.2%).

The mean cup/disk ratio was 0.2±0.05 (range 0.1–0.3) in both eyes. Mean deviation (MD) was found to be -2.97±1.93 dB in the right eyes (range -6.31 to 1.93 dB) and -2.91±1.74 dB in the left (range -6.91 to 0.09 dB) at the initial visit. The mean corrected pattern standard deviation (CPSD) was 2.20±1.67 dB in the right eyes (range 0–6.70 dB) and 2.00±1.54 dB in the left (range 0–6.35 dB).

The mean corneal thickness values were found to be 551.63±34.27 µm in the right eyes and 553.53 ±33.76 µm in the left, which decreased to 547.85±30.61 µm in the right eyes (mean decrease, 8.60±10.43 µm) and 548.35±32.33 µm in the left (mean decrease, 7.72±7.73 µm) ($p=0.000$) at the third month. The mean decrease in corneal thickness did not change significantly at the ninth month visit in the in the right eye group with a mean decrease of 3.63±13.31 µm ($p=0.209$). Mean corneal thickness value in the left group further declined to 549.10±29.69 µm (mean decrease, 5.03±9.75 µm) at the ninth month visit ($p=0.016$) (Tab. I). There was a decrease in corneal thickness in all but one of the right eyes and two of the left eyes in the third month visit. Although most of the eyes (18 of the right eyes, 69.6%, and 23 of the left eyes, 79.3%) demonstrated a decrease in corneal thickness at the ninth month of the medical therapy, 11 of the right eyes (30.3%) and 6 of the left eyes (20.6%) demonstrated an increase in corneal thickness.

Serum free T_3, free T_4, and TSH levels returned to normal limits with the initiation of a L-thyroxine replacement therapy within a short time in all of the patients (Tab. II, $p<0.05$). The mean decrease in IOP levels was not correlated with the changes in thyroid hormone levels in right or left eyes (Spearman's correlation test, $p>0.05$). The mean increase in serum free T_3 and serum free T_4 levels and the mean decrease in serum TSH levels at the ninth month of the therapy were found to be correlated with the decrease in corneal thickness in the left eyes (Spearman's correlation test, $R=-0.593$ and $p=0.003$, $R=-0.468$ and $p=0.028$, $R=0.463$ and $p=0.023$, respectively, Figs. 1–3).

No correlation was found between the changes in IOP and corneal thickness in right or left eyes at the third and ninth months of the thyroxine replacement therapy (Spearman's correlation test, $p>0.05$).

When we consider the RNFLT measurement results; the number, symmetry, superior ratio, inferior ratio, superior nasal, maximum modulation, superior maximum, inferior maximum, average thickness, ellipse modulation, ellipse average, superior average, inferior average, and superior integral were the parameters evaluated with NFA-GDx. There were 1.6±0.1 parameters out of normal range per eye. The mean of the parameter number was found to be 26.50±21.08 in the right eyes and 23.62±18.93 in the left at the initial examination. There was no significant change between the initial, third, and ninth month measurement results (Wilcoxon signed rank test, $p>0.05$).

DISCUSSION

An increase in IOP in Graves' thyroid orbitopathy is a very well known entity that may occur due to variable conditions including contraction of extraocular muscles, raised episcleral venous pressure secondary to orbital congestion, secondary angle closure, and increased mucopolysaccharide deposition within the aqueous outflow pathways (9). However, the effects of hypothyroidism on IOP have not been

entirely established. In hypothyroidic state, hyaluronic acid accumulates in connective tissues secondary to the diminished degradation of hyaluronic acid compared with its production. The extreme accumulation of hyaluronic acid leads to the deposition of water, secondary to strong-water binding capacity of the substance, within the tissues such as skin, gastrointestinal tract, skeletal muscle, and heart (10). As a result myxoedema, weight gain, constipation, stiffness and cramping of the muscles, cardiac dilatation and pericardial effusion, periorbital edema, and blepharoptosis may develop consecutively (7, 10). The accumulation of hyaluronic acid in various tissues has been demonstrated to reverse with medical treatment (10). Although there are previous studies reporting an association between hypothyroidism and POAG (2, 4, 5), some others failed to report such association (3, 6). Smith and colleagues investigated POAG patients for hypothyroidism by measuring serum TSH level (2). They have detected hypothyroidism in 23.4% of 64 POAG patients, half of which being newly diagnosed. The authors suggested that a significant subset of patients with POAG have undiagnosed hypothyroidism (2). In another study by Smith et al, 25 hypothyroid patients were examined and they reported a reduction of outflow facility in hypothyroidic state (5). IOP increase was suggested to be secondary to the accumulation of mucopolysaccharides in the trabecular meshwork and/or external outflow pathways reducing the aqueous outflow (5). They have found a significant improvement in the aqueous outflow with the treatment of hypothyroidism and proposed that glaucoma would resolve with the treatment of the primary disease (4, 5). Karadimas et al, on the other hand, evaluated 100 newly diagnosed hypothyroid individuals; however, they did not report any patient with glaucoma (6).

Although IOP levels of the patients in the present study also decreased with the achievement of euthyroidism, we could demonstrate glaucoma in only one patient (3.4%), which was a pigmentary glaucoma, a type of secondary open-angle glaucoma, and this was probably a coincidental association.

In this study, we have suggested that corneal thickness might also increase secondary to the deposition of mucopolysaccharides in corneal stroma in hypothyroidic individuals and this may affect the IOP measurements causing an apparent increase in IOP levels. Confirming this, we have found that corneal thickness significantly decreased after treatment of hypothyroidism (Tab. I). IOP measurement with applanation tonometry has recently been demonstrated to be significantly affected by the central corneal thickness (11-16). Several reports have suggested that IOP may be overestimated in thick and underestimated in thin corneas (11-16). Ocular hypertensive individuals have been reported to have a thicker central cornea than normal subjects and patients with glaucoma (14-16). In the present study, we have suggested that IOP levels may be overestimated because of the corneal thickening secondary to hypothyroidism. Similarly we have observed a concomitant decline in both IOP and corneal thickness values after the achievement of euthyroidism. Although we failed to demonstrate a direct correlation between corneal thickness change and IOP change, we suggest that the decrease in IOP might be secondary to the decrease in corneal thickness. The normal values of RNFLT and visual fields in all cases also support this suggestion. The number, which is a parameter studied significantly to be an indicator of glaucomatous damage in NFA-GDx, was also found to be within normal limits. The high IOP values in hypothyroid patients seem to be non-glaucomatous IOP increases, which may be a pseudohypertension due to increased corneal thickness caused by hypothyroidism.

To our knowledge, this study is the first of its kind where hypothyroid individuals were examined for corneal and RNFL thicknesses. In conclusion, hypothyroidism seems to cause a reversible increase in corneal thickness and IOP. IOP changes may be secondary to the changes in corneal thickness. RNFLT parameters measured with scanning laser polarimeter do not seem to be affected by hypothyroidism. The prevalence of glaucoma in hypothyroidism may not be as high as previously reported (2-5).

The authors have no proprietary interest in any aspect of the article.

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