Changes in subfoveal choroidal thickness and choroidal extravascular density by spectral domain optical coherence tomography after haemodialysis: a pilot study

Ji Won Jung, Hee Seung Chin, Dae Hyung Lee, Myung Hun Yoon, Na Rae Kim

ABSTRACT
Aims To examine the changes in the subfoveal choroidal thickness (SFCT) and choroidal density using spectral domain optical coherence tomography (SD-OCT) before and after haemodialysis (HD).

Methods 28 eyes of 19 patients with chronic renal failure (CRF) undergoing HD were included. Ophthalmologic examinations including SD-OCT were performed 1 h before and after HD. The SFCT was measured manually using Image J software, and the relationships between the change in SFCT and in the systemic parameters after HD were evaluated. The changes in choroidal extravascular density of the OCT image after HD were evaluated by comparing brightness value obtained with Adobe Photoshop software.

Results The mean SFCT of all eyes increased significantly from 276.94±58.73 μm to 288.29 ±65.57 μm (p=0.003). In the univariate generalised estimating equation (GEE), the SFCT increased significantly after HD (p=0.006). After adjusting for age, gender and other significant factors in univariate analysis, the SFCT increased significantly after HD (p=0.032). The decrease in systolic blood pressure (SBP) was associated with the increase in SFCT (p=0.013). The choroidal extravascular density of OCT image increased after HD (p<0.001) and the mean change was 12.35±9.72.

Conclusions In the SD-OCT image, the SFCT became thicker and the choroidal extravascular density increased after HD in patients with CRF. The decrease in SBP after HD was associated with an increase in SFCT. The choroidal autoregulatory control of ocular haemodynamic change and shifting of fluid and molecules between the blood and choroidal interstitium might be involved in the mechanism of these choroidal changes.

INTRODUCTION
Recently, optical coherence tomography (OCT) technology has advanced and currently incorporates spectral-domain (SD) imaging, which offers significant advantages over traditional time-domain OCT techniques, including a faster scanning speed and higher resolution. SD-OCT has allowed visualisation of the choroid using an enhanced depth imaging technique or high penetration OCT with a long wave length.1–3

The choroid is the tissue with the highest blood supply per area.4 A previous study suggested that the choroidal vessels are poorly autoregulated and perfusion pressure affects the blood flow directly.5 Conversely, recent investigations have shown that choroidal autoregulation or baroregulation can compensate for systemic blood pressure (SBP) fluctuations.6–7 Diurnal or circadian variations of choroidal thickness, and of other ocular parameters such as intraocular pressure (IOP), anterior chamber depth and axial length (AL) in normal healthy subjects, have been reported and these changes have been associated with changes in the SBP.8–9

The main objective of haemodialysis (HD) is to control the composition and volume of body fluid by removal of water and uraemic substances. The changes in systemic haemodynamic parameters induced by HD are relatively well known. HD usually reduces blood pressure (BP), which is associated with a decrease in body weight and plasma volume.10 The serum osmolality decreases and the concentration of plasma proteins increases with the elimination of water during HD, leading to an increase in plasma colloid osmotic pressure. This increase in colloid osmotic pressure develops a colloid osmotic pressure gradient between the plasma and interstitial fluid, causing water to shift from the interstitial fluid to the plasma.11

The purpose of this study is to evaluate the choroidal change in response to systemic haemodynamic change induced by HD in patients with chronic renal failure (CRF) patients with systemic vascular disease.

MATERIALS AND METHODS
Subjects
Thirty patients with CRF undergoing HD in the Dialysis Unit of Inha University Hospital were enrolled in this study. Twenty-eight eyes of 19 patients (7 men/12 women) gave clear choroidal images. Informed consent was obtained from all subjects according to the Helsinki declaration. Institutional Review Board approval was also obtained. Inclusion criteria included a best corrected visual acuity (BCVA) better than 20/200. The exclusion criteria were the presence of ocular disease that would prevent an examination of the corneal and macular state or the presence of prior ocular surgery, laser and/or an injection over the previous 3 months. The subjects underwent an average of 3–4 h HD sessions three times per week using a high-performance dialyser at a blood flow rate of 250 mL/min. The causes of CRF in the 19 patients included diabetes mellitus (DM; n=9), hypertensive nephrosclerosis (n=5), polycystic kidney disease (n=1), chronic glomerulonephritis (n=3) and IgA nephropathy (n=1). Patients with CRF and DM

(n=9) were diagnosed with either non-proliferative diabetic retinopathy (n=3) or proliferative diabetic retinopathy (PDR; n=6). The patients with PDR had previously undergone panretinal photocoagulation laser treatment. Two patients previously underwent a focal and grid laser or intravitreal injection for diabetic macular oedema.

Protocol
The ophthalmologic examination including BCVA, IOP and SD-OCT scans were performed on each subject 1 h before and 1 h after a single HD session using the same time intervals. Refraction was obtained using autorefractometry (Topcon KR-8800; Topcon Co. Ltd, Tokyo, Japan). The IOP was measured using a slit-lamp mounted Goldmann applanation tonometer.

The pre-HD and post-HD venous blood samples were collected using standard venipuncture techniques before and after HD. The serum osmolarity and the plasma total protein and albumin levels were measured, and the plasma colloid osmotic pressure was calculated using the following formula: plasma colloid osmotic pressure = 5.5 × concentration of plasma albumin + 1.4 × concentration of plasma globulin before and after HD. The body weight and systolic and diastolic blood pressure (SBP, DBP) were measured before and after HD.

OCT measurements
The SD-OCT scans of the patients with CRF were performed using Spectralis OCT (software V5.3, Heidelberg Engineering, Dossenheim, Germany). The scan was a line scan of 30 degree consisting of 768 A-scans per frame. The enhanced depth imaging option was not used but images of full thickness choroid, which enable one to examine the choroidal thickness, were selected. One hundred frames were averaged together with the aid of eye tracking.

The images with the best visualisation of the border between the choroid and sclera, that is, the choroid–scleral interface (CSI), were used. The subfoveal choroidal thickness (SFCT) was defined as the distance between the hyperscattering line of retinal pigment epithelial cells and that of the CSI (figure 1). All selected images with scale bar were exported from SD-OCT. To compensate for the changes in the OCT image quality after HD, the image contrast was adjusted until the contrast of the retinal layer was similar before and after HD. The images were then rescaled to a unified scale, overlaid with a grid indicating the length of the sectors to be measured, and finally measured using Image J software (National Institutes of Health, Bethesda, Maryland, USA) (figure 1A). The change in choroidal extravascular density of the OCT image after HD was evaluated by image analysing software (Photoshop, version CS5; Adobe System, Mountain View, California, USA). An optical density plot of the selected choroidal layer was generated by the histogram tool and the mean staining intensity was recorded (figure 1B).

All patient information was concealed in OCT images and randomisation of image sequence was performed. The measurements were performed three times and an OCT reader was masked to the previous measurements.

Statistical analysis
For the intragrader reliability, test–retest variability, intraclass correlation coefficient (ICC), and coefficients of variation (CV) were performed. A paired t test was used to compare the systemic haemodynamic parameters and ocular variables before and after the HD session. The effects of HD, age, gender, diabetes, duration of dialysis, ocular parameters, and systemic haemodynamic parameters on the SFCT were evaluated using univariate generalised estimating equation (GEE), correcting for the within-subject correlation. The multivariate GEE was used to incorporate age, gender and other factors, showing a significant difference with a p value<0.1 in univariate analysis. The associations between the changes in SFCT and other parameters after HD were evaluated using GEE.

SPSS V19.0 (SPSS Inc., an IBM Company) was used for all statistical analyses and a p value<0.05 was considered significant.

RESULTS
Subject characteristics
A total of 28 eyes from 19 subjects with CRF were enrolled. Table 1 summarises the demographic and clinical characteristics of the subjects. The mean spherical equivalent was −0.45 ± 1.72 (mean ± SD) dioptres. Nine subjects had diabetes mellitus and subjects underwent dialysis over a period of 3.50 ± 1.50 years (median ± IQR) (table 1).

Repeatability of choroidal measurements
For the intragrader reliability in SFCT and choroidal extravascular density measurements, test–retest variability, ICC and CV were evaluated. The intragrader agreements were excellent. Test–retest variability for the SFCT and choroidal extravascular density were 6.76 μm and 6.69. The ICC values for the
Table 1  Characteristics of the subjects (28 eyes from 19 individuals)

<table>
<thead>
<tr>
<th>Variable</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>51.21±9.47 (mean±SD)</td>
</tr>
<tr>
<td>Male eyes</td>
<td>10 (35.7%)</td>
</tr>
<tr>
<td>Right eyes</td>
<td>14 (50.0%)</td>
</tr>
<tr>
<td>Spherical equivalent (dioptre)</td>
<td>−0.45±1.72 (mean±SD)</td>
</tr>
<tr>
<td>Diabetes mellitus (yes)</td>
<td>13 (46.4%)</td>
</tr>
<tr>
<td>Duration of dialysis (years)</td>
<td>3.50±1.50 (median±IQR)</td>
</tr>
</tbody>
</table>

Changes in the systemic haemodynamic parameters before and after HD
The body weight decreased significantly from 63.17±9.75 to 61.01±9.81 kg after HD (p<0.001). The SBP decreased significantly from 158.68±24.24 to 142.16±22.64 mm Hg after HD (p=0.018). The DBP decreased from 78.68±14.26 to 78.26±14.85 mm Hg, but the difference was not significant (p=0.859). The plasma colloid osmotic pressure increased significantly from 25.12±1.63 to 29.42±2.62 mm Hg after HD (p<0.001). The serum osmolarity before and after the HD session was 312.74±25.12±1.63 to 29.42±2.62 mm Hg after HD (p<0.001). No significant association was observed among the other factors, such as age, gender, DM, spherical equivalent, DBP and SFCT (table 2). After adjusting for age, gender, duration of dialysis, body weight and serum osmolarity, the SFCT increased significantly after HD (p=0.006). The longer duration of dialysis was marginally related to the thinner SFCT (p=0.062). The decrease in body weight and SBP was associated with an increase in SFCT (p=0.012 and <0.001). The decrease in serum osmolarity and the increase in plasma colloid osmotic pressure were marginally related to the increase in SFCT (p=0.050 and 0.051). No significant association was observed among the other factors, such as age, gender, DM, spherical equivalent, DBP and SFCT (table 2).

Changes in the ocular variables before and after HD
The change in the mean IOP was not significant (p=0.902). The mean ocular perfusion pressure decreased after HD, although the difference was not statistically significant (p=0.052).

Effect of HD on the SFCT
The mean choroidal thickness of all eyes increased significantly from 276.94±58.73 to 288.29±65.57 μm (p=0.003). The spaghetti plot provides individual eye information for the change in the SFCT before HD (baseline) and after HD (figure 2). The degree of the changes in the SFCT was different in individual eyes, but the trend showed an increase in SFCT after HD in the majority of eyes (23 of 28 eyes, 82.1%). This demonstrates the significant amount of changes in some individual eyes. Figure 3 shows a representative SD-OCT image. The SFCT became thicker after HD in the representative cases.

An analysis of the factors affecting the SFCT was performed using GEE, correcting for the within-subject correlation in cases, in which both eyes were examined. The factors examined by this model were performing HD, demographic characteristics, ocular parameters, systemic haemodynamic parameters. In univariate analysis, the SFCT increased significantly after HD (p=0.006). The longer duration of dialysis was marginally related to the thinner SFCT (p=0.062). The decrease in body weight and SBP was associated with an increase in SFCT (p=0.012 and <0.001). The decrease in serum osmolarity and the increase in plasma colloid osmotic pressure were marginally related to the increase in SFCT (p=0.050 and 0.051). No significant association was observed among the other factors, such as age, gender, DM, spherical equivalent, DBP and SFCT (table 2).

Associations between the changes in SFCT and other parameters before and after HD
The associations between the difference of SFCT and those of the other parameters before and after HD were evaluated. Among IOP, body weight, SBP, DBP, serum osmolarity and plasma colloid osmotic pressure, the change in SBP after HD was significantly related to the change in SFCT after HD (p=0.012). The change in SBP showed a significant negative correlation with the change in SBP after HD (slope=−0.414, p=0.001) (figure 4).

Effect of HD on the choroidal extravascular density
The choroidal extravascular density was evaluated using quantified value in image analysing software. The mean brightness values of the choroidal layer increased in all eyes and these values were 111.40±25.08 before HD and 123.75±25.28 after HD. The mean change was 12.35±9.72 after HD (p<0.001). Figure 3 shows the change in the choroidal extravascular tissue density after correcting for the difference in quality induced by HD using the contrast control.

**DISCUSSION**
Patients with CRF are treated with a range of blood filtration mechanisms. One of the most widely used filtration mechanisms is HD, which uses a semipermeable membrane. HD corrects the excessive accumulation and abnormal distribution of body fluid. The systemic haemodynamic parameters, such as BR, body weight, serum osmolarity, and plasma colloid osmotic pressure change significantly after a single HD session. The choroid has been known as the tissue with the highest blood supply per area. Given the choroidal vascular nature, this study examined the changes in the SFCT and the choroidal density before and after HD. Although the degree of the changes and trends were different in individual eyes, the SFCT and the choroidal density tended to increase in most eyes after HD.

Previous studies have reported the factors affecting the choroidal thickness, such as age, AL, AL and refractive error. Recently, Tan et al. reported the significant diurnal variation of choroidal thickness. The amplitude of the variation was associated with age, AL, refractive error and the change in SBP Usui.
et al also revealed a circadian change in the SFCT in healthy subjects. The SFCT was significantly negatively correlated with SBP. In our study, change in SFCT after HD showed a significant negative correlation with the change in SBP after HD as in the previous studies.

According to the following reports, the circadian variation of choroidal thickness could be supposed as an effect of the choroidal autoregulation by change of SBP. Some studies have shown that choroidal autoregulation or baroregulation can compensate for SBP fluctuations. In other words, the choroidal autoregulates or baroregulates for the maintenance of choroidal blood flow despite the changes in perfusion pressure by variation of BP or IOP. Two hypotheses have been proposed to explain the choroidal regulation mechanism, one is a myogenic theory and another involves a neuronal component. A myogenic mechanism is the response of the arteriolar smooth muscle to stretch by the change in perfusion pressure. The neuronal component involves sympathetic vasoconstriction with high BP or parasympathetic vasodilation with low BP. Polska et al reported the choroidal autoregulatory capacity during the change in ocular perfusion pressure. Their data indicated that the choroid shows more pronounced regulatory capacity to change in transmural pressure in the arterial system than an experimental increase in IOP.

Choroidal autoregulation could affect the thickness because of the choroidal composition or vascular nature. Tanabe et al reported a significant correlation between the diameters of the choroidal vessels and the choroidal thickness in normal subjects. They showed a significant correlation between the ratio of the vertical and horizontal diameters and the choroidal thickness measured in the OCT. Vance et al examined the effects of phosphodiesterase-5 inhibitor, sildenafil citrate on the choroidal thickness. This drug has the vasodilatory effect of nitric oxide through relaxation of smooth muscle and appears to increase the choroidal thickness.

Our subjects had CRF caused mainly by diabetes mellitus or hypertension, which induces a systemic microangiopathy. Previous literatures reported that longstanding diabetes can affect the choroidal blood flow due to an increase in choroidal vascular resistance. The choroidal autoregulatory response that occurred in patients with CRF may be somewhat different from that in normal subjects. However, the short-term change in SBP after HD is significantly larger than diurnal variation of SBP. Even though the autoregulatory ability of patients with CRF is deficient, the haemodynamic change after HD might be large enough to cause the significant response.

We had reported that the quality of the OCT image significantly decreased and these changes were mainly due to the ocular surface change before and after HD. In the present study, an increase in choroidal extravascular density was observed in SD-OCT images before and after HD, correcting for the difference in quality using contrast control. The authors suggest that this result might be caused by the removal of fluid.

Figure 3  Representative images of three subjects showing changes in the subfoveal choroidal thickness (SFCT) and the choroidal extravascular density in spectral-domain optical coherence tomography (OCT) before and after haemodialysis (HD). The left shows the location of the scan and the middle shows an OCT image before HD, the right shows an OCT image after HD. In the first image of a 41-year-old woman with non-proliferative diabetic retinopathy, the SFCT increased from 296.05 μm (before HD) to 310.03 μm (after HD) and the choroidal extravascular density changed from 100.03 to 145.65. In the second image of a 51-year-old man with hypertensive nephrosclerosis, the SFCT was 162.03 μm (before HD) and 168.02 μm (after HD) and the density was 125.47 (before HD) and 144.17 (after HD). The third image of a 37-year-old man with polycystic kidney disease and no other ocular pathology shows the changes in the SFCT from 228.12 μm (before HD) to 238.80 μm (after HD) and the choroidal extravascular density changed from 61.55 to 80.83.

retention in choroidal interstitium, leading to an increase in plasma colloid osmotic pressure after HD. The increase in colloid osmotic pressure develops a colloid osmotic pressure gradient between the plasma and interstitial fluid, causing water to shift from the interstitial fluid into the plasma.11 De Moraes et al23 reported choroidal expansion during the water drinking test. After the water drinking test, a transient decrease in blood colloid osmotic pressure shifts the fluid from the blood to the choroidal extravascular tissue.

Another possible explanation for the changes in choroidal density of OCT images is the high permeability of choroid. The wall of the choriocapillaries below Bruch’s membrane is fenestrated.24 Therefore, the leakage of macromolecules such as albumin and small molecules such as glucose and/or amino acids is possible.25 The concentration of glucose and amino acids in the choroidal extravascular space is not so different from that in blood.26 After HD, the concentration of molecules such as protein and glucose can change and leak from the choroidal vessels to the extravascular space. If these molecules have a high optical scattering property, the choroidal extravascular density may change after HD.

The limitations of this study include the use of a small sample size and no use of enhanced depth imaging method. However, OCT images of the full-thickness choroid were selected, which enable one to examine the choroidal thickness. The repeatability of the choroidal thickness measurements was also excellent. All subjects did not have normal eyes. These eyes might have any form of retinal and choroidal pathology. However, none of our subjects had active retinopathy requiring treatment. The AL is known as a factor which affects the choroidal thickness in previous reports. However, the influential factors did not include AL in this study. In addition, circadian rhythm, which is the determinant of the choroidal thickness, was not considered in this study.

In the SD-OCT image, the SFCT became thicker and the choroidal extravascular density increased after HD in patients with CRF. The decrease in SBP after HD was associated with an increase in SFCT. After HD, changes in the systemic haemodynamic parameters such as SBP could cause choroidal vasodilation by choroidal autoregulatory capacity that finally might cause choroidal thickening measured in the SD-OCT images. Shifting of fluid and molecules between the choroidal capillary and the interstitial space might contribute to the change in the choroidal extravascular density of OCT images after HD. Future studies which incorporate normal subjects are required to reveal the additional evidence with regard to choroidal compensatory function.

**Table 2** Influential factors on the subfoveal choroidal thickness (SFCT) using univariate analysis

<table>
<thead>
<tr>
<th>Variables</th>
<th>Estimate</th>
<th>Standard error</th>
<th>p Value</th>
<th>Direction of effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Performing HD (yes)</td>
<td>11.353</td>
<td>4.152</td>
<td>0.006</td>
<td>After HD, increase in SFCT</td>
</tr>
<tr>
<td>Age</td>
<td>−0.255</td>
<td>1.17</td>
<td>0.827</td>
<td></td>
</tr>
<tr>
<td>Gender (men)</td>
<td>−13.164</td>
<td>27.35</td>
<td>0.630</td>
<td></td>
</tr>
<tr>
<td>DM (yes)</td>
<td>28.036</td>
<td>25.34</td>
<td>0.269</td>
<td></td>
</tr>
<tr>
<td>Duration of dialysis</td>
<td>−5.080</td>
<td>2.721</td>
<td>0.062</td>
<td>The longer duration, decrease in SFCT</td>
</tr>
<tr>
<td>SE</td>
<td>−15.606</td>
<td>9.792</td>
<td>0.111</td>
<td></td>
</tr>
<tr>
<td>Body weight</td>
<td>−4.322</td>
<td>1.726</td>
<td>0.012</td>
<td>Decrease in Bwt, increase in SFCT</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>−0.505</td>
<td>0.123</td>
<td>&lt;0.001</td>
<td>Decrease in SBP, increase in SFCT</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>−0.037</td>
<td>0.430</td>
<td>0.932</td>
<td></td>
</tr>
<tr>
<td>Serum osmolarity</td>
<td>−0.416</td>
<td>0.212</td>
<td>0.050</td>
<td>Decrease in osmolarity, increase in SFCT</td>
</tr>
<tr>
<td>Plasma colloid osmotic pressure</td>
<td>1.668</td>
<td>0.856</td>
<td>0.051</td>
<td>Increase in osmotic pressure, increase in SFCT</td>
</tr>
</tbody>
</table>

Univariate generalised estimating equation was performed. p value<0.1 statistically significant.

**Table 3** Influential factors on the subfoveal choroidal thickness (SFCT) using multivariate analysis

<table>
<thead>
<tr>
<th>Variables</th>
<th>Estimate</th>
<th>Standard error</th>
<th>p Value</th>
<th>Direction of effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Performing HD (yes)</td>
<td>14.068</td>
<td>6.571</td>
<td>0.032</td>
<td>After HD, increase in SFCT</td>
</tr>
<tr>
<td>Age</td>
<td>−1.249</td>
<td>1.222</td>
<td>0.307</td>
<td></td>
</tr>
<tr>
<td>Gender (men)</td>
<td>−35.553</td>
<td>26.508</td>
<td>0.180</td>
<td></td>
</tr>
<tr>
<td>Duration of dialysis</td>
<td>−6.538</td>
<td>3.598</td>
<td>0.069</td>
<td></td>
</tr>
<tr>
<td>Body weight</td>
<td>0.590</td>
<td>1.669</td>
<td>0.724</td>
<td></td>
</tr>
<tr>
<td>Systolic BP</td>
<td>−0.387</td>
<td>0.156</td>
<td>0.013</td>
<td>Decrease in SBP, increase in SFCT</td>
</tr>
<tr>
<td>Serum osmolarity</td>
<td>0.361</td>
<td>0.330</td>
<td>0.273</td>
<td></td>
</tr>
</tbody>
</table>

Age, gender, significant variables in univariate test (p value<0.1) were included. Dominant variable was included among serum osmolarity and plasma colloid osmotic pressure due to multicollinearity.

**Figure 4** The association between the changes in subfoveal choroidal thickness and systolic blood pressure after haemodialysis (slope=−0.414, p=0.001).

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**Authors’ contributions** All authors were qualified for authorship, based on contribution to conception and design (JW, HSC, NRK), acquisition of data (JW, MHY, NRK) and analysis and interpretation of data (JW, NRK, DHL); drafting the article and revising it critically for important intellectual content; and final approval of the version to be published.

**Competing interests** None.

**Patient consent** Obtained.
**Clinical science**

**Ethics approval** Ethics approval was provided by Institutional Review Board of Inha university hospital, Incheon, Korea. All parts of the study were performed according to the tenets of the Declaration of Helsinki.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**REFERENCES**

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