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Changes in Choroidal Thickness after Hemodialysis and the Influence of Diabetes

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Purpose: To evaluate the changes in subfoveal choroidal thickness (SFCT) after hemodialysis (HD) and to investigate the possible impact of diabetes mellitus (DM).

Methods: This prospective, interventional case series included 18 patients undergoing HD due to chronic renal failure. Mean SFCT was measured before (pre-HD) and after HD (post-HD), and the differences (ΔSFCT) were calculated for each eye. In addition, the ratio of SFCT change (%SFCT; ΔSFCT/baseline SFCT × 100, percent, %) was calculated.

Results: Ten patients (55.6%) had DM as the underlying etiology for HD. The mean SFCT was 311.8 ± 64.9 μm (177.5-468.0 μm) pre-HD and 311.2 ± 65.1 μm (191.5-454.5 μm) post-HD (p = 0.877). The mean ΔSFCT was -4.4 ± 20.0 μm (-64.0 to 29.0 μm), and the mean %SFCT was 4.3 ± 4.4% (0 to 19.5%). The mean ΔSFCT was significantly larger in patients with DM than those without DM (-14.1 ± 18.2 μm and 7.8 ± 15.6 μm; p = 0.006), but the mean %SFCT was not significantly different between the groups (4.4 ± 5.5% and 4.2 ± 2.6%; p = 0.315).

Conclusions: The mean SFCT was not significantly changed after HD. The change in mean SFCT was significantly larger in patients with DM than in those without.

Keywords: Choroid; Choroidal thickness; Diabetes mellitus; Hemodialysis

Introduction
The choroid is a highly vascularized structure derived primarily from the long and short ciliary arteries with some contribution from the anterior ciliary arteries [1,2]. The main function of the choroid is supplying oxygen and nutrients to the outer retina [1,3,4]. In addition, the choroid plays various roles including light absorption, thermoregulation via heat dissipation, modulation of intraocular pressure via vasomotor control of blood flow, and drainage of aqueous humor from the anterior chamber [1]. Thus, the choroid is an important tissue that maintains the integrity of the outer retina and ultimately preserves visual function.

Choroidal circulation is under neurogenic control [1,2]. Sympathetic innervation includes both noradrenergic and neuropeptide fibers [1,2,5,6]. Parasympathetic innervation is primarily cholinergic [1,2,6]. Parasympathetic innervation is primarily cholinergic [1,2,6]. In addition, it has been suggested that varying degrees of autoregulation exist in human
choroids [1]. These findings imply that systemic factors such as perfusion pressure have some effect on the choroid.

With the introduction of enhanced-depth imaging optical coherence tomography (EDI OCT), numerous studies have noninvasively investigated the microstructures and characteristics of the choroid [7,8]. Various factors can affect the choroidal thickness including physiological factors such as age, sex, and diurnal variation [9-14]. Systemic administration of sildenafil citrate, caffeine, smoking, and ethanol also affect choroidal thickness [15-19].

Hemodialysis (HD) is effective in correcting the composition and volume of body fluids in patients with end-stage chronic renal failure (CRF) who have increased interstitial and extracellular water volume. Fluid is removed by ultrafiltration to achieve fluid balance. HD usually induces changes in body fluid, thus affecting systemic blood pressure (BP) [20]. HD is associated with a wide range of ocular findings including refractive change, dry eye, increased tear osmolarity, lenticular opacity, and increased intraocular pressure [21-24]. Recently, a few studies have investigated the effect of HD on choroidal thickness (CT) [25-27]. However, the results are somewhat inconclusive. One study demonstrated an increase in mean subfoveal choroidal thickness (SFCT) after HD [25], whereas another study showed a decrease in mean CT after HD [26]. In addition, it has been suggested that mean CT decreases in non-diabetic HD patients [27].

In the present study, we investigated changes in mean SFCT and the impact of diabetes mellitus (DM) on these changes after HD.

Materials and Methods

Enrollment of study subjects

This prospective, interventional case series included 18 patients who underwent HD in the Hemodialysis Unit of Catholic Kwandong University College of Medicine, International St. Mary’s Hospital. All subjects underwent an average of 3-4 hours of HD in the morning, starting at 8:30, three times per week. The study protocol was approved by the Institutional Review Board of Catholic Kwandong University College of Medicine, International St. Mary’s Hospital (IS14OISI0019) and adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from all participants. Inclusion criteria were as follows: no intraocular surgery such as pars plana vitrectomy, scleral buckling, phacoemulsification, intravitreal injections, or phakic intraocular lens implantation surgery over the previous 3 months and axial length less than 26.5 mm with no sign of pathologic myopia such as a lacquer crack or posterior staphyloma.

Ocular examination

At the first visit, a baseline examination was performed and included a slit lamp examination, an intraocular pressure measurement using a non-contact tonometer, and a fundus examination. Refractive error was measured using an autorefractor and then converted to spherical equivalents (diopters [D]). The axial length of each eye was measured using partial coherence interferometry (IOLMaster; Carl Zeiss, Dublin, CA, USA).

CT was measured using spectral domain OCT (Spectralis; Heidelberg Engineering, Dossenheim, Germany) with the EDI modality. EDI OCT imaging was performed by positioning the objective lens of the Spectralis OCT scanner close enough to each eye to invert the image. At least two good quality horizontal and vertical scans across the fovea were obtained for each eye. The OCT images saved after 100 frames were averaged using the automatic averaging and eye tracking system of the Spectralis OCT scanner. SFCT was measured in the subfoveal region in both horizontal and vertical images and then averaged. Two independent observers who were blind to the clinical data of each patient (HMK and JHC) measured SFCT.

Systemic evaluation

Pre-HD and post-HD venous blood samples were obtained and analyzed. Pre-HD and post-HD blood urea nitrogen (BUN) values were obtained to establish the difference in HD (delta BUN, ΔBUN). Urea reduction rate was calculated as follows: pre-HD BUN – post-HD BUN/pre-HD BUN, showing the efficiency of HD. The laboratory concentrations of creatinine, calcium, phosphorus, urea reduction rate, potassium, sodium, chloride, and parathyroid hormone (PTH) were also analyzed. Pre-HD and post-HD systolic BP (delta
SBP, ΔSBP) and diastolic BP (delta DBP, ΔDBP) were measured in each subject, as were pre-HD and post-HD body weight (Wt) (delta weight, ΔWt).

Study protocol
On the day of HD, each subject reported to the ophthalmology clinic 30 minutes before starting HD. The SFCT for each patient was measured using EDI OCT in both eyes. Within 30 minutes of the completion of HD, the SFCT for each patient was also measured using EDI OCT. After measuring SFCT at each visit, the difference in SFCT (delta SFCT, ΔSFCT) was calculated. In addition, the ratio of change (%SFCT) was also obtained: [absolute value of ΔSFCT/baseline SFCT] × 100 (percentage; %). For a short time before and after HD, the participants were instructed not to eat food or drink liquids in order to minimize the effects on choroidal thickness. Then, we performed subgroup analysis according to the presence of DM as the underlying etiology of HD. For the statistical analysis, the data of the right eye in each patient was used.

Statistical analysis
IBM SPSS Statistics ver. 21.0 software for Windows (IBM Corp., Armonk, NY, USA) was used for statistical analyses. Repeated-measures analysis of variance (ANOVA) was used to assess the significance between repeatedly measured variables. For comparison between two subgroups, the Mann-Whitney U-test for continuous variables and the Chi-square test for categorical variables were used. In addition, we investigated the possible factors correlated with ΔSFCT in the HD patients using stepwise multiple regression analysis. To assess intraobserver and interobserver reliability, the intra-class correlation coefficient (ICC) was calculated. Mauchly’s test of sphericity and Kolmogorov-Smirnov analyses were used to confirm statistical validity. Results with p < 0.05 were considered statistically significant.

Results

Baseline characteristics
A total of 18 patients participated in this study. Among these, 7 patients (38.9%) were male, and the mean age at the time of the study was 54.3 ± 9.5 years (range, 34-69 years). Baseline characteristics of the study subjects are summarized in Table 1. The calculated ICC for interobserver reliability was 97.2% (p < 0.001). The ICC for intraobserver reliability was 97.6% (p = 0.001, HMK) and 96.8% (p = 0.001, JHC), respectively.

Change in choroidal thickness after hemodialysis
The mean SFCT at pre-HD was 311.8 ± 64.9 μm (177.5-468.0 μm), while that at post-HD was 311.2 ± 65.1 μm (191.5-454.5 μm). There was no significant difference between pre-HD

Table 1. Systemic and ocular characteristics of the study population

| Characteristics                        | Value |
|----------------------------------------|-------|
| Age (years)                            | 54.3 ± 9.5 |
| Sex (male, n [%])                      | 10 (55.6) |
| Diabetes mellitus (n, %)               | 10 (55.6) |
| Pre-HD weight (kg)                     | 61.8 ± 14.1 |
| Pre-HD systolic blood pressure (mmHg)  | 139.0 ± 14.6 |
| Pre-HD diastolic blood pressure (mmHg) | 80.2 ± 10.6 |
| Pre-HD BUN                             | 62.1 ± 15.9 |
| Post-HD weight (kg)                    | 59.7 ± 13.7 |
| Post-HD systolic blood pressure (mmHg) | 139.4 ± 21.1 |
| Post-HD diastolic blood pressure (mmHg)| 82.8 ± 14.1 |
| Δ Weight (kg)                          | 2.0 ± 1.1 |
| Δ Systolic blood pressure (mmHg)       | 0.9 ± 24.8 |
| Δ Diastolic blood pressure (mmHg)      | 3.3 ± 10.6 |
| Parathyroid hormone                    | 300.5 ± 220.7 |
| Urea reduction rate                    | 68.5 ± 5.8 |
| Creatinine                             | 8.7 ± 3.2 |
| Phosphate                              | 5.4 ± 1.5 |
| Calcium                                | 8.3 ± 1.1 |
| Potassium                              | 4.5 ± 0.7 |
| Axial length (mm)                      | 23.6 ± 1.0 |
| Refractive error (spherical equivalence, diopter) | -0.6 ± 1.7 |
| Pre-HD subfoveal choroidal thickness   | 311.8 ± 64.9 |
| Post-HD subfoveal choroidal thickness  | 311.2 ± 65.1 |
| Δ Subfoveal choroidal thickness        | 0.2 ± 21.5 |

Values are presented as mean ± SD or n (%) unless otherwise indicated.
HD = hemodialysis; BUN = blood urea nitrogen; Δ = delta (difference of pre-HD and post-HD values).
and post-HD SFCT ($p = 0.877$). The mean $\Delta$SFCT was -4.4 ± 20.0 μm (-64.0 to 29.0 μm), and the mean %SFCT was 4.3 ± 4.4% (0 to 19.5%).

### The effect of diabetes mellitus on choroidal thickness after hemodialysis

After assessment of SFCT changes, the patients were then further classified depending on presence of comorbid DM (the DM group and non-DM group). The mean SFCT was 316.4 ± 32.0 μm (263.5 to 356.5 μm) in the DM group and 316.1 ± 104.5 μm (177.5 to 468.0 μm) in the non-DM group ($p = 0.897$) at baseline. The mean $\Delta$SFCT in the DM group was -14.1 ± 18.2 μm (-64.0 to 0 μm) in the DM group and 7.8 ± 15.6 μm (-21.0 to 29.0 μm) in the non-DM group ($p = 0.006$). The mean %SFCT was 4.4 ± 5.5% (0 to 19.5%) in the DM group and 4.2 ± 2.6% (0.4 to 7.9%) in the non-DM group ($p = 0.315$). The comparisons between the two groups are shown in Table 2.

### The possible factors significantly correlated with the changes in subfoveal choroidal thickness after hemodialysis

After analysis, we further perform stepwise multiple regression analysis to investigate the possible factors correlated with the $\Delta$SFCT in the study population (Table 3). Ophthal-
mologic characteristics of axial length and baseline SFCT and systemic characteristics of age, sex, ΔBUN, ΔSBP, ΔDBP, and presence of DM were evaluated. Among the various characteristics, the presence of DM was the only factor significantly correlated with ΔSFCT (B = 21.913, β = 0.559, p = 0.016).

### Discussion

In this study, we evaluated the changes in mean SFCT after HD and the effect of comorbid DM on mean SFCT change. The mean SFCT was not significantly changed after HD in these patients. Then, we classified the patients into two groups according to the presence of DM. The mean SFCT was not significantly different between the two groups before HD or after HD. However, the mean ΔSFCT was significantly different between the two groups, showing significantly larger SFCT changes in the patients with DM than in those without [28,29]. The results of current study are consistent with these studies and support the hypothesis that DM and its effect on choroidal vasculature can lead to significant changes in SFCT after HD.

We also investigated the possible factors affecting on SFCT changes after HD. Previous studies have investigated the possible factors, but the results are inconsistent. One study suggested that body weight loss and changes in serum osmolarity and SBP were significantly correlated with SFCT changes after HD [28]. Another study suggested that amount of body fluid removal was significantly correlated with the SFCT in patients without DM, but no in those with DM [29]. The results of our study showed that DM was the only factor significantly correlated with SFCT changes after HD. These inconsistent results might be due to different study designs, various systemic and ocular factors considered in the studies, and relatively small study populations.

However, it is obvious that the presence of DM has significant effect on the SFCT changes after HD. Several investigations suggest that DM affects choroidal vasculatures as well as retinal vessels [30,31]. Choroidopathy in patients with DM includes obstruction and/or dropout of the choriocapillaris, increased formation of vascular loops, microaneurysms, vascular remodeling, intrachoroidal neovascularization, and subsequent impaired choroidal circulation [32-40]. In patients with DM, underlying DM choroidopathy can affect the choroidal changes after HD. A previous study has suggested that systemic fluid accumulation has a greater effect on the diabetic choroid due to diabetic choroidopathy in such patients [29]. Diabetic choroidopathy and the possibility of impaired choroidal autoregulation can result in large SFCT changes after HD.

However, the results of the current study raised another question, although the effect of DM seems to be significant on the SFCT changes after DM. We further investigated the ratio of SFCT change (ΔSFCT/baseline SFCT), which was

### Table 3. The results of multiple regression analysis investigating the factors associated with the changes of subfoveal choroidal thickness after hemodialysis

| Factors      | Beta (β) | p-value |
|--------------|----------|---------|
| DM           | 0.559    | 0.016   |
| ΔWt          | 0.242    | 0.274   |
| ΔSBP         | 0.184    | 0.397   |
| ΔDBP         | 0.409    | 0.053   |
| ΔBUN         | -0.067   | 0.797   |
| Age          | 0.068    | 0.755   |
| Sex          | 0.056    | 0.799   |
| Baseline SFCT| -0.081   | 0.710   |

DM = diabetes mellitus; Δ = delta (difference of pre-hemodialysis [HD] and post-HD values); Wt = weight; SBP = systolic blood pressure; DBP = diastolic blood pressure; BUN = blood urea nitrogen; SFCT = subfoveal choroidal thickness.
not performed in previous studies. Unlike SFCT changes, the ratio of SFCT changes was not significantly different between the patients with and without DM. Our results suggest that other factors, not only DM, affect the SFCT changes after HD, and adjusted SFCT changes might not be significantly different between patients with and without DM. Some other etiologies of HD, such as hypertension, are systemic diseases affecting the whole vascular system, and the adjusted ratio of SFCT changes might not be significantly different with diabetic patients. Based on our results, further prospective studies with a larger study population should be performed.

This study has several limitations including a relatively small study population, which might limit the generalized application of the current findings. In addition, if a large study population can be recruited, the effect of severity of diabetic retinopathy should be also investigated. There is evidence that the severity of diabetic retinopathy affects choroidal thickness [41-44], and it might affect the choroidal changes after HD. Further studies with a larger study population and various follow-up intervals after HD should be performed to strengthen our findings.

In conclusion, mean SFCT was not significantly different after HD. Subgroup analysis showed that mean SFCT was significantly reduced after HD in the patients with DM, but not in those without DM. DM was the only significant factor correlated with the changes in SFCT after HD.

Contributions of authors
Designed and conducted the study (HMK, JHC, and SJK); collected the data (HMK, JHC, SJK, SJM, and CHK); managed, analyzed, and interpreted data (HMK, JHC, SJK, SJM, and CHK); prepared, reviewed, and approved the manuscript (HMK, JHC, SJK, SJM, and CHK).

Conflicts of interest
The authors have no conflicts to disclose.

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