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# Effects of pulse glucocorticoid treatment on retinal blood flow in patients with active Graves' orbitopathy

Hedayatullah Mohammadi<sup>1</sup> , İrfan Botan Güneş<sup>2\*</sup> and Şeyhmus Arı<sup>3</sup>

## Abstract

**Background** Various studies have shown decreased retinal blood flow in patients with active Graves' orbitopathy (GO). We investigated whether retinal blood flow returned to normal levels after intravenous glucocorticoid treatment in active GO patients.

**Methods** Thirty-two eyes of 32 patients with moderate or severe active GO and 32 eyes of 32 healthy participants were included. The blood flow in the superficial plexus (SP), deep retinal plexus (DP), external retinal (ER) capillary plexus and choriocapillaris was measured via OCT-Angiography before treatment with methylprednisolone and one week after the completion of treatment. In addition, central macular thickness, intraocular pressure, and best corrected visual acuity, were compared with those of the control group.

**Results** Retinal blood flow (RBF) in the macula at SP, DP, ER and choriocapillaris levels was  $48.38 \pm 2.04$ ,  $54.17 \pm 3.11$ ,  $0.42 \pm 0.14$  and  $2176.45 \pm 147.53$  in the control group and  $45.91 \pm 4.56$ ,  $51.55 \pm 3.84$ ,  $0.35 \pm 0.34$  and  $2030.15 \pm 132.15$  in the active GO group, respectively. The RBF was significantly lower in the active GO group than in the control group at all angiographic levels ( $p < 0.001$ ). Although blood flow increased after treatment, it remained lower than that in the control group ( $p < 0.001$ ). The mean CMT was significantly greater in active GO patients before treatment than in the controls and after treatment ( $p < 0.001$ ). No serious systemic or ocular side effects were observed in any of the patients.

**Conclusions** After pulse glucocorticoid treatment, retinal blood flow increases but remains low compared with that in the healthy control group.

**Keywords** Glucocorticoids, Graves' ophthalmopathy, Optical coherence tomography angiography, Pulse therapy, Vessel, retinal blood

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## Introduction

Graves' orbitopathy (GO) is an inflammatory autoimmune disease in which autoantibodies against common antigens of the thyroid gland and orbital soft tissues, play important roles [1]. Although the pathogenesis of this disease has not been fully elucidated, autoantibodies are thought to activate of thyroid-stimulating hormone receptor (TSH-R) and lead to the uncontrolled release of thyroid hormones by mimicking thyroid-stimulating hormone (TSH) [1–3]. In addition, these autoantibodies also lead to inflammation of the orbital soft tissues, expansion of the extraocular muscles and an increase in the volume of orbital adipose tissue by activating orbital fibroblasts via cross-reactivity [3]–[4].

Patients with GO are divided into active and inactive subgroups on the basis of the presence and severity of clinical findings, and immunomodulatory treatment planning is based on the activity and severity of the disease [5–7]. The clinical activity score (CAS) is widely used in assessing the activity level of GO [6]. According to the EUGOGO guidelines active GO is described as mild, moderate to severe, or sight-threatening [8]. Glucocorticoids are the first choice for immunomodulatory treatment in patients with moderate or severe active GO [9].

In patients with active GO, symptoms of proptosis and diplopia occur as a result of the inflammation and increased volume of orbital soft tissues, whereas effects such as eyelid edema, conjunctival redness, chemosis and caruncle swelling occur because of impaired ocular blood flow [4, 10, 11]. Previous studies have demonstrated changes in ocular blood flow in GO patients via color Doppler ultrasonography (USG) and retinal flowmetry whereas a decrease in ocular blood flow was detected by Doppler USG; conversely, an increase in blood flow was detected via retinal flowmetry [11, 12]. In addition, OCT angiography (OCT-A) has recently been introduced as an established retinal imaging modality. With OCT-A, retinal blood flow in eye diseases and in systemic diseases with potential eye involvement can be visualized noninvasively on a micrometer scale [13].

There is only one previous study evaluating the effect of glucocorticoid treatment on retinal blood flow in Graves' orbitopathy using OCT angiography, which revealed an increase in retinal blood flow after treatment. Our study included a control group, unlike the previous study, and compared the retinal blood flow after treatment with that of the healthy control group.

## Methods

The present study had a prospective case control design and was carried out under the 1961 Declaration of Helsinki revised by the World Medical Association (WMA) for the Ethical Principles for Medical Research Involving

Human Subjects amended in October 2013. Approval was obtained from the Local Ethics Committee for the Clinical Practices of Gaziantep University (Reg. number: 07/25/2021 – 205); additionally, written informed consent was obtained from all participants.

Thirty-two eyes of 32 patients diagnosed with active GO (with more the proptotic eye selected) and the 32 right eyes of 32 participants in the control group were included in the study. All participants were assessed for age, sex, the presence of comorbid diseases, thyroid hormone status and history of medical or surgical treatment, and the data obtained were recorded. The best corrected visual acuity (BCVA) values of all participants were measured and the results were recorded as the logarithm of the minimum angle of resolution (logMAR). The findings of the anterior segment examinations were recorded using slit lamp microscopy, and the findings of the posterior segment examinations were determined using a 90-D lens. Proptosis was also determined with a Hertel exophthalmometer device (K-0161, Inami & Co. Ltd. Japan).

Participants aged 18–75 years with visual acuity  $\leq 0.3$  logMAR, an open visual axis and sufficient pupil dilation and fixation for OCT-A were included in the study. Participants aged  $< 18$  or  $> 75$  years; with BCVA  $\geq 0.4$  logMAR and spherical equivalent  $\geq 6$ ; with anterior segment pathology that obstructed the visual axis; with disorders affecting the optic disc, retina or choroid; with systemic diseases other than Graves' disease; or with a history of glaucoma, dysthyroid optic neuropathy, previous orbital surgery, or orbital radiotherapy; with OCT-A image quality  $< 6$ ; or with a cup-to-disc ratio  $\geq 0.3$  were not included in this study.

The clinical status of the patients was assessed using the Clinical Activity Score (CAS). The status is defined as active if the score is  $\geq 3$ , and consists of the following seven items and binary responses (yes/no) [14]:

- Spontaneous retrobulbar pain.
- Pain on attempting up and down gaze.
- Redness of eyelids.
- Redness of conjunctivae.
- Swelling of eyelids.
- Inflammation of the caruncle and/or plica.
- Conjunctival edema.

Disease severity was assessed according to the criteria of the European Group on Graves' Orbitopathy (EUGOGO) [6]. Patients with moderate to severe active GO who had a CAS  $\geq 3/7$  during follow-up received pulse glucocorticoid therapy. Patients with active GO were treated with intravenous (i.v.) pulse methylprednisolone at a dose of 500 mg/week with a cumulative dose of 4.5 g for six weeks and an additional 250 mg/week for the second six weeks.

Eye examination was performed by the same specialist (H.M) using the OCT-A device (AngioVue, RTVue-XR,

Fremont, California, USA). The examinations included a 3×3 mm macular area centered on the fovea at four angiographic levels; [superficial plexus (SP), deep plexus (DP), external retinal (ER) plexus and choriocapillaris (CC)] and a 4.5×4.5 mm peripapillary area centered on the optic disc. The central macular thickness (CMT), foveal avascular zone (FAZ), and peripapillary vascular density (VD) were automatically scanned via OCT-A before treatment and 13 weeks after the start of methylprednisolone treatment (one week after the completion of all administrations) (Figs. 1 and 2). The measurements obtained were compared with those of the control group. The black-to-white pixel ratios of the scanned areas in the OCT-A images are expressed indicators of blood flow in percent (%); this percentage represents an indirect measure of blood flow.

### Statistical analysis

All the statistical analyses were carried out using the Statistical Package for the Social Sciences software \*, version 20.0 (IBM Corp., SPSS, Armonk, NY). Descriptive characteristics are presented as the mean ± standard deviation (SD) (minimum - maximum) values. Since the sample size was small, the Shapiro -Wilk test was performed to determine normality. A normal distribution was observed for all variables in all groups ( $W > 0.90$ ,  $p > 0.05$ ). The independent samples t test was used for comparisons between the control group and the patient groups. The

paired samples t test was used to compare the pre- and post treatment data of patients with active Graves' orbitopathy. The Spearman coefficient was used for the correlation tests, and the chi-square test was used to examine the categorical variables. The results were analyzed at a 95% confidence interval (CI), and a p-value of  $< 0.05$  was considered to indicate statistical significance.

### Results

Thirty- two eyes of 32 patients (18 females and 14 males) with moderate to severe active GO and 32 eyes of 32 healthy participants (17 females and 15 males), as a control group, were included in the study. The mean age of the patients in the active GO group was  $40.62 \pm 12.45$  years (between 21 and 62 years), and that in the control group was  $41.12 \pm 11.2$  years (between 20 and 60 years) ( $p = 0.642$ ). The mean CAS was  $4.18 \pm 0.62$  before treatment and  $1.22 \pm 0.84$  ( $p < 0.001$ ) after treatment.

In active GO patients, the mean proptosis values before treatment were significantly greater than both the post treatment values and those in the control group ( $p < 0.001$ ); however, no significant differences were found in the mean BCVA or intraocular pressure (IOP) ( $p = 0.392$  and  $p = 0.685$ , respectively) (Table 1).

The mean CMT was greater in active GO patients before treatment than in both the control group and post treatment patients ( $p < 0.001$ ). The mean FAZ values did

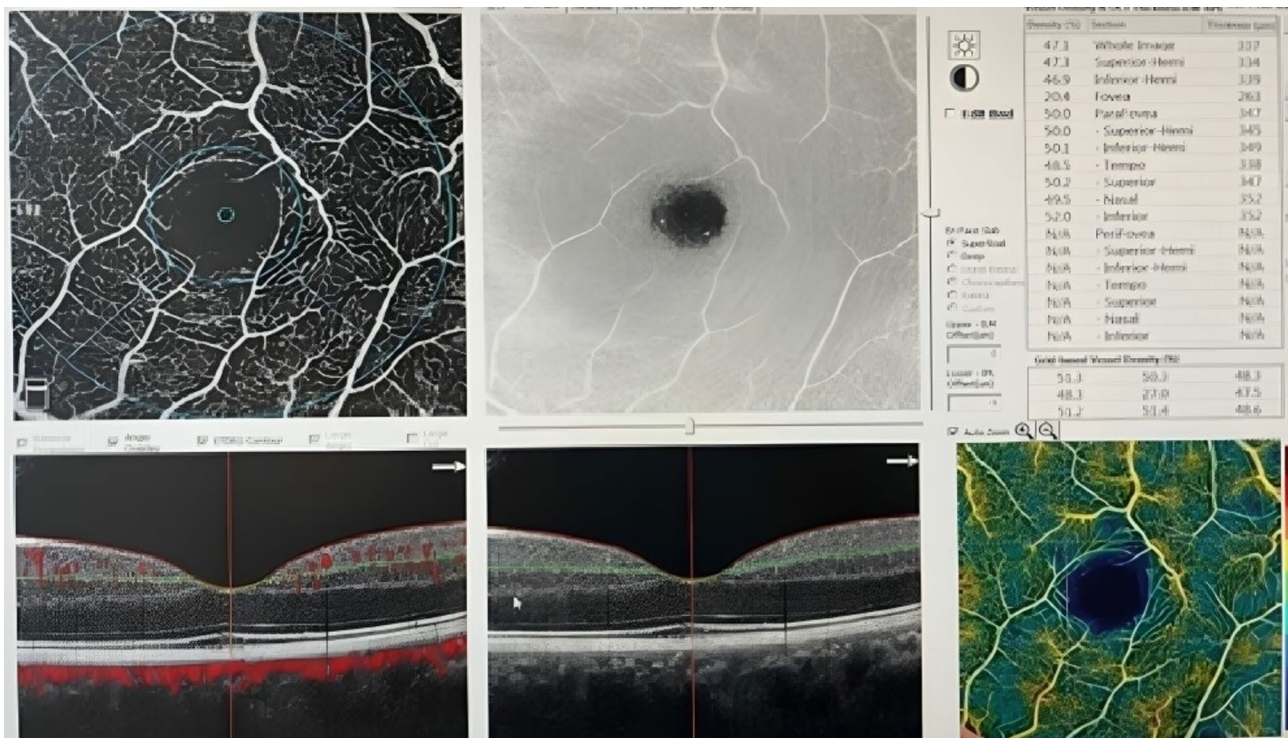


**Fig. 1** Optical coherence tomography angiography (OCT-A) image showing a 3×3 mm macular area centered on the fovea

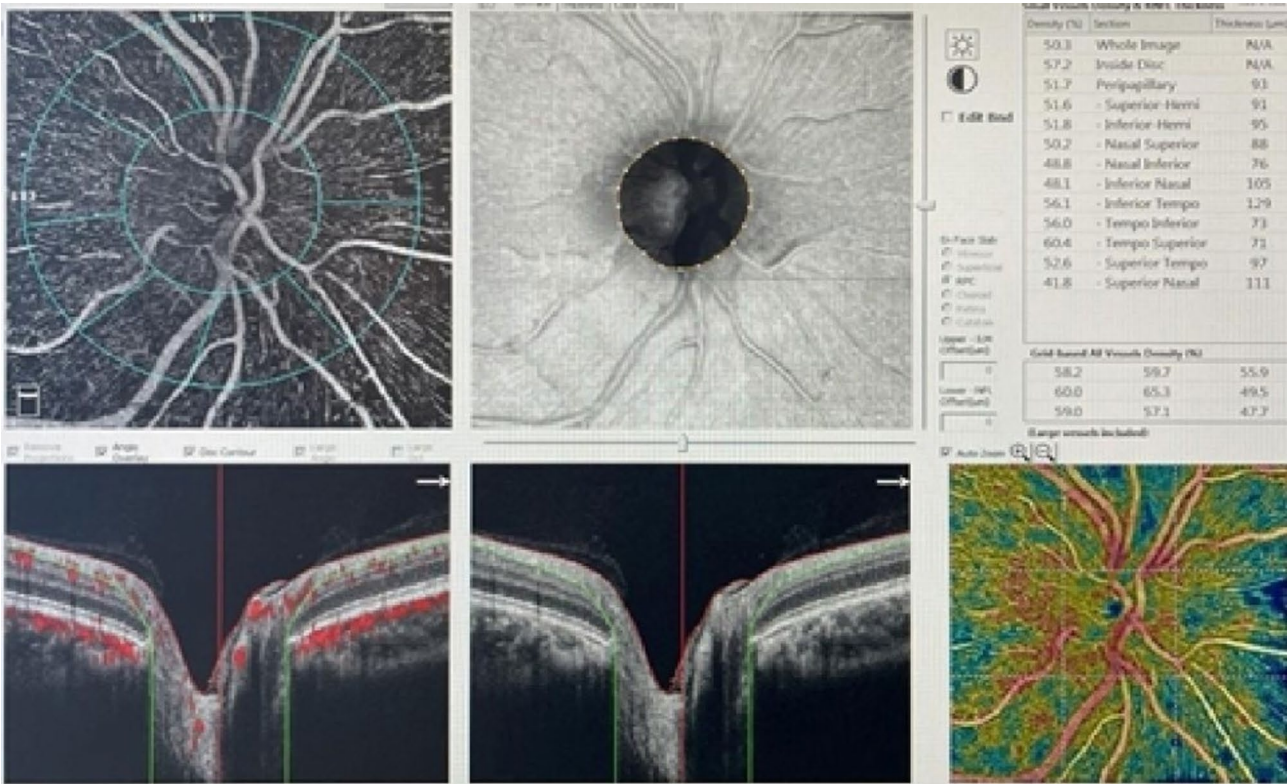


**Fig. 2** Optical coherence tomography angiography (OCT-A) image showing a 4.5 × 4.5 mm region of the peripapillary area centered on the optic disc

**Table 1** Intraocular pressure, best-corrected visual acuity, Hertel exophthalmometer measurements of both groups and clinical activity scores in patients with active graves’ orbitopathy

|                     | Control Group<br>(1)<br>n:32  | Active GO Pre-treatment Values (2)<br>n:32 | Active GO Post-treatment Values (3)<br>n:32 | p                                                                             |
|---------------------|-------------------------------|--------------------------------------------|---------------------------------------------|-------------------------------------------------------------------------------|
| IOP<br>mmHg ± SD    | 18.14 ± 1.13<br>(13–22)       | 18.27 ± 2.74<br>(12–22)                    | 18.46 ± 2.08<br>(13–21)                     | 1–2p=0.585 <sup>a</sup><br>1–3p=0.386 <sup>a</sup><br>2–3p=0.461 <sup>b</sup> |
| BCVA<br>logMAR ± SD | 0.05 ± 0.07<br>(0.00–0.30)    | 0.08 ± 0.03<br>(0.00–0.30)                 | 0.06 ± 0.05<br>(0.00–0.30)                  | 1–2p=0.392 <sup>a</sup><br>1–3p=0.786 <sup>a</sup><br>2–3p=0.541 <sup>b</sup> |
| Hertel<br>mm ± SD   | 18.05 ± 2.01<br>(16.00–21.00) | 21.64 ± 2.28<br>(17.00–23.00)              | 20.69 ± 2.46<br>(16.00–22.00)               | 1–2p<0.001 <sup>a</sup><br>1–3p<0.001 <sup>a</sup><br>2–3p<0.001 <sup>b</sup> |
| CAS                 | -                             | 4.18 ± 0.62<br>(3–6)                       | 1.22 ± 0.84<br>(0–3)                        | <0.001 <sup>b</sup>                                                           |

Descriptive characteristics were given as mean ± standard deviation (SD) (minimum–maximum), n: Number of eyes, GO: Graves’ Orbitopathy, IOP: Intraocular pressure, BCVA: Best-corrected visual acuity, CAS: Clinical activity score, <sup>a</sup> Independent samples t-test, <sup>b</sup> Paired samples t-test, p-value < 0.05 was accepted as statistically significant

not significantly differ between the groups ( $p=0.392$ ). (Table 2). While the mean value of the peripapillary vascular density was significantly lower in the active GO group than in the control group, no significant difference was found between pretreatment and posttreatment values. ( $p<0.001$  and  $p=0.254$ ). The mean intraoptic disc vascular density was significantly lower in the active GO group than in the control group, and the values before

treatment were significantly lower than those after treatment ( $p<0.001$ ) (Table 2). In the control group, the blood flow in the macula at the SP, DP, ER and CC was  $48.38 \pm 2.04$ ,  $54.17 \pm 3.1$ ,  $0.42 \pm 0.1$  and  $2176.45 \pm 147.5$  respectively. Macular blood flow in the active GO group was significantly lower than that in the control group at all angiographic levels, and although blood flow increased after treatment, it remained lower than that in the control group ( $p<0.001$ ) (Table 3). No

**Table 2** Average central macular thickness, foveal avascular zone and vascular density of the intra-optic disc, peripapillary capillary plexus before and after treatment

|                                     | Control Group<br>(1)<br>n:32 | Active GO Pre-treatment Values (2)<br>n:32 | Active GO Post-treatment Values<br>(3)<br>n:32 | p                                                                                   |
|-------------------------------------|------------------------------|--------------------------------------------|------------------------------------------------|-------------------------------------------------------------------------------------|
| CMT ( $\mu\text{m} \pm \text{SD}$ ) | 246.81 $\pm$ 15.34           | 251.05 $\pm$ 21.37                         | 246.36 $\pm$ 24.12                             | 1–2p < 0.001 <sup>a</sup><br>1–3p = 0.164 <sup>a</sup><br>2–3p < 0.001 <sup>b</sup> |
| FAZ ( $\text{mm}^2 \pm \text{SD}$ ) | 0.32 $\pm$ 0.11              | 0.31 $\pm$ 0.22                            | 0.32 $\pm$ 0.08                                | 1–2p = 0.392 <sup>a</sup><br>1–3p = 0.764 <sup>a</sup><br>2–3p = 0.346 <sup>b</sup> |
| Intra-optic VD<br>(% $\pm$ SD)      | 52.21 $\pm$ 5.10             | 49.17 $\pm$ 4.65                           | 50.64 $\pm$ 6.24                               | 1–2p < 0.001 <sup>a</sup><br>1–3p < 0.001 <sup>a</sup><br>2–3p < 0.001 <sup>b</sup> |
| Peripapillary VD<br>(% $\pm$ SD)    | 51.97 $\pm$ 2.51             | 49.96 $\pm$ 2.15                           | 50.04 $\pm$ 4.16                               | 1–2p < 0.001 <sup>a</sup><br>1–3p < 0.001 <sup>a</sup><br>2–3p = 0.254 <sup>b</sup> |

Descriptive characteristics were given as mean  $\pm$  standard deviation (SD), n: Number of eyes, GO: Graves' Orbitopathy, CMT: Central macular thickness, FAZ: Foveal avascular zone, VD: Vascular density,

<sup>a</sup> Independent samples t-test, <sup>b</sup> Paired samples t-test, p-value < 0.05 was accepted as statistically significant

**Table 3** Macular blood flow at different retinal levels

|                                            | Control Group<br>(1)<br>n:32 | Active GO Pre-treatment Values (2)<br>n:32 | Active GO Post-treatment Values (3)<br>n:32 | p                                                                                   |
|--------------------------------------------|------------------------------|--------------------------------------------|---------------------------------------------|-------------------------------------------------------------------------------------|
| SP BF (% $\pm$ SD)                         | 48.38 $\pm$ 2.04             | 45.91 $\pm$ 4.56                           | 46.11 $\pm$ 3.45                            | 1–2p < 0.001 <sup>a</sup><br>1–3p < 0.001 <sup>a</sup><br>2–3p = 0.001 <sup>b</sup> |
| DP BF (% $\pm$ SD)                         | 54.17 $\pm$ 3.11             | 51.55 $\pm$ 3.84                           | 52.69 $\pm$ 3.92                            | 1–2p < 0.001 <sup>a</sup><br>1–3p < 0.001 <sup>a</sup><br>2–3p < 0.001 <sup>b</sup> |
| ER BF area ( $\text{mm}^2 \pm \text{SD}$ ) | 0.42 $\pm$ 0.14              | 0.35 $\pm$ 0.34                            | 0.37 $\pm$ 0.53                             | 1–2p < 0.001 <sup>a</sup><br>1–3p < 0.001 <sup>a</sup><br>2–3p < 0.001 <sup>b</sup> |
| CC BF area ( $\text{mm}^2 \pm \text{SD}$ ) | 2176.45 $\pm$ 147.53         | 2030.15 $\pm$ 132.15                       | 2098.20 $\pm$ 183.16                        | 1–2p < 0.001 <sup>a</sup><br>1–3p < 0.001 <sup>a</sup><br>2–3p < 0.001 <sup>b</sup> |

Descriptive characteristics were given as mean  $\pm$  standard deviation (SD) (minimum-maximum), n: Number of eyes, GO: Graves' Orbitopathy, BF: Blood flow, SP: Superficial plexus, DP: Deep plexus, ER: External retina, CC: Choriocapillaris, <sup>a</sup> Independent samples t-test, <sup>b</sup> Paired samples t-test, p-value < 0.05 was accepted as statistically significant

participants developed cataracts, hypertension, blood sugar dysregulation, worsening of liver function tests or allergic reactions during treatment or follow-up.

## Discussion

The main orbital vascular structures and changes in retinal microvascular circulation in GO patients and their effects on the eyes were investigated using various imaging techniques such as Heidelberg retinal flowmetry, oculodynamometry, color Doppler USG, OCT, and OCT-A [11, 15–17]. In the present study, we investigated the effects of pulse glucocorticoid treatment on IOP, BCVA, CMT and retinal blood flow in patients with active GO using OCT-A, which provides noninvasive angiographic images of the optic disc and retinal microvascular structures within seconds. Since the clinical activity scores of both eyes were the same in the vast majority of patients

included in the study, more proptotic eye was selected for each.

Owing to their anti-inflammatory and immunosuppressive effects, glucocorticoids have been used for several years as first-line treatments for many inflammatory diseases. The European Thyroid Association (ETA) recommends intravenous glucocorticoid pulse therapy as the first-line treatment for active and moderate to severe GO [18–20]. In our study, we also implemented the treatment protocol recommended by the ETA in our patients, and none of our patients experienced serious cardiovascular or cerebrovascular complications or serious systemic complications such as acute liver failure during the treatment period.

The CAS is used to evaluate and determine disease activity and assess patient response to immunomodulatory treatment by allowing rapid assessment in the office setting and independent of other imaging modalities [14].

A study conducted by Tortora et al. it was revealed that the CAS is beneficial for the accurate diagnosis of GO patients and that the correlation of the CAS with other imaging modalities is satisfactory [21]. In our study, the mean CAS before treatment was  $4.18 \pm 0.62$ . The mean CAS after treatment was  $1.22 \pm 0.84$ . Due to the anti-inflammatory effect of glucocorticoid treatment, a significant decrease in CAS was observed in patients after treatment. Similarly, a significant decrease in the mean posttreatment Hertel exophthalmometer readings was observed in GO patients. We found no significant difference between the mean IOP or BCVA before or after treatment or between patients and the control group. Similarly, no significant difference was found in the IOP values of patients after glucocorticoid treatment in the study by Hall et al. [22].

In previous studies examining retinal blood flow using OCT-A in AGO patients, Tehrani et al. reported that the VD in the macula, parafoveal area, and peripapillary area was lower in active GO patients than in healthy controls [23]. Dave et al. reported that peripapillary and macular VD values were also lower in active GO patients than in patients with inactive GO and reported no significant difference between inactive GO patients and healthy controls [24]. In another study by Wu et al. the VD in the superficial and deep capillary plexus was lower in active GO patients than in healthy individuals [25]. The reason for the decrease in retinal blood flow in active GO patients in all the above studies was the increase in volume owing to inflammation in the orbital soft tissues and extraocular muscles, which led to a decrease in retinal blood flow because of the effect of compression on normal retinal blood flow. In contrast to the findings of the above studies, Ye et al. reported an increase in both superficial and deep retinal VD in active GO patients and attributed this result to the increase in ocular blood flow owing to inflammation and increased cardiac output caused by hyperthyroidism [26].

To our knowledge, only one previous study in the literature investigated the effects of glucocorticoid treatment on retinal blood flow in active GO patients using OCT-A [27]. In the study by Del Noce et al. an increase in the VD in all retinal layers of the macula was found after i.v. pulse glucocorticoid treatment in active GO patients [27]. Del Noce et al. demonstrated that the decrease in inflammation in orbital soft tissues and the increase in blood flow in the retina owing to the decrease in intraorbital pressure after treatment with pulse steroids were responsible for the increase in VD in all retinal layers of the macula [27]. Although the effect of glucocorticoid treatment on retinal blood flow in active GO patients was evaluated in the study conducted by Del Noce et al. we could not evaluate whether the blood flow reached normal levels

after treatment because there was no control group in the study.

The quality of the images obtained in an OCT-A examination may affect the quantitative values. Kamali-pour A. et al. demonstrated in their study that Angiovue examinations with an image quality score above 4 (range 1 to 10) produced reliable results [28]. In our study, we excluded examinations with an image quality score below 6. Additionally, most of the images obtained for the present study have an image quality score of 7 or above.

In our study, blood flow in the peripapillary area, intra optic disc and all angiographic levels of the macula (SP, DP, ER and coriocalpilaris) in active GO patients increased significantly after pulse glucocorticoid treatment but did not reach the level of healthy control participants in any area. We believe that the lower retinal blood flow in active GO patients than in control patients is related to the decrease in orbital blood flow due to the compressive effect of the volume increase associated with inflammation in orbital soft tissues, as predicted by the authors in previous studies [23–25].

Previous studies have shown that Graves' disease and hyperthyroidism trigger inflammation and increase the number of adhesion molecules in vascular endothelial structures, thereby increasing the risk of atherosclerosis and vascular occlusion [29, 30]. We suggest that this may contribute to the decrease in retinal vascular density in patients with Graves' disease. However, we believe that OCT-A data, which indirectly show retinal blood flow, are insufficient for this evaluation and that fluorescein angiography and retinal flowmetry examinations, which directly indicate blood flow, would be more accurate.

After pulse glucocorticoid treatment, the volume of the soft tissues in the orbit decreases owing to the decrease in inflammation and the compressive effect on blood vessels also decreases. The significant decrease in proptosis after treatment supports our hypothesis. However, in our study, retinal blood flow was still significantly lower in the treated group than in the control group. The fact that the proptosis measurements were still significantly greater after treatment than those in the control group showed that the soft tissue volume in the orbit was still larger than normal.

The vascular density in the choriocalpilaris layer, which supplies the outer segment structures of the retina, increased after treatment. This finding suggests that the choroidal blood flow may have increased as a result of the same factors that caused the increase in retinal blood flow.

Previous studies have shown that a decrease or slow-down in retinal blood flow may predispose patients to normotensive glaucoma, retinal artery stenosis, branch retinal vein occlusion and choroidal neovascularization [31–33]. We believe that we do not yet have sufficient

evidence to evaluate the importance of the statistically significant numerical decrease in retinal blood flow in terms of eye health and clinical practice. However, we believe that active GO patients, whose retinal blood flow is below normal levels despite treatment should be followed carefully to monitor for retinal vascular diseases and normotensive glaucoma.

In this study, although a decrease in the thickness of the CMT was found after pulse glucocorticoid treatment, there was no significant difference in the mean FAZ area. Previous studies have reported a decrease in superior ophthalmic vein flow and venous congestion in the orbit in active GO patients [34–36]. We hypothesize that the decrease in CMT after treatment with i.v. glucocorticoids in our study was attributable to the regression of venous congestion in the orbit, which resulted from the decrease in inflammation and edema in the soft tissues after treatment.

The limitations of the study include the small sample size, short patient follow-up period, lack of orbital imaging showing orbital congestion after treatment and lack of measurement of the axial lengths of the participants included in the study, which was one of the most important limitations. Additionally, we were unable to obtain measurements adjusted for diurnal effects, which is another shortcoming of our study.

## Conclusions

In conclusion, we found that retinal blood flow was reduced in active GO patients. The retinal blood flow in active GO patients increased after pulse glucocorticoid treatment but remained low compared to that of the healthy controls. According to the results of our study, OCT-A can be used to evaluate the efficacy of glucocorticoid treatment. To explain the clinical significance of the statistically significant decrease in retinal blood flow, studies with larger sample sizes and longer follow-up periods are needed.

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Not applicable.

## Author contributions

Conceptualization: IBG and HM; Methodology: IBG, HM and SA; Software: IBG; Validation: HM and IBG; Formal Analysis: HM, IBG and SA; Investigation: HM, IBG and SA; Resources: IBG and HM; Data Curation: IBG and SA; Writing-Original Draft Preparation: IBG; Writing-Review and Editing: IBG, HM and SA; Visualization: HM and IBG; Supervision: SA; Project Administration: HM and SA; All authors have read and agreed to the published version of the manuscript.

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## Data availability

The datasets during and/or analysed during the current study available from the corresponding author on reasonable request.

## Declarations

### Ethics approval

For the present study, approval was obtained from the Local Ethics Committee for Clinical Practices of Gaziantep University (Reg. number: 07/25/2021 – 205) under the 1961 Declaration of Helsinki and its later amendments. Informed consent was obtained from all individual participants included in this study.

### Consent for publication

Not applicable.

### Competing interests

The authors declare no competing interests.

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