DOI: 10.4274/tjo.galenos.2022.02489
Turk J Ophthalmol 2023;53:97-104

Original Article

Choroidal Vascularity Index and Choroidal Thickness Changes Following Renal Transplantation

Mustafa Aksoy*, Leyla Asena**, Mustafa Agah Tekindal***, Ebru Hatice Ayvazoğlu Soy****, Gürsel Yılmaz**, Mehmet Haberal****

*Yüksek İhtisas University Faculty of Medicine, Department of Ophthalmology, Ankara, Türkiye
**Başkent University Faculty of Medicine, Department of Ophthalmology, Ankara, Türkiye
***Selçuk University Faculty of Veterinary Medicine, Department of Biostatistics, Konya, Türkiye
****Başkent University Faculty of Medicine, Department of General Surgery, Ankara, Türkiye

Abstract

Objectives: This study aimed to evaluate changes in subfoveal choroidal thickness (SFCT), choroidal vascularity index (CVI), estimated glomerular filtration rate (GFR), mean arterial pressure (MAP), and intraocular pressure (IOP) after renal transplantation.

Materials and Methods: A total of 49 renal transplantation patients were included in this prospective study. CVI and SFCT on enhanced-depth imaging optic coherence tomography (EDI-OCT), MAP at the cubital fossa, GFR, and IOP were measured preoperatively and at postoperative 1 week and 1 month. In the analysis of EDI-OCT images, luminal area (LA) and stromal area of the choroid were determined using the image binarization method. CVI was defined as the ratio of LA to total choroid area. The effects of GFR, IOP, and MAP on CVI and SFCT were investigated.

Results: The study included 23 women (47%) and 26 men (53%) with a mean age of 26.28±8.25 years (range: 18-52). Changes between preoperative, postoperative 1-week, and postoperative 1-month GFR values, CVI, and SFCT measurements were evaluated. There were significant differences between preoperative and postoperative GFR and SFCT measurements ($p<0.001$), but no significant differences between preoperative and postoperative CVI ($p=0.09$), MAP ($p=0.14$), or IOP ($p=0.84$) measurements.

Conclusion: The present study demonstrated that SFCT increased significantly with GFR, while there was no change in CVI values.

Keywords: Binarization, renal transplantation, glomerular filtration rate, choroidal thickness, choroidal vascularity index

Address for Correspondence: Mustafa Aksoy, Yüksek İhtisas University Faculty of Medicine, Department of Ophthalmology, Ankara, Türkiye
E-mail: mustafa-aksoy@hotmail.com **ORCID-ID:** orcid.org/0000-0003-1513-7686
Received: 20.02.2022 **Accepted:** 21.06.2022

Cite this article as: Aksoy M, Asena L, Tekindal MA, Ayvazoğlu Soy EH, Yılmaz G, Haberal M. Choroidal Vascularity Index and Choroidal Thickness Changes Following Renal Transplantation. Turk J Ophthalmol 2023;53:97-104

Introduction

Chronic renal failure is among the top health issues worldwide.[1] In the 1970s, dialysis was considered the most appropriate treatment of chronic renal failure.[2] However, increased success in renal transplantation surgery together with improved survival rates and quality of life has caused a shift of opinion.[3] New advancements in surgical methods and postoperative immunosuppression after renal transplantation has greatly increased renal allograft survival rates. Renal transplantation is now the primary choice of treatment in end-stage renal failure.[4,5]

Ocular pathologies are detected in over 50% of renal transplantation patients. These include posterior subcapsular cataract, opportunistic ocular infections, steroid-induced raised intraocular pressure, and primary disease-related vascular complications.[6] The choroid is a highly vascular tissue that supplies blood to the outer layers of the retina and plays a major role in the pathogenesis of many primary and secondary diseases involving the posterior segment of the eye.[7,8] In addition to toxemia of pregnancy, pheochromocytoma, and malignant hypertension, renal diseases have also been associated with hypertensive choroidopathy.[9] Increased systemic blood pressure has also been shown to reduce choroidal thickness.[10]

Previous studies have reported reduced choroidal thickness following hemodialysis in patients with chronic renal failure. This change has been attributed to changes in diastolic blood pressure.[11] Another study indicated that changes in choroidal thickness were associated with changes in systolic blood pressure.[12] Hypertension is a common occurrence after renal transplantation.[13] Drugs listed among the risk factors for hypertension after renal transplantation include cyclosporine A/G, corticosteroids, and tacrolimus.[13,14]

Choroidal vascularity index (CVI) has been recently proposed as a new marker in addition to subfoveal choroidal thickness (SFCT) for the evaluation of choroidal changes with optical coherence tomography (OCT).[15,16] CVI is a new imaging tool for the measurement and analysis of the choroidal vascular system by quantifying both the luminal and stromal choroidal components. Numerous reports have been published so far regarding CVI and its potential applications in healthy eyes as well as in the evaluation and management of several chorioretinal diseases. In addition, CVI measurement has been shown to be a more stable parameter that has lower inter-assay variability and is less dependent on physiological factors compared to choroidal thickness.[17] According to one study, there was a significant decrease in SFCT after hemodialysis in patients with end-stage renal failure, whereas no change in CVI was observed in the same population.[18]

To the best of our knowledge, changes in choroidal thickness following renal transplantation have not been studied before. CVI is known to be important in monitoring disease progression and prognosis in patients.[19] The present study was conducted to investigate the importance of CVI and SFCT measurements in renal function alterations. This prospective study aimed to evaluate alterations in the choroid in terms of SFCT and CVI following renal transplantation, and to correlate these parameters with the estimated glomerular filtration rate (GFR), mean arterial pressure (MAP), and intraocular pressure (IOP).

Materials and Methods

This prospective study was conducted on patients admitted to the ophthalmology department between July 2015 and April 2017 who were scheduled to undergo renal transplantation in the general surgery department for end-stage renal disease secondary to causes not related to diabetes and hypertension (e.g., recurrent kidney infection, polycystic kidney disease, prolonged urinary tract obstruction, glomerulonephritis). The study received ethics approval from the Başkent University Faculty of Medicine Scientific Research Projects Advisory Board (project no: KA16/271).

Study Sample

A total of 49 right eyes of 49 patients (23 women, 26 men) diagnosed with end-stage renal disease and who were hospitalized for renal transplantation were included in the study. Complete ophthalmological examination and assessments of CVI, SFCT, IOP, GFR, and MAP were conducted preoperatively and at 1 week and 1 month postoperatively. Patients were administered a postoperative treatment protocol comprising acetyl salicylic acid (100 mg; Bayer, İstanbul, Turkey), trimethoprim/sulfamethoxazole (40 mg/200 mg; Deva, Tekirdağ, Türkiye), valganciclovir (450 mg; Roche, Mississauga, Canada), tacrolimus (0.1 mg/kg; Astellas Pharma, Killorglin, Ireland), prednisolone (1.5 mg/kg; Gensenta, İstanbul, Türkiye), and mycophenolate (30 mg/kg; Koçakfarma, Tekirdağ, Türkiye).

Slit-lamp anterior segment and dilated fundus examinations were performed and visual acuity, IOP, GFR, CVI, SFCT, and MAP were assessed in all patients. Patients with additional macular or choroidal disease, myopia ≥3 diopters (D) or hypermetropia ≥+3 D, history of ocular or orbital surgery, ocular inflammation, diabetes mellitus, and systemic hypertension were not included in the study.

IOP was measured with a non-contact pneumotonometer (Reichert 7; Reichert Inc., New York, USA). Systemic blood pressures were manually measured from the cubital fossa separately by both researchers. MAP was calculated as follows: diastolic blood pressure +1/3 (systolic blood pressure-diastolic blood pressure). All measurements were obtained by the same researchers (M.A., L.A.).

The patients were consecutively operated in this study. Only two patients with cataract were excluded, because they did not have high quality choroidal measurements due to cataracts. There was no kidney rejection or any complications during follow-up.

Ophthalmic Imaging

Choroidal imaging was non-invasively obtained with spectral domain enhanced depth imaging OCT (EDI-OCT, Heidelberg Spectralis, Heidelberg, Germany). All participants were examined during the same part of the day (between 9:30

and 10:00 AM) to eliminate the effects of physiological diurnal alterations. The images were obtained after pupil dilation, using a horizontal scan centered on the fovea (**Figure 1 A1,B1,C1**).

Choroidal thickness was assessed as the distance between the outer margin of the hyperreflective retinal pigment epithelium (RPE) and choroid-sclera interface (CSI).[20] Patients with visible and measurable choroid were included in the study and choroidal thickness was manually measured in EDI-OCT images of the subfoveal cross-section by two different researchers (M.A., L.A.). The program's measurement feature was used to measure the vertical line between the RPE and CSI to determine choroidal thickness (**Figure 2**).

For CVI measurement, the binarization method was utilized for all scans acquired. Image processing was performed using open-source software (http://fiji.sc/) and analyzed as described by Agrawal et al.[16] Briefly, z scans were viewed using the ImageJ version 1.53a platform and total choroid area (TCA), which was added to the region of interest (ROI) manager, was selected

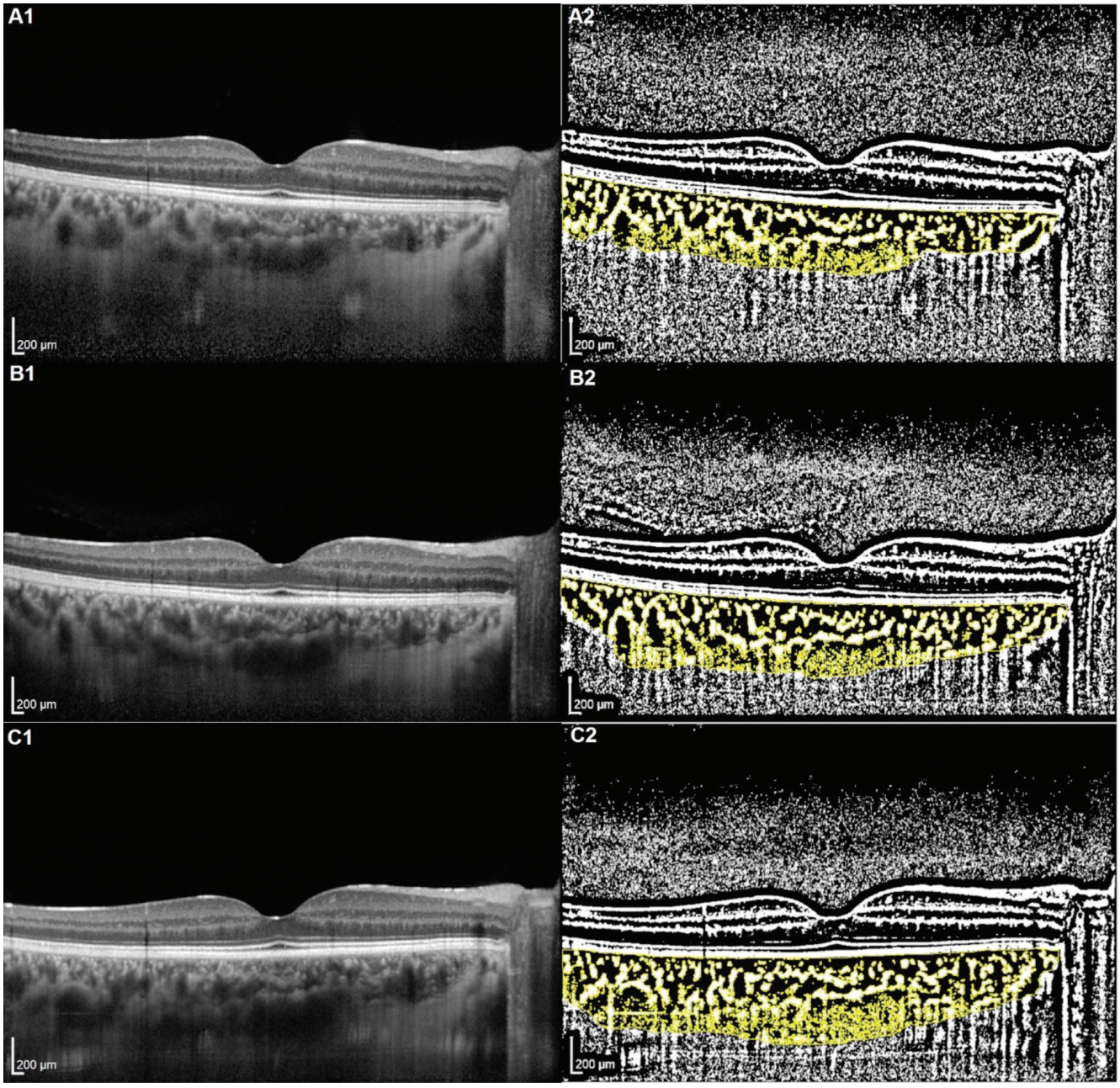

Figure 1. Left: Images from horizontal scans centered on the central foveal region in a participant preoperatively (A1) and at postoperative 1 week (B1) and 1 month (C1). Right: Choroidal vascularity index measurements from the same images using ImageJ software. The luminal area (dark pixels) is represented as yellow lines using the color threshold tool, and stromal area is represented as bright pixels

using the polygon tool. After converting the image to 8-bit, Niblack's auto local thresholding was employed, which provided the mean pixel value with standard deviation for all points. On EDI-OCT scans, the luminal area (LA) was indicated by using the color threshold (**Figure 1 A2,B2,C2**). To determine the LA within the selected polygon, both areas in ROI manager were selected and combined using the "AND" operation of ImageJ. The composite third area was added to the ROI manager. The first area corresponded to the total selected choroid, and the third composite area indicates the LA or vascular area. The CVI value was obtained as the ratio of LA to TCA. The light color pixels indicated stromal area, which was calculated by subtracting the LA from the TCA.

Both SFCT and CVI values were examined separately by two researchers (M.A., L.A.) who were blinded to the patients' clinical data. The mean values of the measurements obtained by the two researchers were used for statistical analysis.

The intraobserver and interobserver reliability of the SFCT and CVI values was assessed using intraclass correlation coefficients (ICC) with a 95% confidence interval (CI). ICC values between 0.75 and 0.90 were regarded as satisfactory and values greater than 0.90 as excellent.

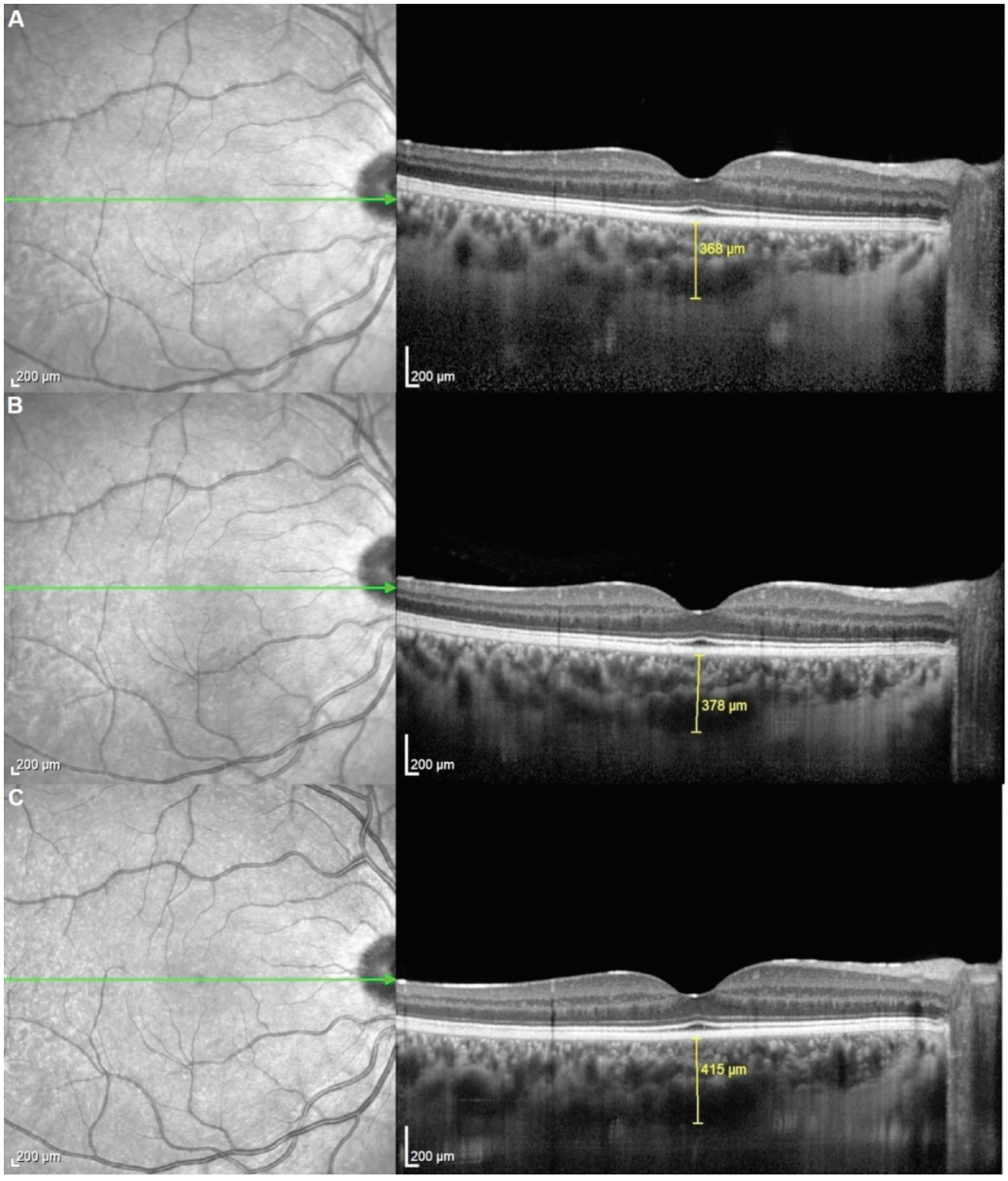

Figure 2. Image of SFCT measurement centered on the central foveal region in a participant preoperatively (A) and at postoperative 1 week (B) and 1 month (C)
SFCT: Subfoveal choroidal thickness

Statistical Analysis

IBM SPSS Statistics 22.0 (IBM Corp., Armonk, NY, USA) was used for statistical analyses. Power analysis was performed for the repeated-measures analysis of variance (ANOVA) method, in which the sample size was determined as at least 49 individuals in each group. In this case, the power of the test was approximately 80.5%. As the data met the parametric test criteria, repeated-measures ANOVA and Bonferroni test were used for analysis. Correlations between parameters were assessed using Pearson correlation analysis.

Results

A total of 49 eyes of 49 patients (23 women, 26 men) were included in the study. The mean patient age was 26.28±8.25 years (range: 18-52). All patients had visual acuity of 20/20 according to Snellen chart before and after renal transplantation. Preoperatively, the mean dialysis duration was 36.00±19.25 months. There were statistically significant differences between preoperative and postoperative 1-month, preoperative and postoperative 1-week, and postoperative 1-week and postoperative 1-month mean SFCT measurements and GFR values (p<0.001 all) (**Table 1, Figure 3**,4).

According to CVI measurements, there was no statistically significant difference between preoperative and postoperative 1-week or postoperative 1-month measurements (preoperative vs. postoperative 1-week: p=0.41; preoperative vs. postoperative 1-month: p=0.63; postoperative 1-week vs. postoperative 1-month: p=0.11) (**Table 1**).

The increase in SFCT was significant between preoperative and postoperative 1-week and postoperative 1-month, and also showed a strong positive correlation with the amount of change in GFR value (r=0.976, p<0.001 and r=0.711, p=0.009; respectively). The SFCT was not significantly correlated with MAP in the comparisons between preoperative and postoperative 1-week and between postoperative 1-week and postoperative 1-month values (r=0.101, p=0.368; r=0.124, p=0.416).

According to MAP values, there was no statistically significant difference between preoperative and postoperative 1-week or postoperative 1-month measurements (p=0.36 and p=0.19, respectively) (**Table 1**).

Mean preoperative IOP was 13.79±3.48 mmHg. Mean postoperative IOP was measured as 13.85±3.32 mmHg at 1 week and 13.81±3.32 mmHg at 1 month. There was no significant difference among preoperative, postoperative 1-week, and postoperative 1-month mean IOP values (p=0.84).

SFCT had ICC values of 0.918-0.951 for interobserver reliability and 0.928-0.971 for intraobserver reliability. For CVI, ICC values were 0.947-0.953 for interobserver reliability and 0.927-0.951 for intraobserver reliability (**Table 2**).

Discussion

To the best of our knowledge, this is the first study in the literature to evaluate preoperative and postoperative CVI and SFCT in renal transplantation. While CVI, MAP, and IOP values did not significantly change, there was significant increase in SFCT and GFR after renal transplantation.

Shin et al.[18] compared SFCT and CVI values before and after hemodialysis in patients with end-stage renal failure. Despite acute and severe fluid loss after hemodialysis, there was no significant change in CVI in their study population. Their study also demonstrated decrement in SFCT measurements. The present study demonstrated increase in SFCT following renal

Table 2. Intraclass correlation coefficients for CVI and SFCT measurements in the participants

	Interobserver variability (95% CI)	Intraobserver variability (95% CI)
CVI		
PO-1W	0.918 (0.911-0.942)	0.971 (0.959-0.977)
PO-1M	0.951 (0.929-0.978)	0.928 (0.912-0.968)
1W-1M	0.933 (0.891-0.964)	0.931 (0.906-0.975)
SFCT		
PO-1W	0.953 (0.932-0.984)	0.927 (0.908-0.949)
PO-1M	0.947 (0.929-0.963)	0.949 (0.931-0.976)
1W-1M	0.948 (0.931-0.969)	0.951 (0.923-0.965)

CI: Confidence interval, CVI: Choroidal vascularity index, SFCT: Subfoveal choroidal thickness, PO: Preoperative, 1W: Postoperative 1 week, 1M: Postoperative 1 month

Table 1. Statistical comparison of SFCT and CVI measurements, MAP, and GFR values

	Mean SFCT (SD), µm	Mean CVI (=LA/TCA) (SD)	Mean MAP (SD), mmHg	Mean GFR (SD), mL/min/1.73 m²
Preoperative (PO)	306.33 (±74.50)	65.42 (±2.19)	85.37 (±6.64)	9.02 (±4.50)
Postoperative 1 week (1W)	320.61 (±74.1)	65.59 (±2.24)	87.06 (±7.93)	61.03 (±15.48)
Postoperative 1 month (1M)	345.76 (±74.28)	65.29 (±2.11)	87.45 (±7.24)	68.2 (±17.90)
P value: PO vs. 1W	**<0.001***	0.41	0.36	**<0.001***
P value: PO vs. 1M	**<0.001***	0.63	0.19	**<0.001***
P value: 1W vs. 1M	**<0.001***	0.11	1.00	**<0.001***

SFCT: Subfoveal choroidal thickness, CVI: Choroidal vascularity index, LA: Luminal area, TCA: Total choroidal area, MAP: Mean arterial pressure, GFR: Glomerular filtration rate, SD: Standard deviation. *Statistically significant p values

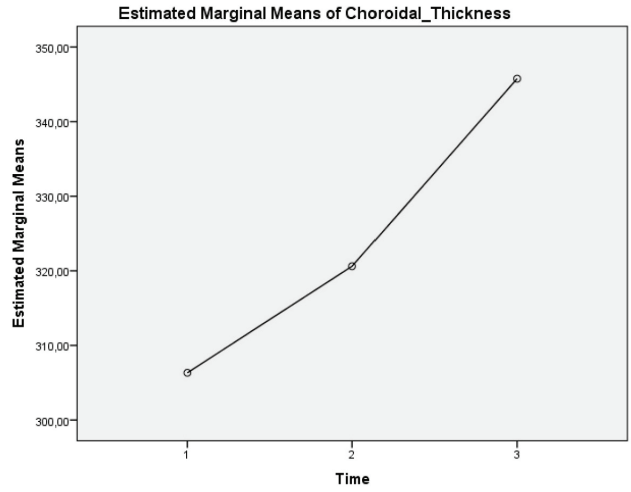

Figure 3. Change in choroidal thickness over time (1: Preoperative, 2: Postoperative 1 week, 3: Postoperative 1 month)

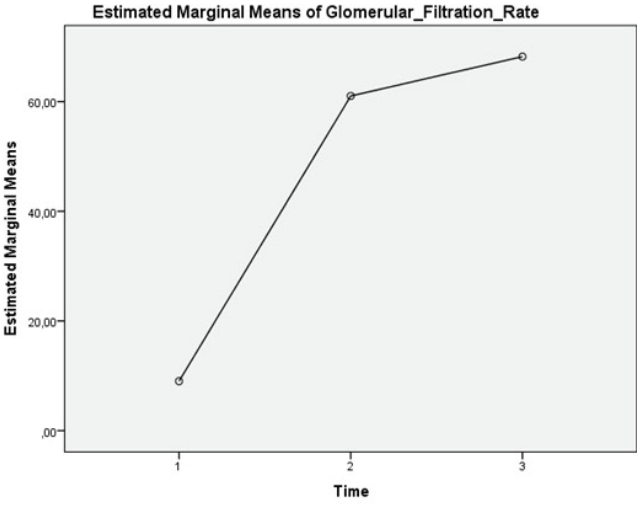

Figure 4. Change in glomerular filtration rate over time (1: Preoperative, 2: Postoperative 1 week, 3: Postoperative 1 month)

transplantation, while no difference was found in CVI values. These findings suggest that CVI values were more stable and less affected by physiological alterations compared to SFCT.[21]

Although studies have shown increased systemic blood pressure after renal transplantation, we did not observe a significant change in MAP in our study.[22,23] This inconsistency with the literature may be attributed to the treatment protocol including cyclosporine and tacrolimus. The second possible cause is that systemic blood pressure was remeasured in a short one-month follow-up period after the use of corticosteroids.

In this study, all patients received intravenous corticosteroid treatment after renal transplantation. Han et al.[24] investigated choroidal thickness 1 day, 1 week, and 1 month after pulse steroid treatment but detected no significant changes in choroidal thickness. Other studies reported significant reduced choroidal thickness after high-dose steroid treatment.[25,26] We believe that corticosteroid treatment given after renal transplantation does not increase choroidal thickness. Future studies on isolated postoperative treatment regimens after renal transplantation with different patient groups will help form a more accurate assessment.

In the present study, a significant increase in SFCT measurements was observed 1 week and 1 month postoperatively. In our previous report, IOLMaster 700 measurements were evaluated before and 1 month after renal transplantation. The study results demonstrated significant decrement in axial length despite significant thinning in central corneal thickness measurements at postoperative 1 month.[27] The present study demonstrated a significant increase in choroidal thickness. Therefore, the decrease in axial length measurements may be secondary to an increase in choroidal thickness.

The literature reports reduced choroidal thickness following hemodialysis. This has been attributed to changes in diastolic and systolic blood pressure.[11,12] In this study, while there was no change in systemic blood pressure after renal transplantation, follow-up showed increased choroidal thickness. Although choroidal thickness decreases after hemodialysis, it seems to increase after renal transplantation according to the results of the present study. This difference may be caused by hypotensive changes in systemic blood pressure after dialysis.[28] In addition, hemodialysis may have a more acute and rapid effect on a larger volume of blood compared to renal transplantation, leading to volume loss.[29] This may be due to acute and large fluid shifts that occur during dialysis.[18]

Although we found no change in blood pressure, choroidal thickness increased after renal transplantation. Increase in choroidal thickness independent from systemic blood pressure may be related to autonomic nervous system dysfunction in chronic renal failure. Since choroidal circulation has autonomic innervation, increased sympathetic activity in chronic renal disease may have contributed to choroidal thinning.[30] Improved renal functions after renal transplantation may lead to changes in autonomic regulation, thus leading to increased choroidal thickness after renal transplantation.[31] In our study, indicators of sympathetic activity were not examined. Future studies that evaluate sympathetic activity after renal transplantation are needed.

One study found that choroidal thickness is not associated with blood pressure in chronic renal failure. The same study revealed a correlation between choroidal thickness and GFR.[31] In addition, it is already known that preoperatively low GFR increases significantly after renal transplantation.[32] In this study, while there was no change in blood pressure, there was increased choroidal thickness after renal transplantation. In addition, there was a significant postoperative increase in GFR, which positively correlated with choroidal thickness. One likely cause of increased postoperative choroidal thickness may be increased GFR following renal transplantation, associated with reduced protein leakage (such as albumin) from the kidneys and increased vascular volume.[33] In light of these findings, GFR levels may be a useful tool for monitoring changes in choroidal thickness in patients with chronic renal disease.

The literature also showed that IOP was associated with choroidal thickness measurements. Hata et al.[34] indicated that elevated IOP following darkroom prone provocative test was associated with decreased choroidal thickness. In this study, we found no significant change in IOP after renal transplantation. This suggests that changes in SFCT are independent from IOP.

CVI, which was first introduced by Agarwal et al.,[16] is the ratio of LA to TCA, and a new parameter to quantitatively define choroidal vasculature. The current literature suggests that CVI is less variable and influenced by fewer physiological factors than choroidal thickness.[17] Iovino et al.[35] investigated choroidal changes in patients with central serous chorioretinopathy following photodynamic therapy and demonstrated a decrease in choroidal thickness but no change in CVI. They emphasized the decrease in both LA and TCA as an underlying reason for stable CVI. Similar to the literature, the present study showed increase in SFCT but no significant alteration in CVI.

Study Limitations

This study included patients with chronic renal failure secondary to various etiologies (other than diabetes and hypertension) who underwent renal transplantation. Increased choroidal thickness following renal transplantation is likely independent from diseases causing renal failure. Nevertheless, further studies with similar design on renal failure secondary to a single etiology will be more reliable and allow more accurate conclusions.

Furthermore, we believe this study should be repeated and supported by studies with longer follow-up period after renal transplantation. Drugs administered during postoperative treatment may have primarily affected measurements. The isolated use of these drugs and their effects on choroidal thickness should be evaluated separately for each drug.

Conclusion

The present study demonstrated that SFCT was affected by GFR, while no change occurred in CVI values. This suggests that CVI seems to be more stable parameter than SFCT. GFR is measured to evaluate renal functions in the follow-up of patients with end-stage renal disease. In light of our findings, we believe that SFCT measurements may also be used as an indicator of renal function.

Ethics

Ethics Committee Approval: The study received ethics approval from the Başkent University Faculty of Medicine Scientific Research Projects Advisory Board (project no: KA16/271).

Informed Consent: Obtained.

Peer-review: Internally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: M.H., Concept: M.H., G.Y., Design: M.H., G.Y., Data Collection or Processing: M.A., L.A., E.H.A.S., M.A.T., Analysis or Interpretation: M.A., L.A., E.A.S, M.A.T., Literature Search: M.A., E.H.A.S., Writing: M.A., E.H.A.S.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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