Choroidal Thickness Evaluation Before and After Hemodialysis in Patients With and Without Diabetes

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Purpose. We evaluated the effect of hemodialysis on the choroidal thickness in patients with and without diabetes who have end-stage kidney disease (ESKD).

Methods. Forty-one patients with ESKD were recruited and divided into two groups: those with ESKD due to diabetic nephropathy (DM group, 37 eyes of 20 patients) and those with nondiabetic ESKD (NDM group, 40 eyes of 21 patients). Using spectral-domain optical coherence tomography (SD-OCT), the subfoveal choroidal thickness (SCT) was measured before and after hemodialysis, and the change ratio (ΔSCT [%]) was calculated.

Results. The SCT decreased in all eyes after hemodialysis. The ΔSCT value in the DM group (−12.6 ± 2.7%) was significantly (P = 0.00027) larger than that in the NDM group (−6.9 ± 2.5%). Moreover, the ΔSCT per body fluid removal (BFR [L]) in the DM group was significantly (P = 0.013) greater than in the NDM group. In the DM group, the mean ΔSCT in the eyes treated with panreatinal photocoagulation (PRP; n = 19) was significantly (P = 0.035) larger than that in eyes not treated with PRP (n = 18). The relationship between the ΔSCT and BFR was not significant (R² = 0.0038, P = 0.80) in the DM group but was significant (R² = 0.54, P = 0.00013) in the NDM group.

Conclusions. The current results may reflect that systemic fluid accumulation has a greater effect on the diabetic choroid, probably due to damage to the choroidal vasculature, in patients with ESKD.

Keywords: choroidal thickness, hemodialysis, diabetic retinopathy, diabetes, optical coherence tomography

Evaluation of the choroid using spectral-domain optical coherence tomography (SD-OCT) was recently reported to be valuable because choroidal change has been associated with the pathogenesis of several ocular diseases such as Vogt-Koyanagi-Harada disease, central serous chorioretinopathy, AMD, and diabetic retinopathy (DR). In addition, variations in ocular parameters such as IOP, refractive error, and axial length, and systemic factors such as circadian rhythm also may affect the choroidal thickness even in healthy subjects.

End-stage kidney disease (ESKD) is a common cause of systemic accumulation of bodily fluid. Hemodialysis can remove excessive water and uremic substances and correct the composition and volume of the bodily fluids. Hemodialysis usually reduces body weight and blood pressure and increases the plasma/interstitial osmotic pressure in patients with ESKD. Almost all patients who underwent hemodialysis due to diabetic nephropathy had severe DR and patients with DR also had “diabetic choroidopathy,” which reported in previous histopathologic studies as marked basement membrane thickening, capillary dropout, focal scarring, and leukostasis in the choroidal vessels. Recently, Kim et al. reported that the choroidal thickness was significantly greater in the eyes with PDR than in less severe DR, but another study showed that the choroidal thickness decreased with increasing DR. These conflicting data confused the relation between the choroidal thickness and the severity of DR, but otherwise, the choroidal thickness was reported to be greater in eyes with macular edema accompanied by a serious retinal detachment. These researchers suggested that the choroidal changes may reflect the concurrent progression of diabetic choroidopathy and be related to the pathogenesis of subretinal fluid in diabetic macular edema.

It is likely that these dynamic and systemic changes before and after hemodialysis may directly affect the choroidal thickness, but the reports of choroidal changes before and after hemodialysis are few and have been controversial. Ulas et al. showed that hemodialysis did not alter the retinal thickness but caused significant choroidal thinning and IOP decreased in nondiabetic patients with ESKD. However, Jung et al. reported that the subfoveal choroidal thickness (SCT) became thicker after hemodialysis in patients with ESKD, and a decreased systolic blood pressure was associated with the increased choroidal thickness. However, the former study was performed on “nondiabetic” patients with healthy eyes, and the latter study had a mixed population with and without diabetes. The diabetic choroid may have different responses to hemodialysis compared with the nondiabetic choroid. Moreover, the diurnal changes in the choroid have been related to the changes in systolic blood pressure, suggesting that a systemic condition may directly affect the choroidal thickness.
Moreover, the choroidal thickness significantly increased after the water drink test (ingesting 1000 mL water); this may be due to acute systemic fluid collection leading to engorgement of the choroidal vasculature.21,22

In the current study, we tested the hypothesis that the choroidal changes in patients with ESKD and diabetes before and after hemodialysis may differ from those without diabetes because of the pathologic changes in the diabetic choroid. Therefore, we investigated the effect of hemodialysis on the choroidal thickness in patients with ESKD and diabetes and in those without diabetes and the systemic parameters that affected these changes.

METHODS

Subjects

Forty-one patients with ESKD undergoing hemodialysis in the Dialysis Center of Nayoro City General Hospital (Nayoro, Japan) were recruited for this study, which was performed according to the tenets of the Declaration of Helsinki. The institutional review board approved the study. All patients provided informed consent. The inclusion criteria were a best-corrected visual acuity exceeding 20/200 and no history of chronic ocular diseases such as glaucoma, uveitis, AMD, and retinal artery/vein occlusion, except for DR. The exclusion criteria were the presence of ocular diseases that prevented examination of the cornea, lens, and retina, and an ocular surgery and/or laser treatments performed during the previous 3 months. The subjects underwent a 3- to 4-hour hemodialysis session three times weekly using a high-performance dialyzer at a blood flow rate of 250 to 300 mL/min. We enrolled subjects whose body fluid removal (BFR) during the hemodialysis session exceeded 0.5 L. Patients were divided into two groups: those with ESKD due to diabetic nephropathy (DM group, 20 patients) and those with nondiabetic ESKD (NDM group, 21 patients). The causes of the nondiabetic ESKD in the NDM group included polycystic kidney disease (n = 4), chronic glomerulonephritis (n = 4), hypertensive nephrosclerosis (n = 5), IgA nephropathy (n = 2), renal excision due to renal cancer (n = 2), lupus nephritis (n = 1), microscopic polyangiitis (n = 1), focal crescentic glomerulonephritis (n = 1), and chronic renal failure of unknown etiology (but not diabetes mellitus; n = 3). The patients in the DM group were diagnosed with either nonproliferative DR (NPDR; n = 10) or proliferative DR (PDR; n = 10). All patients with PDR had previously undergone panretinal photocoagulation (PRP) laser treatment.

Measurements

The patients were refracted using an autorefractometer (NT-4000; Nidek, Gamagori, Japan). The IOP was measured using a slit-lamp mounted Goldmann applanation tonometer. The systemic parameters of body weight, heart rate, systolic blood pressure (BP), diastolic BP, and mean BP were measured before and after hemodialysis. The BFR during the hemodialysis session was assessed.

All eyes were examined using SD-OCT (RetinaScan RS-3000; Nidek). This instrument has a light source with an 880-nm wavelength and a scan rate of 53,000 A-scans/s. Using this machine, we measured the thickness of the retina and choroid in the macula. To evaluate the central macular thickness, the macular map analysis protocol on the RS-3000 SD-OCT was used. The central macular thickness was defined as the average of all points in the inner circle (radius of 1 mm) at the center of the nine sectors defined by the Early Treatment Diabetic Retinopathy Study grid.55 The SCT was measured as the perpendicular distance from the hyperreflective outer border of the RPE layer to the choroid-scleral interface (Fig. 1). To improve choroidal visualization, each image consisted of 50 averaged B-scans in a single line scan, and the SD-OCT device was positioned close to the eye to visualize the image on the top of the monitor in a standard manner (uninverted image).9 Moreover, the latest version of the SD-OCT software (NAVIS-EX version 1.4.0.1; Nidek)
enhances the signal of the averaged scan frame and clearly visualizes the choroid. The images with the best visualization of the inner scleral border were used. Both the horizontal and vertical sections of the SCT were measured through the center of the fovea, and the average of the two was recorded. The reported SCT measurements represented the average of the horizontal and vertical measurements made by two coauthors (AI and YM) who were masked to the clinical status.

In this study, the IOP and SD-OCT scans were measured 30 minutes before and after a single session of hemodialysis without pupillary dilation. Furthermore, in several patients (nine eyes in the DM group and seven eyes in the NDM group), the SCT values before and after hemodialysis were measured repeatedly every other day when consecutive hemodialysis sessions were performed.

Statistical Analysis

All values were expressed as the mean ± SD. The Wilcoxon test was used to compare the systemic hemodynamic parameters and ocular variables before and after the hemodialysis session in each group, and the Mann–Whitney U test was used between the groups. The ocular perfusion pressure (expressed in millimeters of mercury) was calculated by the formula: (ocular perfusion pressure) = [(mean BP) − IOP]. The choroidal change ratio (ΔSCT) was defined by the formula: ΔSCT = ((SCT after hemodialysis) − (SCT before hemodialysis))/(SCT before hemodialysis) × 100 (%). The ΔSCT value divided by the BFR (ΔSCT/BFR) also was calculated to evaluate the difference in the choroidal changes per unit of BFR. Correlations between the variables were analyzed using Pearson’s correlation model and linear regression analysis. In the assessments of the correlations between the ΔSCT and systemic parameters, the ΔSCT value from the left eye in all subjects was used except for two subjects in whom the right eye was used because their left eyes met the exclusion criteria. Subsequently, multiple regression analysis was performed for factors related to the changes in the choroidal thickness. SPSS version 19.0 (SPSS, Inc., Chicago, IL, USA) was used for all statistical analyses. P less than 0.05 was considered significant.

RESULTS

Subject Characteristics

The demographic characteristics of each group are shown in Table 1. Three eyes in the DM group were excluded because of a macular hole (one eye) and an inability to obtain good-quality scans due to severe cataract (two eyes), and two eyes of two patients in the NDM group also were excluded because of brachial retinal vein occlusion and severe cataract. In the DM group, 19 eyes with PDR were treated with PRP (PRP+ eyes), and 18 eyes with NPDR had not been treated with PRP (PRP– eyes). The estimated duration of diabetes in the DM group (n = 20) was 17.9 ± 7.1 years. The duration of hemodialysis in the DM group was 3.9 ± 5.0 years, and that in NDM group was 5.5 ± 5.3 years. The durations did not differ significantly (P = 0.34) between the two groups. The averaged BFR in the DM group (2.77 ± 0.63 L) was significantly (P = 0.013) larger than that in the NDM group (2.14 ± 0.95 L).

Changes in Systemic Hemodynamic Parameters Before and After Hemodialysis

After hemodialysis, the mean body weight decreased significantly from 58.1 ± 9.4 kg to 55.5 ± 9.3 kg in the DM group (P = 1.6 × 10⁻¹⁵) and from 57.7 ± 13.0 to 55.8 ± 12.8 kg in the NDM group (P = 7.8 × 10⁻⁸; Table 2). After hemodialysis, the heart rate decreased significantly from 72.4 ± 12.4 to 70.2 ± 14.9 beats/minute in the DM group (P = 0.020) and from 73.4 ± 9.0 to 66.0 ± 10.1 beats/min in the NDM group (P = 0.0015). After hemodialysis, the systolic BP also decreased significantly from 168.5 ± 23.4 to 151.9 ± 19.8 mm Hg in the

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* P < 0.01.
‡ P < 0.05.
DM group \((P = 0.0039)\) and from 155.4 ± 26.9 to 143.5 ± 28.8 kg in the NDM group \((P = 0.037)\). The systolic BP before hemodialysis in the DM group was slightly higher than in the NDM group, but this difference did not reach significance \((P = 0.11)\).

**Changes in Ocular Variables Before and After Hemodialysis**

Whereas the changes in the mean IOP were not significant in both groups, the mean ocular perfusion pressure decreased significantly after hemodialysis in both groups \((P = 0.014\) in the DM group, and \(P = 0.016\) in the NDM group). The mean central macular thickness values before and after hemodialysis were 259 ± 40 μm and 260 ± 33 μm in the DM group and 263 ± 29 μm and 268 ± 28 μm in the NDM group, respectively. There were no significant differences in the ocular perfusion pressure or central macular thickness between the groups.

**Effect of Hemodialysis on the SCT**

The SCT decreased in all eyes after hemodialysis. In the DM group, the mean SCT values before and after hemodialysis were 268 ± 75 μm and 234 ± 69 μm, respectively (Table 2). In the NDM group, the mean SCT values were 233 ± 78 μm and 217 ± 72 μm, respectively (Table 2). Repeated measurement of the SCT before and after hemodialysis every other day in several patients (nine eyes in the DM group, and seven eyes in the NDM group) showed that the SCT repeatedly increased before hemodialysis and decreased after hemodialysis in both groups (Supplementary Fig. S1). The mean ΔSCT values in the DM and NDM groups were \(-12.6 ± 3.4%\) and \(-6.9 ± 2.3%\), respectively; the decrease in the SCT in the DM group was significantly \((P = 0.00027)\) greater than in the NDM group (Fig. 2). In the DM group, the mean ΔSCT value of PRP+ eyes \((n = 19)\) was \(-13.5 ± 2.7%\), but in PRP- eyes \((n = 18)\) the ΔSCT was \(-11.7 ± 2.4%\), differences that reached significance \((P = 0.035\); Fig. 3). Linear regression analysis showed a significant relationship between the right and left ΔSCT values in the DM group \(\left( \frac{R^2 = 0.28, P = 0.023; \text{Fig. 4A}}{R^2 = 0.70, P = 8.6 \times 10^{-6}; \text{Fig. 4B}} \right)\).

**Associations Between Changes in the SCT and Other Parameters Before and After Hemodialysis**

Because the average BFR in the DM group was significantly larger than that in the NDM group (Table 1), we calculated the ΔSCT/BFR value to evaluate the choroidal changes per unit of body fluid changes. The ΔSCT/BFR value in the DM group \((-4.7 ± 1.5%/L)\) was significantly \((P = 0.019)\) greater than in the NDM group \((-3.6 ± 1.1%/L; \text{Fig. 5})\). However, linear regression analysis showed that the relationship between the ΔSCT and BFR was not significant in the DM group \((R^2 = 0.0038, P = 0.80; \text{Fig. 6A})\) but was significant in the NDM group \((R^2 = 0.54, P = 0.00013; \text{Fig. 6B})\). By multiple regression analysis (Tables 3, 4), the BFR was correlated independently with the ΔSCT in the NDM group \((P = 0.00040; \text{Table 4})\), but no such relationship was seen in the DM group \((P = 0.57; \text{Table 5})\).

**DISCUSSION**

The current study showed that the choroidal thickness decreased after hemodialysis in the patients with ESKD and for the first time revealed that the change in the choroidal thickness was greater in patients with diabetes than in the patients without diabetes. Although previous reports had examined the effect of hemodialysis on the choroidal thickness, the results were controversial. Ulas et al. showed that hemodialysis caused significant choroidal thinning in nondiabetic patients with ESKD. However, another group reported that the mean SCT after hemodialysis “increased” in patients with ESKD; however, that study contained a mixed population of subjects with and without diabetes. Moreover, they did not use the enhanced-depth imaging technique.
choroid-scleral interface, particularly in cases with a thick choroid. In the current study, we identified the choroid-scleral interface in all enrolled eyes (Fig. 1) and excluded eyes in which the interface was not identified properly by our OCT device. Moreover, the decrease in the SCT between the right and left eyes in the same patient was correlated significantly during the same hemodialysis session (Figs. 4A, 4B). In addition, repeated SCT measurements in patients undergoing hemodialysis on different days showed that the SCT increased repeatedly on interdialytic days and decreased after hemodialysis was completed (Supplementary Fig. S1). Therefore, we confirmed that the choroidal thickness of all eyes after hemodialysis decreased in this study.

The choroid is a fully vascularized and cavernous structure, which plays an important role in providing oxygen and nutrients to the outer retina; choroidal disorders can be related to various ocular and systemic diseases. Although the number of noninvasive methods to observe the choroid is limited, recent advances in SD-OCT imaging have enabled us to visualize the full choroidal length; therefore, many researchers have investigated the choroidal thickness in various ocular and systemic conditions. The changes in choroidal thickness are believed to be associated with various physiologic and pathologic factors in the choroid such as circadian rhythm, inflammatory swelling, and vascular hyperpermeability, but they also may have multifactorial causes. Some groups have reported that the water drink test (ingesting 1000 mL water in a short time) induced a significant increase in the choroidal thickness in healthy subjects, in eyes with angle closure, and in patients with POAG. Because the investigators found that the increased choroidal thickness was not associated with the changes in IOP and BP, short-term intake of a large amount of water may cause an engorgement of the choroidal vasculature; therefore, the transient decrease in the plasma colloid osmotic pressure may lead to fluid accumulation in the choroidal interstitium. Regarding the patients with ESKD who underwent hemodialysis, almost all gained weight compared with their dry weight because of fluid accumulation in the predialysis state. Hemodialysis leads to an increased plasma colloid osmotic pressure and transcapillary colloid osmotic gradient and results in a parallel decrease in plasma volume and interstitial fluid volume. In the choroid, the vasculature is well fenestrated and the extravascular (interstitial) compartment has very high permeability of fluid and small molecules. In the current study, the ΔSCT/BFR value in nondiabetic patients was significantly negatively correlated with the BFR, which was the parameter with the highest correlation with the ΔSCT in the multiple regression analyses (Fig. 6D; Table 4). These results suggested that systemic fluid accumulation before hemodialysis may be linked to fluid accumulation in the intravascular and interstitial compartments of the choroid. After hemodialysis, the decreased SCT was associated with removal of the intravascular and interstitial fluid because of the increased transcapillary colloid osmotic gradient. These results also may explain the difference between the ΔSCT in the previous study (approximately −10%) and that in the nondiabetic patients in the current study (−6.9%). It may be because the ultrafiltration volume (i.e., BFR) in the subjects of

**Figure 4.** Relationship between the right-eye and left-eye change ratio of the subfoveal choroidal thickness (ΔSCT) in the ESKD due to diabetic nephropathy (DM) group (A) and in the nondiabetic ESKD (NDM) group (B). The relationships are significant in the DM group ($R^2 = 0.28$, $P = 0.023$) and in the NDM group ($R^2 = 0.70$, $P = 8.6 \times 10^{-6}$).

**Figure 5.** The change ratio of the subfoveal choroidal thickness per body fluid removal (ΔSCT/BFR) value in the ESKD due to diabetic nephropathy (DM) group versus the nondiabetic ESKD (NDM) group. The values (%/L) are expressed as the means ± SDs. The ΔSCT/BFR in the DM group is significantly larger than in the NDM group (*$P = 0.019$, Mann-Whitney U test).
Body fluid removal, L

Change of heart rate, beats/min

Change of systolic blood pressure, mm Hg

$R^2 = 0.00377$

$y = -0.2994x + 0.0129$

$R^2 = 0.54497$

**Figure 6.** The scatterplot shows the association between the change ratio of the subfoveal choroidal thickness ($ΔSCT$) and body fluid removal (BFR) in the ESKD due to diabetic nephropathy (DM group (A)), and the nondiabetic ESKD (NDM) group (B). The relationship between the $ΔSCT$ and BFR is not significant in the DM group ([A]; $R^2 = 0.0058, P = 0.80$) but is significant in the NDM group ([B]; $R^2 = 0.54, P = 0.00015$).

The previous study (3.04 L) was larger than that in our nondiabetic subjects (2.14 L).

However, the $ΔSCT$/BFR in the DM group was significantly larger than in the NDM group (Fig. 5), indicating that the same level of BFR had a greater effect on the decrease in the SCT after hemodialysis in diabetic patients than in the nondiabetic patients. However, the $ΔSCT$ value in the diabetic patients was not significantly correlated with the BFR or other parameters (Fig. 6A; Table 5). This discrepancy may be explained by the disorder in the choroidal vasculature of diabetic patients, which means the possible presence of diabetic choroidopathy. It is natural that diabetic microangiopathy is present in both the retina and choroid; previous histopathologic reports have reported that the choriocapillaris and other choroidal vessels displayed marked basement membrane thickening and accumulated periodic acid-Schiff positive materials in their walls, which resemble glomerular changes in diabetic nephropathy.17,18,28 Choroidal compromise also has been suggested by the luminal narrowing of the capillaries, capillary dropout, focal scarring, choroidal aneurysms, and choroidal neovascularization.17,18,28,29 Moreover, an electron microscopic evaluation showed that masses of multilaminar, homogeneous, and disordered banded basement membrane lay along the inner wall of the deeper choroidal vessels28 and that proteinaceous fluid leaked into the choroidal stroma.18 We speculated that this histopathologic destruction of the vasculature in the diabetic choroid might lead to impaired control of the hydrostatic pressure and the colloid osmotic pressure because of leakage of large molecules such as albumin; therefore, the fluid accumulation in the intra/extravascular compartments of the choroid may vary greatly.

Furthermore, alterations in the choroidal circulation detected by laser Doppler flowmetry in the foveal region were reported previously; the choroidal blood flow decreased in the PRP eyes50 and in the NPDR eyes with macular edema compared with healthy controls.31 However, the choroidal circulation measured by laser Doppler flowmetry mainly reflected the blood flow in the choriocapillaris. On the other hand, we previously reported that pulsatile ocular blood flow, which reflected the total choroidal blood flow, was unchanged independent of the degree of retinopathy in patients with type 2 diabetes.32 These results suggested that the choroidal blood flow in diabetes is rather controversial. However, basically, we recently showed that there were no significant correlations between the absolute value of SCT and the total choroidal blood flow.33 Therefore, we evaluated the "changes" in the choroidal thickness ($ΔSCT$) in the current study. Using indocyanine green (ICG) angiography and choroidal blood flow, but our data showing that the mean $ΔSCT$ value of PRP+ eyes (PDR eyes)
was significantly larger than those of PRP− eyes (NPDR eyes) may reflect the severity of the diabetic choroidopathy in patients with diabetes with PDR (Fig. 1C). However, further clinical studies are needed that simultaneously evaluate the choroidal thickness and choroidal blood flow to investigate the correlations among the changes in the choroidal thickness, blood flow, and severity of DR/choroidopathy.

The current study had some limitations. First, we have not assessed which component, the vasculature or the interstitium, undergoes more changes in the choroid. A previous study reported that the ratio of the vertical and horizontal diameters of the choroidal veins was correlated significantly with the choroidal thickness.39 Sonoda et al.36 recently showed that luminal and interstitial areas of the choroid could be separately analyzed with the binarization of choroidal images recorded by the SD-OCT. Our OCT device did not have enough axial resolution to precisely evaluate the changes in the luminal and interstitial areas, particularly in the deeper choroid. Further study using devices that have a higher penetration (such as swept-source OCT) are needed to assess this limitation. Second, we did not measure the plasma colloid osmotic pressure before and after hemodialysis. However, the hemodialysis treatment apparently increased the plasma colloid osmotic pressure, which contributed to the fluid removal from the interstitial tissues.13 Our results showed that the BFR was the parameter that was most highly correlated with the ΔSCT, but the change in the plasma colloid osmotic pressure also is an important factor in the changes in the choroidal thickness before and after hemodialysis. Third, the choroid is controlled by the autonomic system.37 However, the current multiple regression did not show a significant correlation between the changes in the choroidal thickness and the changes in the BP and heart rate in both groups (Tables 3, 4), suggesting that the current results at least were not affected markedly by the autonomic control of the choroid. However, diabetic patients with ESKD also have diabetic neuropathy that markedly by the autonomic control of the choroid. However, suggesting that the current results at least were not affected changes in the BP and heart rate in both groups (Tables 3, 4),...

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