Effects of hemodialysis on macular and retinal nerve fiber layer thicknesses in non-diabetic patients with end stage renal failure

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ABSTRACT

الأهداف: لتقييم سماكة طبقة الألياف العصبية الشبكية (RNFL) وسماكة بقعة الشبكية بواسطة مجال فوريه نظام التماسك البصري المقطعي (FD–OCT) في المرضى غير المصابين بالسكري في مرحلته النهائية (ESRF) والخاضعين لغسل الكلى (HD).

الطريقة: جرى في هذه الدراسة الاستطلاعية والمراقبة تقييم كلتا العينين لعشرين مريضاً الذين يتلقون HD (مجموعة 1) والأربعة والثلاثين مريضاً في مجموعة التحكم (مجموعة 2) بواسطة FD–OCT. وتمت مقارنة سماكة بقعة الشبكية وسماكة RNFL بين المجموعتين وارتباطها بالتقدم في السن، وبمدة غسيل الكلى وبالجنس. في المجموعة 1، جرى تقييم سماكة بقعة الشبكية وRNFL قبل وبعد بفترة وجيزة من HD في اليوم الأول، والشهر الأول والسادس من المرضى.

النتائج: في المجموعة 1، كان متوسط سماكة RNFL في في الجهة الصدغيّة التحتية في أرق من المجموعة 2 قبل غسيل الكلى. وهذا الترقق لم يكن مرتبط بالعمر. لكن الترقق على المستوى العلوي الأنفي ومتوسّط السماكة أظهرت ارتباطاً سلبياً بمدة HD. بينما كان كلا من سماكة المستوى الأنفي والصّدغي ومتوسّط سماكة بقعة الشبكية كانت أرق عند المريضات الأناث. زيادة سماكة RNFL في شبكة العين وسماكة بقعة الشبكية التي لوحظت بعد HD في اليوم الأول والشهر الأول لم تبد استمرارية في الشهر السادس، ما عدا الربعية العلوية في RNFL.

الخاتمة: سماكة RNFL في شبكة العين وسماكة بقعة الشبكية كانت أرقّ عند المرضى الذين يتلقون HD مقارنة بالأصحاء. العمر ليس له تأثير على هذه الترقّقات. بينما مدّة HD لها تأثير أكبر من تأثير الجنس. جلسة HD تتسبّب في زيادة مستمرّة في الربعية العلوية لطبقة RNFL.

Objectives: To evaluate the thicknesses of retinal nerve fiber layer (RNFL) and macula by fourier-domain (FD) optical coherence tomography (OCT) in non-diabetic patients with end-stage-renal-failure (ESRF) undergoing hemodialysis (HD).

Methods: This is a prospective and observational study. Both eyes of 20 patients receiving HD (group 1) and 34 control patients (group 2) were evaluated by FD-OCT. Macular and RNFL thicknesses were compared between groups and their correlation with age, duration of HD, and gender were examined. In group 1, macular and RNFL thicknesses were evaluated before and shortly after HD in the first day, first and sixth months.

Results: In group 1, pre-HD temporal, inferior, average RNFL thicknesses were thinner than group 2. This thinning did not correlate with duration of HD, age and gender. Pre-HD macular thicknesses were thinner than group 2. These thinnings did not correlate with age, but the thinnings at superior, nasal and average thickness correlated negatively with duration of HD. Nasal, temporal, and average macular thicknesses were thinner in female patients. The thickenings of RNFL and macula that were observed in the after HD first day and first month did not showed consistency in the sixth month except superior quadrant RNFL.

Conclusion: Macular and RNFL thicknesses of patients receiving HD were less than the normal population. Age has no effect on these thinnings. The duration of HD affects more than gender. Hemodialysis session causes a consistent increase in superior quadrant RNFL.

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The patients with chronic renal failure (CRF) in whom glomerular filtration rate (GFR) is below 15 ml/min/1.73 m^2 are classified as stage 5 renal failure. Diabetes mellitus becomes prominent as the most important cause of stage 5 renal failure in the United States. Hypertensive nephropathy often follows it. Most of the patients with ESRF usually treat hemodialysis (HD).[1] The various findings such as band keratopathy, conjunctival calcifications, inflammatory pannus, superior limbic keratoconjunctivitis, osmotic cataract due to uremia, punctate cataract due to hypocalcemia, fluctuations in intraocular pressure (IOP), retinal tear due to disruption of choroidal capillary bed, hemorrhage due to heparinized dialysis and hypertension, anterior ischemic optic neuropathy and uremic optic neuropathy due to hypotension occurred during dialysis and in anemia, retinal changes due to toxicity of desferroxamine and erythropoietin can be seen in patients with CRF.[2-6] Optic neuropathy is a well-defined complication in patients with renal failure treated with dialysis. Severe anemia, hypotension and ischemia due to diffuse atherosclerosis, toxicity, and also concomitant systemic diseases such as diabetes mellitus (DM) and hypertension (HT) are to blame for the development of this condition.[3,4,6] Optical coherence tomography (OCT) is a high-resolution non-contact and non-invasive technique that can analyze the structure of the retina and the optic disc. It was shown that thinning of the retinal nerve fiber layer (RNFL) may be seen in these patients.[7] In Pahor's[8] study, it was determined that the obvious decrease in retinal light sensitivity, which can be observed in more than 1/3 of the HD patients with no marked aortic obstruction, does not correlate with the patient's age and period of HD, but has been observed only in HD patients with hypertensive retionapthy (HTRP). With consideration paid to the case,[9] it was determined with the help of OCT that there occurred a marked decrease in the retinal thickness of patients treated for HD, not correlated with the period of HD, but with the age. The first aim of this prospective study is to compare the RNFL and macular thickness of HD patients with ESRF and without DM with healthy control group by using FD-OCT and investigate the effects of age, gender, and duration of HD on these thicknesses. The second aim is to determine the acute effect of HD on retina in patients with ESRF.

Methods. In this study, 108 eyes of 54 adult patients who applied to the Eye and Nephrology Clinic of Sisli Etfal Teaching and Research Hospital were enrolled. Patients were divided into 2 groups. The first group included 40 eyes of 20 patients with ESRF and without DM and receiving HD, 3 times a week in the nephrology clinic. Etiologies of CRF in the HD group are shown in **Figure 1**. The second group was control group of healthy subjects and included 68 eyes of 34 patients showing compliance with the first study group for age and gender. Patients who were enrolled in our prospective-observational study were asked to sign a standard informed consent form after the approval by the Non-Drug Clinical Research Ethics Advisory Committee of Sisli Etfal Training and Research Hospital, Istanbul.

Patients with previously known history of glaucoma and intraocular surgery, patients with media opacities, such as cataract, band keratopathy, patients with inflammation (uveitis, vasculitis, and so forth), pediatric patients under the age of 15 years, patients above the age of 65 with refraction above -1/+1 diopters, patients with other ocular disease and patients with DM and uncontrolled HT were excluded.

Patients received HD with a dialysate containing Potassium (K^+) 3 mg/dL, Calcium (Ca^{++}) 1,25mmol/L. A 5000 IU standard heparin was used as anti-coagulant. The mean blood flow velocity was set to 350 mL/min as long as the patient tolerated. Dialysate flow rate was 500 mL/min as standard. Dialysis time was 4 hours in all patients. In addition, blood urea, creatinine, total protein, albumin, sodium (Na^+), K^+, Ca^{++}, P^+, hematocrit and hemogram were measured on the first day before dialysis and urea, creatinine and K^+ were measured on the same day after dialysis. The patients' systolic and diastolic blood pressure, total fluid volume removed from the body were recorded at each dialysis session.

Patients underwent routine ophthalmic examination. Visual acuity was determined by the best corrected visual acuity (BCVA) Snellen chart. Intraocular pressure (IOP) was determined by Aplanation tonometry. Fundus examination was carried out using 78 D non-contact lens and biomicroscopy. Retinal nerve fiber layer and MM6 (6 mm^2 macular map) thicknesses were measured by a single person by OPTOVUE RTVue (model-RT 100 version 2.0 OCT Fremont, CA, USA) keeping the signal strength index (SSI) >50.

Acute effect of HD was investigated by measuring RNFL and macular thickness by FD-OCT in group 1 in the first day, first month, and sixth month before

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HD session and 30 minutes after the session. Superior, inferior, temporal, and nasal quadrants of macular thickness measurements were evaluated, based on the average of 1 mm diameter circular central macula (mean macular thickness) and surrounding 3 mm diameter parafoveal area and 6 mm diameter perifoveal area. Retinal nerve fiber layer measurements taken at 3.4 mm diameter peripapillary circular area from the center of the optic nerve head were evaluated at totally 5 regions as superior, inferior, nasal, and temporal quadrants and the average. The effects of patient age, duration of HD and gender on the thickness measurements were also analyzed by comparing with the control group. **Figure 1** shows the classification of etiologies of chronic renal failure in the HD group (Group 1).

Statistical analysis. Number crunching statistical system (NCSS) 2007 & PASS 2008 Statistical Software (Utah, USA) program was used for statistical analysis. Chi-square test was used for comparing categorical data between groups. T test for independent groups and paired t test for intra-group comparisons were used in order to compare quantitatively means and standard deviations of the 2 groups. Pearson's correlation coefficient (r) was assessed in order to evaluate the relationship between 2 quantities. Multiple linear regression analysis was used in order to evaluate the effect of more than one quantity on to one quantity in common. Significance level was considered as $p<0.05$ for all tests.

All applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during this research.

Results. Demographic and clinical characteristics of all patients are shown in **Table 1**. The mean duration of HD of the patients was 4.3 years (range 0.08-12). Comparison of the first day of RNFL and macular thickness measurements of Group 1 before HD compared with the control group is presented in **Table 2**. Mean, temporal, and inferior quadrant RNFL thickness values of patient group were thinner than those of the control group ($p<0.015$). There was no correlation between this thinning and patient age, duration of HD, and gender ($p>0.05$). All the macular thickness values of the patient group were thinner than the control group ($p=0.00$). While this thinning at the superior, nasal quadrants and reduction in the average macular thickness were negatively correlated with the duration of HD, there was no correlation with age of the patient. All macular thickness values except for superior quadrant were thinner in female patients than male patients ($p<0.05$).

Retinal nerve fiber layer and macular thickness values of group 1 measured by OCT before and 30 minutes after HD at the first day, first month, and sixth month are shown in **Table 3**. Superior and average RNFL thickness values after HD were found significantly thicker than before HD at the first day and first month ($p<0.05$). This thickness increase was observed only in the superior quadrant at the sixth month ($p=0.048$). Macular thickness values of all quadrants except for average value were found significantly thicker after HD than before HD on the first day ($p<0.05$). This increase was found significant at the superior, nasal and temporal quadrants in the first month ($p<0.05$). No significant difference was found between the macular thickness values before and after HD in the sixth month ($p>0.05$).

Discussion. It is a known fact that optic neuropathy may develop in some metabolic diseases such as DM, renal failure and dysthyroidism.[3,4,13-16] Thinning of the RNFL as an indicator of optic neuropathy may be determined by OCT successfully, as some authors previously reported the thinning of RNFL in DM and glaucoma.[11-14] In a study conducted by Balazsi et al,[15] the thinning of the RNFL with age was indicated.

Table 1 - Demographic and clinical characteristics of all the patients

Characteristic	Hemodialysis (Group 1)	Control (Group 2)	*P*-values
Number of patients	20	34	
Age, mean ± SD (range)	37.7 ± 12.2 (20-66)	35.5 ± 13.97 (21- 76)	>0.05
Male/Female	15/5	25/9	>0.05
The duration of hemodialysis (years), mean±SD (range)	4.3 ± 3.08 (0.08-12.00)		
Presence of systemic HT	15/20 (stage1- 2 HTRP)	0/34	
IOP, mmHg, mean (range)	17.3 (10-19)	16.5 (12-19)	
BCVA, mean (range)	0.97 (0.6-1.0)	0.95 (0.8-1.0)	

BCVA - best corrected visual acuity, IOP - intraocular pressure, HT - hypertension, HTRP - hypertensive retinopathy

Table 2 - The first day retinal nerve fiber layer (RNFL) and macular thickness values of Group 1 and Group 2 before hemodialysis (HD).

Quadrants	Hemodialysis (group 1)	Control (group 2)	*P*-value
RNFL			
Temporal	76.28 ± 10.71	85.09 ± 14.35	0.00
Superior	128.28 ± 22.41	130.19 ± 16.86	>0.05
Nasal	75.05 ± 16.91	76.96 ± 14.74	>0.05
Inferior	120.95 ± 18.61	135.28 ± 17.71	0.00
Average	101.63 ± 12.29	106.85 ± 9.20	0.014
Macular			
Temporal	279.50 ± 23.26	299.19 ± 20.70	0.00
Superior	281.30 ± 21,62	300.93 ± 19.52	0.00
Nasal	283.35 ± 21.78	302.22 ± 18.35	0.00
Inferior	280.63 ± 22.10	299.88 ± 18.44	0.00
Average	227.23 ± 20.17	240.94 ± 26.35	0.003

P-value was the comparison of group 1 and 2, first day, before HD

Table 3 - Before and after hemodialysis (HD) retinal nerve fiber layer (RNFL) and macular thickness values of the first day, first month and sixth month.

Quadrants	The first day		The first month		The sixth month		*P*-value		
RNFL	**Before**	**After**	**Before**	**After**	**Before**	**After**	**p1**	**p2**	**p3**
T	76.2 ± 10.7	76.4 ± 12.8	75.1 ± 10.4	75.6 ± 10.8	74.7 ± 10.6	74.6 ± 11.8	>0.05	>0.05	>0.05
S	128.2 ± 22.4	133.9 ± 22.9	128.7 ± 20.9	132.3 ± 21.6	127.4 ± 20.7	130.5 ± 21.4	0.003	0.002	0.048
N	75.0 ± 16.9	76.3 ± 17.5	75.2 ± 14.9	76.8 ± 14.4	76.5 ± 15.5	77.7 ± 14.2	>0.05	>0.05	>0.05
I	120.9 ± 18.6	125.5 ± 20.0	123.0 ± 18.3	125.2 ± 19.7	123.3 ± 20.0	126.2 ± 19.7	>0.05	>0.05	>0.05
A	101.6 ± 12.3	103.4 ± 12.8	101.6 ± 12.0	102.9 ± 12.3	102.1 ± 12.6	102.9 ± 12.8	0.028	0.048	>0.05
Macula									
T	279.5 ± 23.2	281.7 ± 24.5	279.9 ± 22.7	281.2 ± 23.5	280.5 ± 22.5	282.0 ± 22.7	0.006	0.022	>0.05
S	281.3 ± 21.6	282.7 ± 22,0	281.9 ± 21.7	283.1 ± 21.7	282.9 ± 21.8	283.3 ± 22.7	0.048	0.025	>0.05
N	283.3 ± 21.8	286.4 ± 21.3	284.9 ± 20.9	286.4 ± 20.3	286.3 ± 19.6	286.0 ± 21.0	0.006	0.045	>0.05
I	280.6 ± 22.1	283.2 ± 21.3	281.5 ± 21.8	282.5 ± 20.9	282.7 ± 21.5	283.7 ± 21.0	0.01	>0.05	>0.05
A	227.2 ± 20.1	229.8 ± 20.2	226.7 ± 18.9	229.1 ± 19.0	228.6 ± 21.9	229.2 ± 20.2	>0.05	>0.05	>0.05

p1 - the comparison of the before and after HD RNFL and macular thickness of the first day (paired t test), p2 - the comparison of the before and after HD RNFL and Macular thickness of the first month (paired t test), p3 - the comparison of the before and after HD RNFL and Macular thickness of the sixth month (paired t test). T - temporal quadrant, S - superior quadrant, N - nasal quadrant, I - inferior quadrant, A - average

Chihara et al[16] emphasized that proliferative diabetic retinopathy, systemic hypertension and advanced age is an independent risk factor for RNFL thinning. Ozdek et al[17] reported that there was a thinning at the RNFL with age and myopia. In a study conducted by Knox et al,[18] a toxic type of optic neuropathy was defined in uremic patients with serum urea nitrogen value above 35.7 mmol/L. Hypertension which is frequently seen in patients with uremia, generalized atherosclerosis (due to blood flow resistance) and severe anemia (due to reduced blood oxygen-carrying capacity) are predisposing factors for ischemic optic neuropathy.[3] Servilla and Groggel[19] reported a patient with ischemic optic neuropathy caused by hypotension associated with HD. Demir et al[7] emphasized that there was a statistically significant thinning at the superior, inferior, nasal, temporal, and average RNFL values compared to control group in HD patients without DM and uncontrolled HT. They emphasized the importance of RNFL analysis in order to detect early uremic optic neuropathy. In our study, a statistically significant thinning at inferior, temporal, and average RNFL values was found in HD patients when compared with the control group. It was found out in our study that this thinning observed in RNFL, compared with the control group, does not correlate with the patient's age and the

period of HD. Pahor et al[9] evaluated 6 mm macular thickness of 24 eyes of 12 HD patients by OCT and compared them with healthy control group. Retinal thickness in the 1 mm foveal region, macular thickness in the superior, inferior, nasal and temporal quadrants at the parafoveolar and perifoveal areas of HD patients was significantly thinner. While reduction at the retinal thickness showed a positive correlation with age, any connection with the duration of dialysis has not been determined. In a study conducted by Hojs,[20] the thickness of intima-media of common carotid artery was found significantly higher in patients receiving HD compared to control patients. This condition showed a positive correlation with age but showed a negative correlation with the duration of HD.

The findings of these studies support the reason for the reduction in retinal thickness due to a subclinical ischemic retinopathy caused by an obstructive carotid artery disease showing a positive relationship with the age of HD patients. There was grade 1 HTRP in 7 of 20 HD patients and grade 2 HTRP in 8 of 20 HD patients in our study. Macular thicknesses of all quadrants and average macular thickness in HD group were determined statistically thinner compared to control group at the first day before HD. It was shown that patient age has no effect on this thinning because of the younger age profile of the patient population. However, there was a negative correlation with the duration of dialysis in all quadrants. When we examined the effect of gender on this thinning of RNFL and macular thickness in HD patients, all macular quadrants and 1 mm diameter circular macula (average) thickness was thinner in female patients except for superior quadrant. There are many studies in the literature reporting that gender has no effect on RNFL. In a study conducted by Hirasawa et al[21] on 251 healthy patients by using SD-OCT, they determined that a significant thinning occurred at the RNFL with increasing patient's age, but patient's gender and axial length had no any effect. In their study on 328 healthy individuals using stratus OCT, Budenz et al[22] found that while RNFL became thinner with the increasing age, axial length and decreasing of optic disc diameter, gender had no effect. Contrarily, in our study macular thicknesses of all quadrants except for superior one were found thinner in female patients. Wong et al[23] also reported that central retinal thickness was thicker in healthy individuals with male gender, greater body mass index, and longer axial length. Although there are several speculations on the acute effect of HD on the retinal and choroidal circulation, there are mostly diabetic case studies in the literature. Matsuo[24] presented 2 cases with DM, who underwent HD 2-3 times a week approximately 3 years after pan laser photocoagulation. The reason for the disappearance of macular hard exudates in the sixth month following the HD was thought to be due to normalization of blood content, blood-retina barrier function and lipid-lowering effect of the HD. Perkovich and Meyers[25] presented a patient with reduced diabetic macular edema one month after initiation of HD.

In their prospective study, Tokuyama et al[6] evaluated 40 eyes of 22 patients with ESRF and preproliferative or proliferative diabetic retinopathy by fluorescein angiography which was applied immediately before HD and 1 month after HD. Macular leakage did not change in 28 of 40 eyes (70%), decreased in 4 eyes (10%) and increased in 8 eyes (20%). As a result, it was suggested that the effect of HD on diabetic macular leakage was very minimal. Although there is an increase in the amount of extracellular fluid before HD, stability of plasma volume before and after HD point out a balance between the plasma and body fluid volume and explains the unchanging macular leakage with HD treatment.

In the study by Auyanet et al,[26] in patients with diabetes and ESRF, there was a tendency of average foveal thickness to decrease after one session of HD, although not significant. The changes of foveal thickness were unrelated to demographic data, laboratory parameters, previous laser treatment or existence of active diabetic retinopathy. They found that bath temperature was higher and conductivity was lower in patients with no change or a decrease of foveal thickness, which may have caused modification of retinal capillary regulation. In previous study,[27] including 36 patients with diabetes and ESRF average macular thickness and total macular volume within the central disc of 6 mm of eyes with diabetic macular edema (DME) were found to be decreased significantly immediately after HD, in patients without DME these values decreased slightly. In a previous study,[28] including 34 eyes of 34 patients (9 eyes with diabetic patients) choroidal thickness, central foveal thickness (CFT), macular volume and RNFL were evaluated before and after HD by OCT. The average choroidal thickness decreased significantly after HD (p<0.001). This change correlated with the amount of body weight lost. The change in macular volume and the small decrease in CFT were not significant. The overall measured change in RNFL was not significant.
The CRF affects both choroidal and retinal circulation. It constitutes a micro-angiopathy that mimics other diseases that affect the microcirculation, such as DM and HT. In diabetic patients, histopathological studies[29,30] showed choroidal ischemia resulting from the narrowing of vascular lumen. In Ulas et al's study,[31]

21 eyes from 21 male patients without DM retinal and choroidal thickness were evaluated before and shortly after HD by OCT. The mean choroidal thicknesses after HD were decreased significantly (p<0.001). But there was no significant difference between the retinal thicknesses before and after HD. In a study by Jung et al[32] in patients with CRF undergoing HD, the macular thickness measured by SD-OCT decreased after HD. The results showed that a significant correlation was not found between the changes in the systemic hemodynamic parameters and retinal thickness.

Vasodilation occurs in retinal blood vessels due to removal of nitric oxide synthase inhibitor from the blood after HD treatment and due to the increased nitric oxide and adrenomedullin. This vasodilation is masked due to the increased vascular resistance and due to increased hematocrit and hypotension following dialysis. Thus, retinal blood flow does not change.[33,34]

This may be the reason why there is no demonstrable acute effect of HD on the thickness of the retina in some studies. In our study, measurement of RNFL and macular thickness before and 30 minutes after dialysis were repeated 3 times on the first day, in the first month and sixth month of follow-up. Our aim was to evaluate whether the acute effect of HD on RNFL and macular thickness show consistency and repeatability during a given time period. In our study, an increase in superior quadrant RNFL thickness was found to be the only consistent acute effect of HD. On the other hand, chronic effect of HD was found to be a significantly thinner mean, temporal and inferior RNFL and thinner macular thickness in ESRF patients when compared with normal controls. The significance of these findings needs to be determined especially considering development of uremic optic neuropathy, loss of RNFL especially when there is coexisting glaucoma and importance of neuroprotection in these patients. The major limitation of our study is relatively small sample size.

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Ethical Consent

All manuscripts reporting the results of experimental investigations involving human subjects should include a statement confirming that informed consent was obtained from each subject or subject's guardian, after receiving approval of the experimental protocol by a local human ethics committee, or institutional review board. When reporting experiments on animals, authors should indicate whether the institutional and national guide for the care and use of laboratory animals was followed.