ORIGINAL RESEARCH

Preliminary Study on the Correlation Between Episcleral Venous Pressure and Intraocular Pressure in TAO Patients and Its Clinical Value

Xinyu Fan, MM; Xu Zha, MD; Ning Wang, MD; Yuanhui Han, MM

ABSTRACT

Objective • To study the correlation between episcleral vein pressure (EVP) with intraocular pressure (IOP), exophthalmos, and optic nerve injury in thyroid-associated ophthalmopathy (TAO) patients and to explore the possibility of higher EVP as an intervention indicator in TAO patients.

Methods • This study was a case-control study, including the TAO group and normal control group. TAO group: 15 patients (30 eyes) were diagnosed with TAO complicated with exophthalmos. Normal control group: 14 cases, 28 eyes. EVP, IOP, exophthalmos, retinal nerve fiber layer thickness, and visual field were measured, respectively in the two groups. Non-parametric test was used to compare the difference between EVP and IOP between the two groups, test the correlation between EVP and IOP or exophthalmos, and analyze the clinical characteristics of optic nerve injury in patients with elevated IOP in the TAO group.

Results • The EVP in the TAO group (15.30±3.48 mmHg) was significantly higher than the normal control group (8.82±1.44 mmHg) ($P < .001$). The IOP in the TAO group (18.55±8.13 mmHg) was significantly higher than in the normal control group (12.98±2.10 mmHg) ($P < .001$) (3) There was a positive linear correlation between EVP (X) and IOP (Y) in TAO group: $Y = 0.9684x + 3.737$ ($rs>0$, $P < .05$); There was a positive linear correlation between EVP (Y) and exophthalmos (X) in TAO group: $Y = 0.9218x - 2.691$ ($rs>0$, $P < .05$); Some TAO patients with elevated EVP had the related manifestations of optic nerve function impairment: thinning of retinal nerve fiber layer and loss of visual field. However, there was no clear correlation between EVP and the thickness of the optic nerve fiber layer ($P = .4354$).

Conclusion • The increase of EVP is an important factor leading to elevated IOP in TAO patients, which may be used as an indicator for intervention treatment in TAO patients. EVP can be used to indirectly evaluate orbital pressure. TAO patients can develop secondary glaucoma with irreversible optic nerve damage due to the continuous Elevation of EVP. (*Altern Ther Health Med.* 2024;30(10):522-527).

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INTRODUCTION

Thyroid-associated ophthalmopathy (TAO), also known as Graves' Ophthalmopathy, is an autoimmune disease of orbit and related to thyroid disease. Currently, it is considered to be an ocular lesion related to the hypothalamus-pituitary-thyroid axis.[1] It has been more than 200 years since TAO was first reported, and it accounts for 20% of adult orbital diseases. The incidence of TAO at home and abroad ranks first among all orbital diseases, and women aged 40-60 have the highest prevalence.[2] However, limited eye movement, soft tissue lesions, and optic neuropathy are more common in male patients over 50 years old. TAO can occur before, during, and after hyperthyroidism, and it also appears in a few Hashimoto's thyroiditis patients[3] and about 10% of patients with normal thyroid function.[4] The disease can cause a variety of eye lesions, such as exophthalmos, diplopia, soft tissue, muscle swelling and optic neuropathy, and among many complications, various reasons can lead to increased intraocular pressure (IOP), and then develop into secondary glaucoma, which is one of the serious complications leading to irreversible visual loss and blindness.

The normal IOP is 10-21mmHg and fluctuates within 8mmHg within 24 hours. As early as 1897, Brailey reported the possibility of elevated IOP caused by thyroid disease, which did not attract the attention of clinicians. As a result, the IOP of some patients continued to increase and then progressed to glaucoma with serious impairment of visual

Figure 1. EVP measuring instrument

Figure 2. Contact head of EVP measuring instrument

function, such as optic nerve atrophy and visual field loss and others. Jin Yaming et al.[15] also observed changes in optic disc, optic nerve damage and elevated IOP in TAO patients who were diagnosed with glaucoma. Glaucoma secondary to TAO can lead to irreversible damage of the optic nerve and even blindness, which causes heavy losses to patients, their families and society. Therefore, high attention should be paid to it.

Relevant studies have shown that the increase of EVP is one of the important factors in the rise in IOP,[6-9,] and some studies have also pointed out that the increase of IOP in TAO patients is the key factor leading to the increase of EVP.[10] The results are quite different.

On the basis of previous research, in this study, the correlation between EVP and IOP in TAO patients was observed, and the injury degree and clinical manifestations of the optic nerve during the course of the disease were monitored. This study aimed to find and analyze the main factors leading to the changes in IOP in TAO patients and provide the theoretical basis of clinical diagnosis and treatment for these patients.

PATIENTS AND METHODS

General Information

In the TAO group, 15 patients (30 eyes) diagnosed as TAO with exophthalmos > 14 mm in our hospital, aged from 17 to 63 years old, including 8 males and 7 females. There were 2 cases with elevated IOP (> 21 mmHg) and nerve injury and 3 cases with elevated IOP but not optic nerve injury. The control group consisted of 14 healthy adults (28 eyes) aged from 25 to 75 years old, including 8 males and 6 females. There were no significant differences in gender and age between the two groups ($P > .05$).

Examinations and methods

Patients were routinely examined for blood, including blood routine, thyroid function, liver and kidney function, electrolytes, blood lipids and blood glucose, 12-lead electrocardiogram, chest orthography, and orbital CT, diagnosed TAO, and exclude other causes which lead to exophthalmia and optic nerve injury. After that, ophthalmic specialized examinations were performed, and EVP was measured using the Episcleral Venomanometer (EV-310) produced by Eyetech (Figure 1, Figure 2). The measurement location was selected at the episcleral vein within the range of 10:00-11:00 and 1:00-2:00 at 3mm from the sclera to the corneal limbus. The average value was taken for 3 independent measurements. IOP was measured by Icare TA01 rebounder tonometer, and optic nerve injury was tested by HEIDELBERG optical coherence tomography (OCT) to monitor the ratio of the cup to disk and the thickness of the retinal nerve fiber layer (RNFL). Humphrey was used to record visual field changes. Hertel exophthalmometer was used to measure exophthalmos.

Statistical Analyses

The data of the experimental group and control group were analyzed by one-way ANOVA. Shapiro-wilk test was used for the normality test, and the results showed that the sample data was non-normality. The levene test was used to test homogeneity of variance, and the data did not completely match the homogeneity of variance, so the Kruskal-Wallis test was used for the non-parametric test. $P < .05$ was taken to indicate statistically significant. Pearson's model was used to analyze the correlation between each measurement metric. The regressive relationship among the metrics with significant correlation was determined by using one-dimensional linear regression analysis. All statistical analysis was performed in R 4.1.3 using the CAR, GGPUBr, and basicTrendline packages.

Table 1. The comparison of age and gender between TAO group and normal control group

Group	TAO Group (n=30)	Normal Control Group (n=28)	t/χ^2	*P* –adjusted	Significance
AGE(YEAR)	43.8±14.457	51.86±19.078	-1.821	.081	*ns*
SEX(male/female)	8/7	8/6	0.042	.837	*ns*

Table 2. The comparison of EVP between TAO group and normal control group

Group	TAO Group (n=30)	Normal Control Group (n=28)	*t*	*P* –adjusted
EVP (mmHg)	21.37±4.369	8.82±1.442	14.475	<.0001

Table 3. The comparison of IOP between TAO group and normal control group

Group	TAO Group (n=30)	Normal Control Group(n=28)	*t*	*P* –adjusted
IOP (mmHg)	18.553±8.1359	12.979±2.0954	3.516	.0018

RESULTS

Fundamental information of TAO group and normal control group

The comparison of age and gender between the two groups was not statistically significant ($P > .05$) as showed in Table 1.

Difference of EVP between the TAO group and the normal control group

The EVP in the TAO Group was overall higher than the normal control group, and the difference was statistically significant ($P < .001$), as shown in Table 2, which indicated that the EVP in TAO patients with exophthalmos was higher than the normal control group.

Difference of IOP between the TAO group and the normal control group

The IOP of the TAO group was overall higher than normal control group, and the difference was statistically significant ($P < .001$) (Table 3), including 8 eyes with IOP >21 mmHg, accounting for 27% of the TAO group (Figure 3).

Difference of exophthalmos between the TAO group and normal control group

The exophthalmos of the TAO group was overall higher than the normal control group, and the difference was statistically significant ($P < .001$), as shown in Table 4, which indicated that the exophthalmos of the TAO patients was higher than normal people.

Difference of RNFL thickness between the TAO group and the normal control group

Compared with the normal control group, the RNFL thickness in the TAO group was decreased, but there was no statistical significance between the two groups ($P > .05$), as shown in Table 5.

Figure 3. Patients with IOP >21mmHg accounted for 27% in TAO group

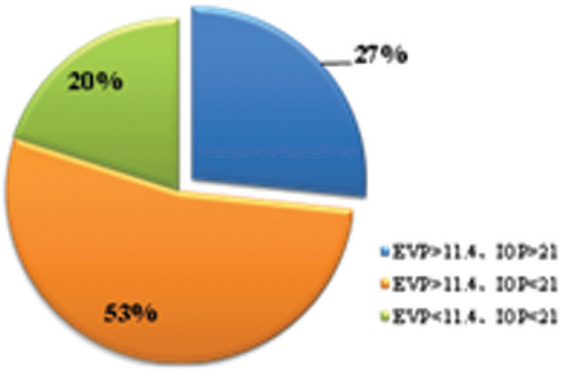


Table 4. The comparison of exophthalmos between TAO group and normal control group

Group	TAO Group (n=30)	Normal Control Group (n=28)	*t*	*P* –adjusted
Exophthalmos (mm)	19.52±2.476	12.21±0.865	14.795	<.0001

Table 5. The comparison of RNFL between TAO group and normal control group

Group	TAO Group (n=29)	Normal Control Group (n=28)	*t*	*P* –adjusted
RNFL thickness (μm)	116.99±20.12	122.42±10.78	-1.268	.24

Figure 4. Correlation between exophthalmos and EVP

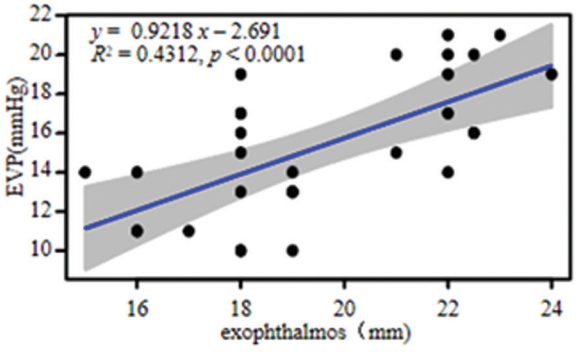


Figure 5. Correlation between IOP and EVP in TAO group

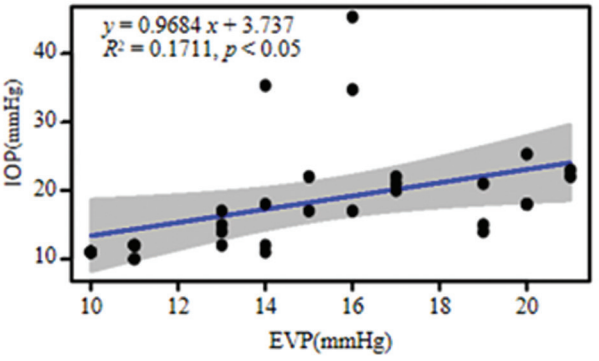


Figure 6. 16 eyes had higher EVP but normal IOP in TAO group

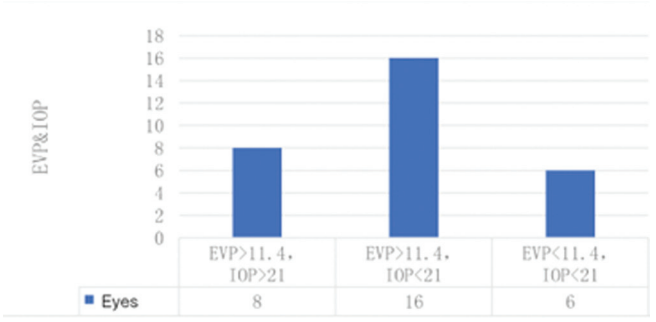


Figure 7. The correlation between exophthalmos and IOP in TAO group

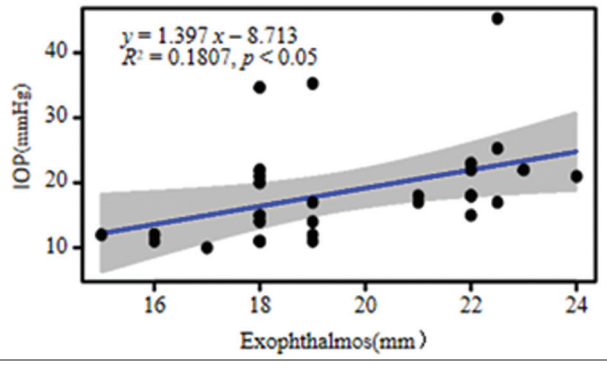
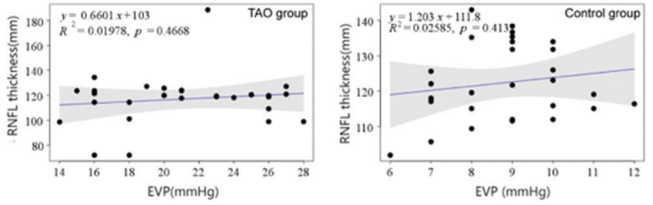


Figure 8. Correlation between EVP and RNFL thickness



Correlation between exophthalmos and EVP

The linear regression analysis tested the data of the normal control group and TAO group and showed the positive linear correlation between exophthalmos (X) and EVP (Y) in the TAO group: Y = 0.9218X - 2.691 (R^2=0.4312, P < .0001), as shown in Figure 4.

Correlation between IOP and EVP in TAO group

The linear regression analysis experiment of the TAO group showed that there was a positive linear correlation between IOP and EVP in the TAO group: IOP =0.9684*EVP +3.737(R^2=0.1711, P<0.05), as shown in Figure 5.

In the TAO group, the EVP was higher than 11mmhg but the IOP was lower than 21 mmHg in 16 eyes, which means the EVP was higher than normal but the IOP within the normal range, as shown in Figure 6.

Correlation between exophthalmos and IOP

The linear regression analysis of the TAO group showed a positive linear correlation between exophthalmos and IOP: Y =1.397x-8.713 (X: exophthalmos, Y: IOP) (R^2=0.1807, P < .05), as shown in Figure 7.

Correlation between EVP and RNFL thickness

Statistical analysis showed that there was no clear correlation between EVP and RNFL thickness in the TAO group and normal control group (P > .05), as shown in Figure 8.

DISCUSSION

One of the serious complications caused by TAO is Dysthyroid optic neuropathy (DON), which occurs in about 5% of TAO patients.[11] Clinical signs of DON include decreased visual acuity, relative afferent pupil block, abnormal color vision, optic disc edema, visual field loss, and orbital apex crowding in imaging.[12] Among many mechanisms leading to optic nerve injury, the increase of IOP is one of the important reasons. TAO-induced elevated IOP was reported by Brailey as early as 1989.[13] Episcleral vein is an important channel for aqueous humor outflow, and it through superior orbital fissure out of the orbit. When the pressure in the orbit is increased, the return of the episcleral vein is blocked, and the intravenous pressure will increase. When the EVP is higher than IOP, blood cells can be seen in the Schlemm tube (aqueous humor outflow channel in the atrial angle), which can be evidence to prove the obstruction of aqueous humor outflow by showing that the blood cells pour back into the Schlemm tube.[14] In this study, EV-310 was used to measure the EVP in the normal control group and TAO group and investigate the correlation between the EVP and IOP, exophthalmos, RNFL thickness, and visual field.

EV-310 is a non-invasive instrument to measure the EVP, and It is similar in shape and structure to the Goldmann tonometer. EV-310 consists of a small pressure chamber filled with air, a transparent and elastic contact head (diaphragm) connected to it, and an adjustable knob with a piston. Turning the knob on the instrument to change the pressure in the pressure chamber by changing the position of the piston in the instrument to perform measuring. The scale range of the knob is 0-30mmHg. The advantages of this instrument is safe, non-invasive, good operability, and good repeatability, but it also exists measuring errors because of intravenous selection, measuring position, and venous blocking. Some of the TAO patients have restrictive strabismus leads to fixed and difficult rotating eyeballs, which causes the selectivity of veins more difficult.

For the above factors, considering with that the Inferior Rectus is more often involved in TAO patients to make the eyeball in the downward transposition more common, the measurement location was selected at the episcleral vein within the range of 10:00-11:00 and 1:00-2:00 at 3mm from the sclera to the corneal limbus, and the average value was taken for 3 independent measurements. At the same time, for TAO patients whose IOP cannot be measured by Goldmann tonometer and non-contact tonometer due to eye disorientation and muscle enlargement to compress the eyeball caused by strabismus, the rebound tonometer was used to measure the IOP and obtain the relatively reliable data.

The results of this study showed that the IOP in TAO group was significantly higher than healthy control, and there was a positive linear correlation between IOP and EVP in TAO patients (rs>0, $P < .05$), indicating that the increase of EVP was an important factor in the elevated IOP in TAO patients. At the same time, we also observed that the IOP in 16 eyes was still within the normal range, although the EVP was increased, suggesting that the EVP was earlier than the increase of IOP. It is speculated that when the early EVP increased under the effect of orbital pressure, the IOP was still in the compensatory range, and the IOP did not increase. When the EVP increased to a higher level, the aqueous circulation was blocked ,the IOP regulation was decompensated, and then the IOP increased. Therefore, the EVP may be one of the risk indicators of TAO patients for requiring intervention, but the critical value remains to be studied.

In this study, it was also found that the EVP was highly positively correlated with exophthalmos and with the highest correlation (Pearson's correlation coefficient was 0.657). There was a highly positive correlation between exophthalmos and IOP, which was second only to the EVP (Pearson's correlation coefficient was 0.425). Previous studies suggested that there was a positive correlation between exophthalmos and orbital pressure in TAO patients.[15] Therefore, it is believed that the increase of EVP can also be used as one of the clinical observation indicators of elevated orbital pressure in TAO patients.

Optic nerve damage is evaluated by structure and function. In this study, Optic nerve structure damage was evaluated by measuring the thickness of the RNFL around the optic disc with retinal OCT. Humphrey measured visual field to assess functional impairment of the optic nerve.

Studies have shown that changes in RNFL thickness may occur in the early stage of TAO disease,[12] so OCT can reflect the changes of RNFL in TAO patients earlier, so it can diagnose and treat optic neuropathy in TAO patients in time. 2 eyes in this study appeared RNFL thinning, vision field loss, and progress with the development of the disease. The matched EVP and IOP were higher than normal, indicating that these 2 eyes had glaucomatous optic nerve damage caused by TAO. It needs to control the IOP in time ,perform orbital decompression surgery, and even perform anti-glaucoma surgery if necessary. Another 3 eyes had high EVP and IOP, but RNFL thickness had no obvious thinning, which was considered when orbital pressure increased in TAO patients. There was a compensatory period before the change of IOP, and as a result of the compensation effect of venous circulation, the patients with elevated IOP will rise slowly.

On the other hand, the short duration of elevated IOP had the limited effect on the structure of optic nerve; however, if the increased IOP continues to be uncontrolled, optic nerve injury may appear over time. Therefore, even if RNFL and IOP are normal, it cannot be ignored to monitor IOP and optic nerve injury if the EVP persists in elevating. At the same time, we also hope to collect more data to clarify the influence of EVP on IOP, the critical duration, and the indication of surgical intervention, which will provide theoretical support for the diagnosis and treatment of optic nerve injury in patients with TAO.

Visual field examination is the most important indicator to evaluate optic nerve function at present, but it is a subjective examination that requires patients to understand the operation and cooperation well, but always with subjective errors, especially in some TAO patients with extraocular muscle enlargement and fibrosis change, which leads to restrictive strabismus and eyeballs fixed in a certain position. In addition, some patients also have inflammation and corneal lesions that affect the accuracy of the visual field; therefore, it is necessary to consider with the specific situation of the patient to analyze the visual field results. In this study, in the visual field examination of 15 patients, 3 patients had abnormal visual field in varying degrees. 2 patients of had no significant improvement in visual field after treatment and IOP control, which indicated that the optic nerve function had been irreversibly damaged. And another one had an improvement in the visual field after treatment. It is speculated that the early optic nerve injury in TAO patients may only have functional impairment; in other words, the functional impairment is earlier than the structural injury. Therefore, the impairment is reversible in some extent. However, considering the small sample in this study, more clinical studies are needed to confirm it. Forte and colleagues[16] also found no significant reduction in RNFL thickness in Graves' ophthalmopathy and patients with IOP > 23 mmHg, and they reported a low correlation between RNFL thickness and visual field abnormalities.

In this study, optic disc edema occurred in 2 eyes in the TAO group. Some investigators believed that the mechanical compression and inflammation cause optic disc edema that occurred in TAO patients due to the increased volume of extraocular muscle and fat and the co-existence of inflammation. McKeag et al.[17] found optic disc edema occurs in more than 50% of TAO patients complicated with optic neuropathy, and they believed this may be a specific indicator of TAO optic neuropathy. Some people also believe that the cause of optic disc edema in TAO patients is the change in retinal and choroid blood flow.[18] Thus, the optic neuropathy caused by TAO is not entirely caused by the increased IOP, which also explains why the correlation between RNFL or visual field and TAO is not as correlated as glaucomatous optic nerve damage.

CONCLUSION

In this study, non-invasive EVP measurement showed a highly positive correlation with IOP and exophthalmos in TAO patients, and the elevated EVP was an important factor for the increase of IOP in TAO patients, which suggested that the increase of EVP may be one of the indicators for requiring clinical intervention. It was also found that the early optic nerve impairment in some TAO patients was reversible at a certain time. As a result, TAO patients with exophthalmos and others, which can lead orbital pressure to increase, should see a doctor in time and monitor the EVP and the

IOP, and find the early optic nerve injury with the examination of RNFL and visual field and take effective treatment as soon as possible, to avoid irreversible optic nerve injury.

CONFLICT OF INTERESTS

The authors declared no conflict of interest.

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AUTHORS' CONTRIBUTIONS

Xinyu Fan and Xu Zha contributed equally to this work. Xu Zha and Wenyi Guo conceived and designed the research; Guojiu WU collected data and conducted research; Xinyu Fan analyzed and interpreted data; Yuanhui Han wrote the initial paper; Ning Wang revised the paper; All authors read and approved the final manuscript.

ETHICAL COMPLIANCE

The ethics committee of The Second Affiliated Hospital of Kunming Medical University approved this study. Signed written informed consent were obtained from the patients and/or guardians.

AVAILABILITY OF DATA AND MATERIALS

The datasets generated and analyzed during the current study are not publicly available due to limitations of ethical approval involving the patient data and anonymity but are available from the corresponding author on reasonable request.

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