Effects of Ketoconazole On Clinical Recovery In Central Serous Chorioretinopathy

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Research Article

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Abstract

Background: Hypercortisolism has long been correlated with choroidal vasorelaxation in central serous chorioretinopathy (CSCR). This may explain the inconsistency of therapeutic responses of the mineralocorticoid receptor (MR) antagonist since hyperaldosteronism has rarely been detected in such cases. Hence, an early treatment using ketoconazole, the first line cortisol inhibitor that also blocks the MR ligand, appears to be rational. This study aimed to evaluate the effects of ketoconazole on CSCR, and to analyze correlations between choroidal thickness and steroid hormones.

Method: In this three-center retrospective cohort, forty-one naïve CSCR eyes of 41 patients were categorized into control (20 eyes) and treatment group (21 eyes). Patients in the treatment group were given oral ketoconazole at a daily dose of 400 or 600 mg for three to six weeks. At week 12, rescue laser therapy was applied to patients exhibiting persistent subretinal fluid (SRF). We performed a survival analysis to determine the time interval from presentation to clinical resolution of SRF. The secondary outcomes consisted of proportion of eyes with persistent SRF, and factors affecting therapeutic response.

Results: Mean 24-hour urinary free cortisol (UFC) were elevated at 181 ± 70 and 150 ± 68 μg/day (range = 20-150) in the treatment and control group ($p = 0.21$). After controlling for age and gender, baseline UFC levels demonstrated a positive correlation with choroidal thickness in both eyes ($p < 0.05$). Ketoconazole significantly accelerated the resolution of CSCR with the median time to resolution of 7 versus 16 weeks ($p < 0.01$), and reduced the proportion of eyes receiving rescue therapy at 12 weeks (23.8% versus 50%, $p = 0.01$). Prolonged CSCR durations were likely found in elderly patients who had thick choroid in fellow eyes.

Conclusions: Elevated glucocorticoids are likely responsible for the pathogenesis of CSCR. Therefore, a temporary decrease in choroidal hyperpermeability using the cortisol blocker could reduce the persistency of CSCR.

Background

Choroidal hyperpermeability in central serous chorioretinopathy (CSCR) has been associated with increases in endogenous corticosteroids [1, 2]. Nonetheless, most patients with CSCR rarely represent Cushing's syndrome. Such elevation of steroids, particularly glucocorticoids, are productions of repetitive hyperactivity of the hypothalamic-pituitary-adrenal axis. These abnormalities in endocrine signaling are potential impacts of predisposing factors for CSCR including constant exposure to stress, psychiatric problems, and chronic sleep deprivation [2, 3]. Modification of factors mentioned combined with deferred laser therapy for CSCR still has one major unsolvable problem - ambiguous information regarding features affecting persistent subretinal fluid (SRF). Potential results include some degrees of permanent visual dysfunction in spite of laser therapy [4, 5]. This concern has led to an early and non-invasive treatment using oral mineralocorticoid receptor (MR) antagonists in recent years [6]. However, the fact that hyperaldosteronism has rarely been detected in CSCR patients may explain the ineffectiveness of

MR antagonists [7–9]. Theoretically, MR antagonists only inhibits the binding of excessive cortisol to the MR while most glucocorticoid receptors on the choroid are still occupied by cortisol; active free cortisol has the same affinity for the MR as aldosterone but is present in much higher concentrations in plasma [10].

Ketoconazole is the first line glucocorticoids inhibitor through an adrenolytic activity at adrenal cortex [11]. It also blocks the MR ligands at the cellular level, and should prevent further choroidal vasodilation. These mechanisms are expected to accelerate the resolution of SRF, and thereby decrease the chance of persistent CSCR. In this study, we aim to evaluate the effects of ketoconazole on clinical outcomes in CSCR eyes, and to analyze relationships between choroidal thickness and steroid hormones.

Methods

This was a three-center, retrospective cohort study conducted at Vajira, Rajavithi and Srinakharinwirot University Hospital in Thailand between July 2018 to August 2020. The Institutional Review Board approvals were obtained, and the principles for this research were based on the Declaration of Helsinki. Currently, oral ketoconazole is not yet approved for the treatment of CSCR.

Patients between ages 20 to 55 years, who were diagnosed with naïve CSCR and exhibited symptoms within the past 6 months, had been consecutively reviewed for this study. In bilateral CSCR, the eye with shorter duration of the disease was selected as the study eye. Simultaneous fluorescein and indocyanine green angiography (Spectralis OCT, Heidelberg engineering, Germany) images were obtained in patients aged 50 years and above to eliminate the possibility of choroidal neovascularization. We excluded patients with the following conditions: high myopia or hyperopia (>4 diopters), other conditions manifesting as serous macular detachment, nephrotic syndrome, chronic kidney disease, liver disease, women during pregnancy and lactation, and conditions depending on a long-term use of steroids. In addition, patients taking drugs interrupting a cytochrome-dependent metabolism, and patients taking antacid or H2 blockers were excluded from the study.

Regarding our hospitals' checklists and guidelines for CSCR patients, patients were routinely advised for a discontinuation of smoking and steroid usage. A psychiatrist consultation had been ordered as indicated. Patients must have completed the STOP-BANG questionnaire, a quick screening tool for obstructive sleep apnea (OSA) [12]. All high-risk patients were required to undergo sleep laboratory tests.

Patients were categorized into ketoconazole-treated and control group. In the treatment group, oral ketoconazole at a daily dose of 400 (BW<50Kg) or 600 mg (BW>50Kg) were given for a maximum duration of 6 weeks. The treatments could be terminated at any evidence of dry fovea detected by the optical coherence tomography (OCT) (clinical resolution of CSCR). The dosage could be decreased by 200 mg in cases of clinical improvement at 3 weeks. Placebos were not given to the control group. Treatment allocations were based on patients' decisions after the differences in risks and benefits between oral ketoconazole and conservative treatment had been thoroughly explained. Rescue laser therapies using either laser photocoagulation or photodynamic therapy were applied to individuals whose

SRF persisted at 12 weeks follow-up. Off-labeled use of anti-vascular endothelial growth factor was given to eyes with thin choroid and diffuse fluorescein leakage involving fovea.

Symptom durations were recorded based on patients' history. The primary outcome was the time interval from presentation to clinical resolution of SRF. The secondary outcomes consisted of proportion of eyes with persistent SRF requiring rescue interventions at 12 weeks follow-up, and predictors of such occurrence. Due to disrupted circadian rhythms in most CSCR patients, periodic collections of urine specimen throughout the 24-hour period are a more reliable sample to detect free cortisol than a single-timed morning serum [13]. Therefore, baseline hormonal profile of endogenous steroids selected in this study comprised 24-hour urinary free cortisol (UFC), serum aldosterone, and total testosterone. Subfoveal choroidal thickness (SFCT) were measured from the back surface of retinal pigment epithelium (RPE) to chorioscleral interface using a horizontal scan of enhanced-depth imaging OCT (Spectralis OCT, Heidelberg engineering, Germany). 1-mm central subfield thickness (CST) and ocular examination were collected at the baseline with one, three-, and six-months.

In the ketoconazole-treated group, potential adverse effects of the drug were monitored and recorded in every visit. These included but not limited to stomach pain, skin rash, headache, dizziness, breast swelling, impotence and elevated liver enzymes [11].

Statistical Analysis

Skewed data were logarithmically transformed before analysis. After validation of the implemented model, a multiple regression analysis adjusting for age and symptom duration were performed to detect relationships between baseline SFCT and each of endogenous steroid levels. Regarding 6-month results, covariate adjustment was applied for each analysis by adding baseline confounders and significant predictors into the model.

We performed a survival analysis to determine the distribution of time to the resolution of SRF using the p-sample log-rank test. Observations were censored at the first detection of dry macula in all eyes including those receiving rescue therapy at 12 weeks. A Cox proportional hazards regression was used to calculate the hazard ratios of predictors of 12-week persistent SRF (Wald p-value). Adjusting for covariates was done by inclusion of the potential predictors in the model (Table 3). Lastly, we assessed whether there were any violations of proportional hazards assumptions on each covariate. The two-sided p value <0.05 was considered statistically significant. Stata version15.0 (Statacorp, College Station, TX) was used for all computations.

Results

After disqualifying 13 eyes from the study because of incomplete imaging, a total of 41 eyes from 41 patients had been categorized into 21 eyes in the treatment and 20 eyes in the control group. Baseline clinical settings and results at 6 months were detailed in Table 1 and 2, respectively.

For baseline characteristics, while ketoconazole-treated patients had significantly longer symptom duration than the controls (19.8 ± 3.9 and 8.5 ± 2.7 weeks, $p = 0.02$), baseline 1-mm CST was comparable between two groups (440 ± 167 in the treatment and 432 ± 143 μm in the control group, $p = 0.90$). Baseline SFCT of CSCR eyes in the treated-patients was slightly thicker than that of the control patients (515 ± 170 and 461 ± 79 μm, $p = 0.22$). Both groups had slight elevations of presenting 24-hour UFC at 181 ± 70 in the treatment and 150 ± 68 μg/day in the control group (range = 20-150 μg/day, $p = 0.21$). Serum aldosterone and total testosterone levels of both groups were within the normal range. After controlling for age, gender and symptom duration, the hormonal profiles of each endogenous steroid were not different between the two groups (Table 1). Baseline mean arterial pressure was normal in all patients (95.5 ± 12.1 mmHg), and had no correlation with SFCT.

After adjusting for age and symptom duration, the scatter plots of data from all patients showed a positive linear correlation between 24-hour UFC level and SFCT (Fig. 1); Figure 1B demonstrates superior correlation consistency with more significant correlations in fellow non-CSCR eyes. Such correlations were not detected in the models using serum aldosterone or testosterone. The formulas are displayed as follows:

24-hour UFC = 118 – 0.66xage + 0.18xSFCT (CSCR eyes), $p = 0.04$

24-hour UFC = 69 – 0.67xage + 0.28xSFCT (fellow eyes), $p = 0.011$

The proposed formulas may be dissimilar to those acquired from different techniques due to variation in reference intervals. For the primary outcome, Kaplan-Meier estimates displayed in Figure 2 showed that ketoconazole significantly accelerated the resolution of CSCR with the median time to complete SRF absorption of 7 versus 16 weeks in the treatment and control group ($p = 0.01$, log-rank test). Additional file 1 demonstrated a typical central serous chorioretinopathy (CSCR) patient that is responsive to ketoconazole.

After controlling for age, symptom duration and baseline CST, ketoconazole decreased the proportion of eyes requiring rescue therapy at 12 weeks from 50% in the treatment group to 23.8% in the control group ($p = 0.01$). It also resulted in more Early Treatment Diabetic Retinopathy Study letter improvement at 6 months (11.5 ± 8.9 and 5.8 ± 9.3 letters in the treatment and control group ($p = 0.01$). Furthermore, after controlling for age and mean arterial pressure, SFCT reduction in the ketoconazole-treated eyes was greater than that in the controls at 3 months (9.3 ± 10.2 versus 4 ± 13.8 μm, $p = 0.20$). However, the differences observed in overall SFCT reduction between two groups did not reach significant level throughout 6 months of follow-up (9.9 ± 24.4 and 9.5 ± 26.4 μm, $p = 0.96$) (Table 2).

Regarding the STOP-BANG questionnaire, abnormal sleep behavior had been detected in 26 cases (63.4%) of all patients. The sleep laboratory tests revealed 7 cases (17%) with moderate to severe OSA (Respiratory Disturbance Index > 15/hour), all which required positive airway pressure therapy. Of all 32 patients whose body mass index ≥ 25 kg/m^2, any stages of OSA were detected in twelve cases (37.5%). Figure 3 showed a chronic CSCR patient who was later diagnosed with severe OSA.

In the control group, Cox regression analysis revealed that patients' advanced age and thick choroid in fellow non-CSCR eyes predisposed persistent CSCR (Table 3). Despite the absence of the appropriate data to validate c-statistic and cut-off values, the 75 percentiles of data, choroidal thickness ≥ 450 μm and age ≥ 45, may be the reasonable cut-off points. Figure 4 showed a case with high-risk features for persistent CSCR.

Referring to the study, four cases (19%) reported minor side effects including stomach problems or skin rashes. In all reported cases, the symptoms disappeared within one week after treatment discontinuation. Liver enzymes were elevated in one patient (4.7%) during the third week post-treatment. After the immediate termination of the ketoconazole treatment, his liver enzymes returned to normal. In comparison of all cases receiving ketoconazole for Cushing's disease, those developing hepatic failure have reportedly received higher doses and longer duration than our protocol [14,15]. These five patients were included in all analyses.

Discussions

Regarding the baseline characteristics, the fact that symptom duration in the treatment group was longer than those in the control group may dispute this study's results on its primary outcome. However, rather than a natural process of spontaneous SRF resolution, the equivalences in baseline macular thickness should support the effects of the medication on shortening the disease course.

In our study, ketoconazole significantly reduced the course length of CSCR and likelihoods of persistent SRF. The time to SRF resolution in the control group (16 weeks) is comparable to that from the previous study (4.1 months) [16]. Similarly, the SFCT reduction was greater in the treatment arm during the first three months (Table 2). This may have reflected the temporary decrease in choroidal hydrostatic pressure by ketoconazole, thus facilitating the fluid absorption across RPE. These findings suggest that early intervention is necessary to minimize the chance of developing high-viscosity SRF, which will decelerate the SRF pumping process [17]. Ketoconazole-treated patients who initially had worse best-corrected visual acuity (BCVA) than the control group showed more letter gain and achieved comparable final BCVA being at approximately 20/32 at 6 months (Table 2).

Some previous studies reported inconsistency in the key hormone responsible for the development of CSCR [1,8,18]. Karahan and his group reported no significant correlation between choroidal thickness and serum cortisol level (p = 0.14). Nevertheless, assessment of serum cortisol at a single time point has many limitations for CSCR interpretation [13]. Their study also carried methodological challenges by enrolling only healthy subjects, which could make the data less distributed [18].

By demonstrating a positive correlation between elevated UFC level and choroidal thickness, the present study supports the hypothesis that increased plasma cortisol levels predispose CSCR; these associations were not observed in serum aldosterone and total testosterone levels. The correlation between cortisol level and SFCT was stronger in fellow non-CSCR eyes (Fig. 1). We speculate that the decompressed choroid in CSCR eyes makes its thickness less predictable. We therefore selected these fellow eyes for

further analysis of potential predictors of persistent CSCR (Table 3). All things considered, these results correspond with the previous study demonstrating that hypothalamic-pituitary-adrenal activity increased slightly in patients with chronic CSCR [2]. Thus, circumstantial evidence supports the principle behind our study that application of a pan-glucocorticoid inhibitor, should alleviate choroidal congestion during the acute stage of CSCR.

Regarding the measurement of free cortisol levels, despite the reliability of 24-hour urine specimen, its downsides include incomplete urinary collection and the requirement for cold storage. In particular, given a rare association between CSCR and Cushing's disease, routine measurement of UFC in CSCR patients would not be practical or beneficial. Alternatively, a direct assessment of bioavailable cortisol reflecting the hormonal activity at the target tissue (choroidal) level may provide ancillary benefits in terms of monitoring hormonal activity alongside with chorioretinal findings. Unfortunately, this test is not yet clinically available [13,19].

There have been only two studies evaluating the effects of ketoconazole on the CSCR. Firstly, a controlled study performed by Golshahi and his group showed no difference in visual outcomes after treating acute CSCR patients with 200 mg/day ketoconazole for 4 weeks [20]. This indifference in visual outcome may be due to inadequate dosage, short follow-up intervals, and favorable natural course of acute CSCR. Regarding the differences in protocols between this study and ours, we applied higher doses with longer duration of treatments. Another small case series done by Meyerle et al reported anatomic improvement in 5 patients with chronic CSCR at 8 weeks follow-up after treating patients with 600 mg/day ketoconazole for 4 weeks [21].

Our study's predictors for persistent CSCR correspond well with those from previous research [22]. Daruich et al concluded that SFCT >500 μm (p = 0.01), and patients' age >40 years (p = 0.01) were significantly associated with longer CSCR episodes [23]. These cut-off values are close to the 75th percentiles of our study's predictive values: choroidal thickness of >450 μm and age of >45 years. In contrast to some reports, we did not observe any association between either baseline BCVA or CST and the disease episode length [24,25].

Nonetheless, pharmacological therapy for CSCR is not without adverse effects. For practical aspects, given that most CSCR has a favorable natural history, we may apply such oral medications to only patients at high risk for persistent subretinal fluid - those in relatively advance age group who have thick choroid in the fellow eyes (>450 μm); this unique set of CSCR patients likely possess high magnitude of choroidal hydrostatic pressure and relatively decreased RPE function.

Apart from the pharmacological treatment, modification of CSCR risk factors on the individual level is imperative to prevent disease recurrences. Our study found that correspondingly 26.8%, 63.4% and 17% of all patients had a history of steroid use, abnormal sleep behavior and OSA requiring airway pressure therapy. These are supported by previous meta-analysis and large cohort study pointing that poor sleep quality (hazards ratio = 1.08) and sleep apnea (odds ratio = 1.56) significantly increase risk of CSCR in

general population [3,26,27]. Such factors are known to be associated with hypothalamic–pituitary–adrenal axis activation and alterations in cortisol levels [28,29]. Our recommendations for the acute CSCR are to identify such features and plan on how we can eliminate them. For instance, referring specialists such as, sleep specialist and respiratory clinic could help patients minimize usage of inhaled steroids or provide a definite treatment for sleep apnea.

Our study limitations include small sample size and the retrospective design resulting in a lack of placebo controls, variation in treatment regimens, differences in symptom duration between the two groups, and lack of treatment randomization. In addition, the effects of pigment epithelial detachment involvement were not evaluated in the Cox regression model. These make the study results less generalizable, in particular for a multifactorial disease like CSCR that can manifest clinically itself in various ways. Well-designed randomized controlled clinical trials are required to warrant the benefits of ketoconazole in terms of shortening the disease duration as compared to the natural recovery. Furthermore, a larger number of patients exposed to the medication is needed to detect unexpected and severe adverse events.

In conclusion, this study addressed the role of elevated glucocorticoid levels as one of the pathogenicity of CSCR. Proactive interventions for CSCR using oral ketoconazole may reinforce faster resolution of subretinal fluid. This drug can be considered as an alternative for cases with high-risk features of persistent CSCR or cases whose adherence to behavioral changes is likely poor.

List Of Abbreviations

central serous chorioretinopathy (CSCR)

mineralocorticoid receptor (MR)

subretinal fluid (SRF)

urinary free cortisol (UFC)

optical coherence tomography (OCT)

obstructive sleep apnea (OSA)

subfoveal choroidal thickness (SFCT)

retinal pigment epithelium (RPE)

central subfield thickness (CST)

best-corrected visual acuity (BCVA)

Declarations

Acknowledgement: not applicable.

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Competing interests: No financial disclosures or conflicting relationship exists for any authors. Oral ketoconazole is not yet approved for the treatment of CSCR.

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Tables

Table 1 Baseline Clinicodemographic and Hormonal Profiles of All 41 Study Patients with Central Serous Chorioretinopathy (CSCR)

	Ketoconazole-treated group (21 eyes)	Control group (20 eyes)	*P* Value
Age (years)	48.1 ± 5.7	44.5 ± 10.4	0.20
Male	85%	72%	0.33
Symptom duration (weeks)	19.8 ± 3.9	8.5 ± 2.7	0.02*
Subfoveal choroidal thickness			
CSCR eye	515 ± 170	461 ± 79	0.22
Fellow eye	468 ± 162	444 ± 67	0.55
1mm-CST (μm)	440 ± 167	432 ± 143	0.90
History of steroid use	28.5%	25%	0.58
24-hour UFC (Normal value < 150μg/day)	181 ± 70 μg	150 ± 68 μg	0.21[a]
Serum aldosterone (Normal value < 15ng/dL)	7.8 ± 1.1	7.2 ± 2.2	0.34[a]
Testosterone (Normal value < 0.8mg/dL)	0.35 ± 0.16	0.38 ± 0.13	0.31[a]
Mean Snellen ± logMAR BCVA	20/50 ± 0.22	20/40 ± 0.18	0.14
Body mass index (kg/m^2)	25.8 ± 3.8	27.8 ± 4.7	0.25

CST central subfield thickness, *UFC* urinary free cortisol, *BCVA* best-corrected visual acuity

*Statistically significant.

[a]Multivariate regression analysis was performed with an adjustment of age, gender and symptom duration

Table 2 Clinical Outcomes of Study Patients in Both Groups At 6 Months

	Ketoconazole-treated group (21 eyes)	Control group (20 eyes)	Adjusted *P*
Median time to SRF resolution	7 weeks	16 weeks	<0.01*
Reduction of SFCT in eyes with CSCR			
3 months (%)	9.3 ± 10.2	4 ± 13.8	0.20
6 months (%)	9.9 ± 24.4	9.5 ± 26.4	0.96
Mean Snellen ± logMAR BCVA	$20/32^{-2}$ ± 0.14	$20/32^{-1}$ ± 0.14	0.24
ETDRS letter improvement	11.5 ± 8.9	5.8 ± 9.3	0.048*
Eyes requiring rescue treatment at 12 weeks	5 (23.8%)	10 (50%)	0.01*
Eyes with SRF at 6 months	0	3 (15%)	N/A
Abnormal sleep behavior[a]	15 (71%)	11 (55%)	0.69
OSA requiring CPAP therapy	4 (19%)	3 (15%)	0.51
Elevated liver enzymes	1 (4.7%)	N/A	

SRF indicates subretinal fluid, *SFCT* subfoveal choroidal thickness, *CSCR* central serous chorioretinopathy, *BCVA* best-corrected visual acuity, *ETDRS* early treatment diabetic retinopathy study, *OSA* obstructive sleep apnea, *CPAP* continuous positive airway pressure

*Statistically significant

[a]Patients who were scored higher than 3 based on STOP-BANG questionnaire

Table 3 A Cox Regression Analysis Demonstrating Predictors for Rapid Subretinal Fluid Resolution in The Control Group (20 eyes)

	Adjusted hazards ratio (95% CI)	*P* Value
Age	0.74 (0.60-0.93)	0.01*
Symptom duration	0.95 (0.88-1.01)	0.15
Baseline SFCT (fellow eyes)	0.95 (0.91-0.98)	0.007*
Baseline 1-mm CST	1.002 (0.99-1.007)	0.39
Baseline 24-hour UFC	1.04 (0.98-1.07)	0.13
Baseline BCVA	<0.01	0.14
Initial Body mass index	0.96	0.87

CI confidence interval, *SFCT* subfoveal choroidal thickness, *CST* central subfield thickness, *UFC* urinary free cortisol, *BCVA* best-corrected visual acuity

*Statistically significant

Figures

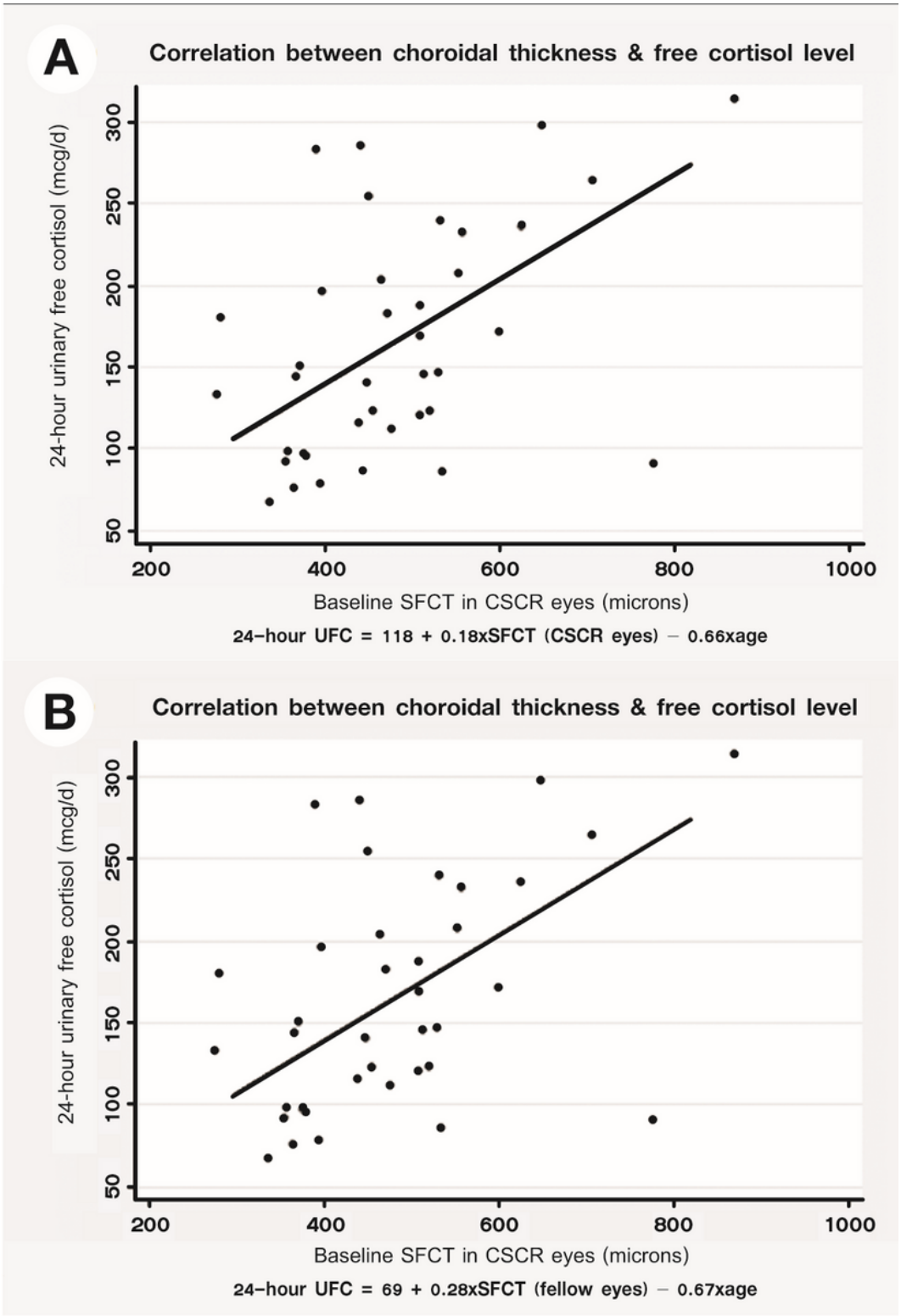

Figure 1

The correlations between choroidal thickness and free cortisol levels. The scatter plots of all study eyes show a positive linear correlation between 24-hour urinary free cortisol levels and subfoveal choroidal thickness in eyes with central serous chorioretinopathy (A) and fellow eyes (B).

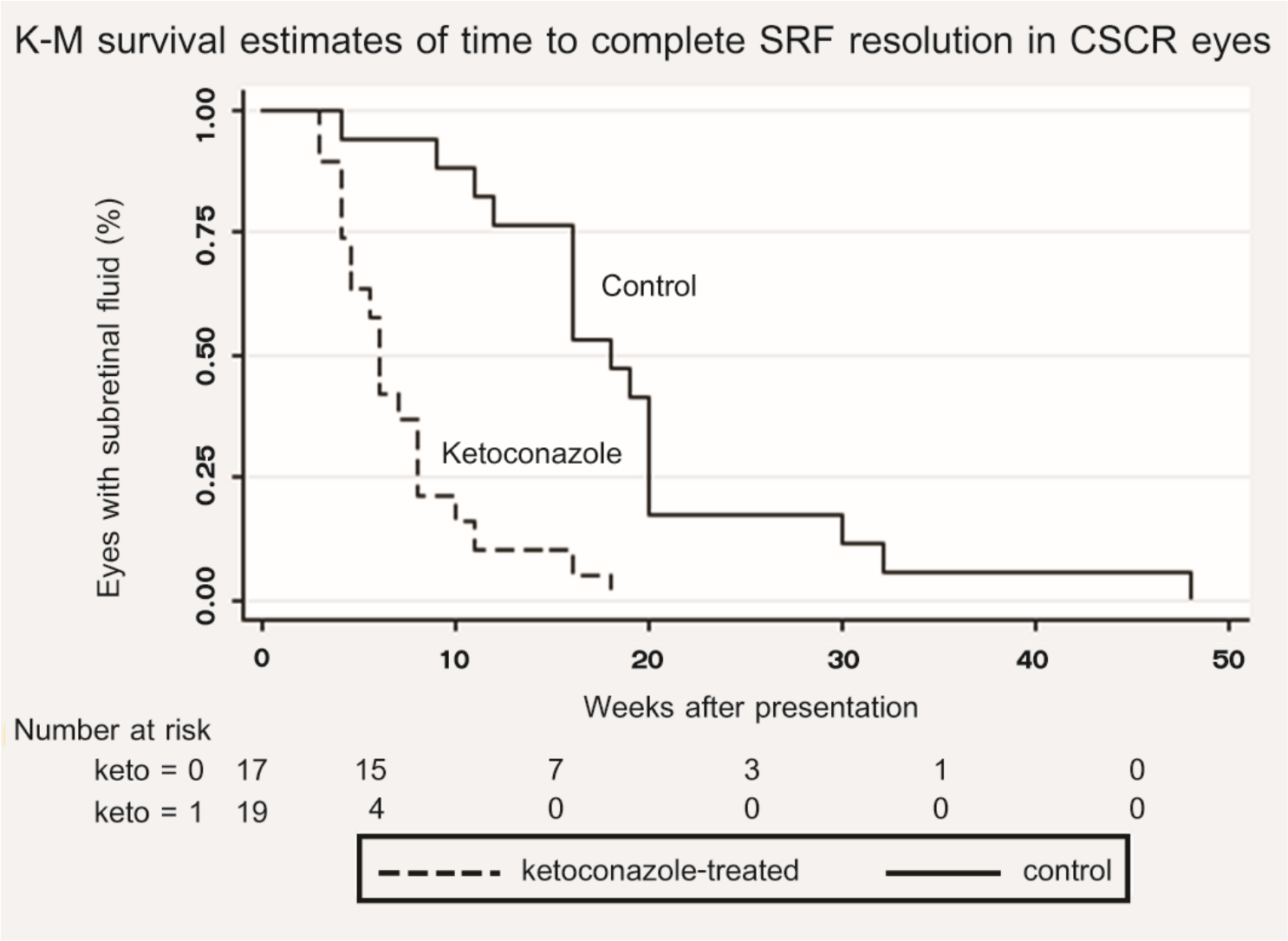

Figure 2

Kaplan-Meier survival estimates of time to complete resolution of central serous chorioretinopathy. These plots indicate that the median time to complete subretinal fluid absorption was 7 weeks in the ketoconazole-treated eyes, and 16 weeks in the control group (p = 0.01, log-rank test).

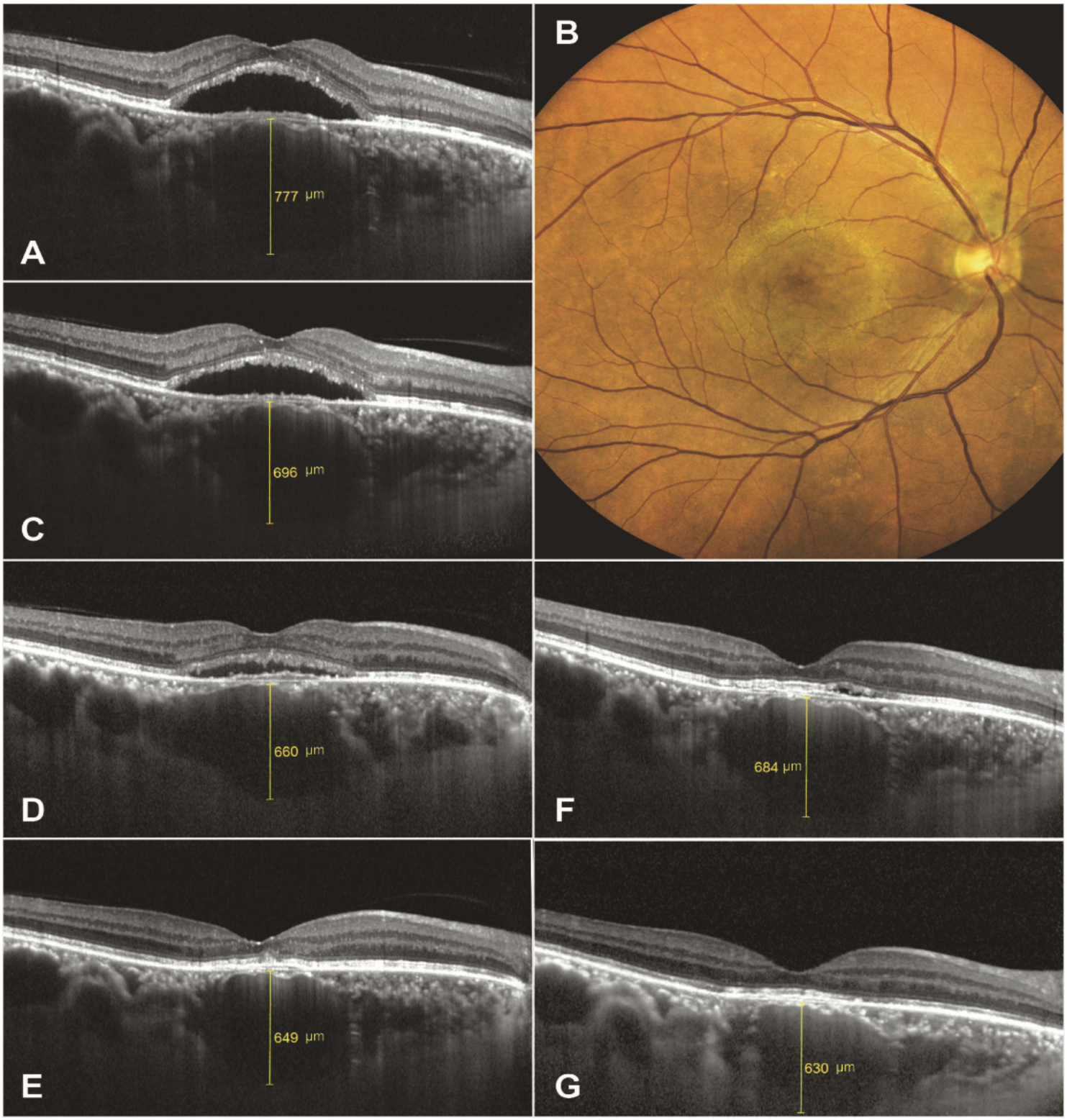

Figure 3

A chronic central serous chorioretinopathy (CSCR) patient who was later diagnosed with obstructive sleep apnea. A B A 54-year-old obese man had been diagnosed with CSCR in the right eye for 6 months before the presentation. The presenting 24-hour urinary free cortisol (UFC) was 190 µg/day. C D After receiving a 6-week course of ketoconazole, the choroidal thickness gradually decreased, E and CSCR resolved at 10

weeks post-treatment (UFC = 90 μg/day). F 6 months later, CSCR recurred; the sleep laboratory revealed 34 episodes of apnea per hour. G The macula was dry after 6 weeks of airway ventilation therapy.

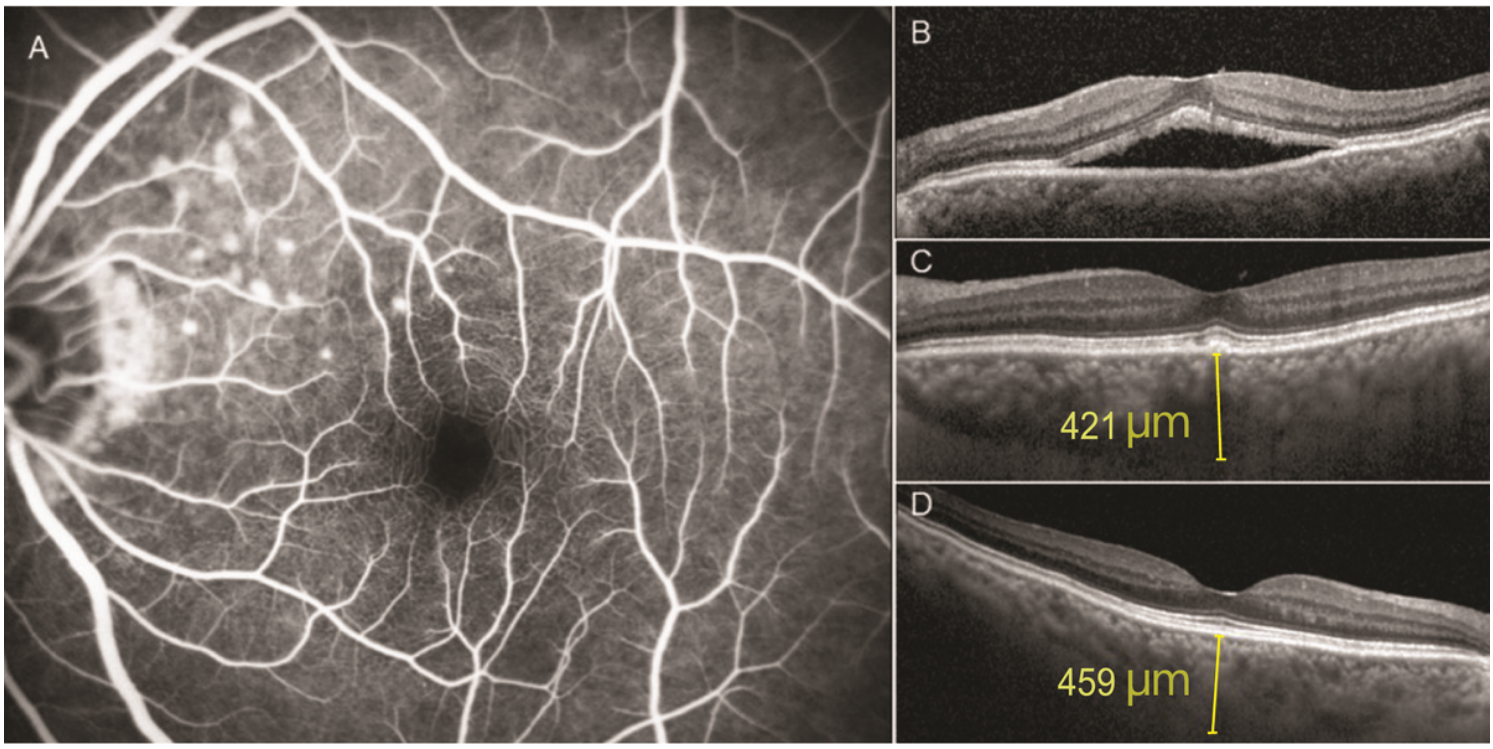

Figure 4

A patient with high-risk features for persistent central serous chorioretinopathy (CSCR). A B A 51-year-old man was referred to our hospital because of an 18-week history of persistent CSCR in the left eye (OS). He discontinued using nasal steroids at least 8 weeks prior to the referral. Fluorescein angiogram demonstrated multiple spots of leakage hyperfluorescence in the superonasal macula. C He received a 6-week course of 400mg/day ketoconazole, which resulted in resolution of CSCR at 7 weeks visit. D Baseline subfoveal choroidal thickness in the right eye was thicker than that in OS (459 and 398 μm).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementalFigure1.tiff