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Original Article / Özgün Araştırma

Comparison of Optic Coherence Tomography Findings of Chronic Renal Failure and Renal Transplant Patients

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Abstract

Objective: To compare the Spectral-Domain Optic Coherence Tomography (SD-OCT) findings of chronic renal failure (CRF) and renal transplant (RTx) patients.

Methods: Sixty eyes of thirty patients with CRF and 60 eyes of thirty RTx patients were enrolled in the study. A thorough ophthalmologic examination was applied to each patient, including the following parameters: best-corrected visual acuity (BCVA), intraocular pressure (IOP), anterior and posterior segment examination, central corneal thickness (CCT), retinal nerve fiber layer thickness (RNFLT), foveal thickness (FT), and choroid thickness (ChT) measurements.

Results: Distribution of the primary disease, gender and the median duration of RTx and CRF (18 and 36 months respectively, p=0.390) were similar between the groups, and the difference was not significant. The mean age of patients in the CRF group was statistically higher than that of the RTx group (57.5±10.6 and 44.4±11.9 years respectively, p<0.001). There was no statistically significant difference in terms of BCVA, IOP, CCT, FT, and ChT values between the groups. Left C/D ratios in the left eye of RTx group were significantly higher than the CRF group (0.401±0.031 and 0.342 ±0.027 respectively, p=0.035). Temporal inferior (TI) RNFLT values in the left eye of RTx group were significantly higher than the CRF group (144.76±4.24µm and 135.09±3.91µm respectively, p=0.005)

Conclusion: There was no remarkable difference in SD-OCT findings between the two groups, except the significantly higher RNFLT (TI) values in left eye of RTx patients. The result of our study shows that renal transplantation might have a positive effect on retinal morphology and retinal functions. Our results should be supported with further studies.

Keywords: choroid thickness; foveal thickness; renal failure; renal transplantation; retinal nerve fiber layer thickness.

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Kronik Böbrek Yetmezliği Olan ve Böbrek Nakilli Hastaların Optik Koherens Tomografi Bulgularının Karşılaştırılması

Öz

Amaç: Kronik böbrek yetmezliği (KBY) olan hastaların Spektral Domain Optik Koherens Tomografi (SD-OKT) bulguları ile böbrek nakilli (RTx) hastaların SD-OKT bulgularını karşılaştırmak.

Yöntemler: Çalışmaya KBY'si olan 30 hastanın 60 gözü ve RTx olan 30 hastanın 60 gözü dahil edildi. Her hastaya, en iyi düzeltilmiş görme keskinliği (EİDGK), göz içi basıncı (GİB), ön ve arka segment muayenesi, santral kornea kalınlığı (SKK), retina sinir lifi tabakası kalınlığı (RSLTK), foveal kalınlık (FK) ve koroid kalınlığı (KK) ölçümleri gibi parametreler dahil olmak üzere kapsamlı bir oftalmolojik muayene yapıldı.

Bulgular: Primer hastalık dağılımı, cinsiyet dağılımı, median KBY ve RTx süreleri (sırasıyla 18 ve 36 ay , p=0.390) gruplar arasında benzerdi ve istatistiksel fark anlamlı değildi. KBY grubundaki hastaların yaş ortalamaları RTx grubuna göre istatistiksel olarak daha yüksekti (sırasıyla 57.5±10.6 ve 44.4±11.9 yıl, p<0,001). Gruplar arasında EİDGK, GİB, SKK, FK ve KK değerleri açısından istatistiksel olarak anlamlı bir fark yoktu. RTx grubunun sol gözünde C/D oranları KBY grubuna göre anlamlı derecede yüksekti (sırasıyla 0.401±0.031 ve 0.342 ±0.027, p=0.035). RTx grubu sol göz temporal inferior (TI) RSLTK değerleri KBY grubunun değerlerinden anlamlı derecede yüksekti (sırasıyla 144.76±4.24µm ve 135.09±3.91µm, p=0.005).

Sonuç: Gruplar arasında RTx hastalarında sol göz RSLTK (TI) değerlerinin anlamlı derecede yüksek olması dışında SD-OKT bulgularında kayda değer bir fark yoktu. Çalışmamızın sonucu, renal transplantasyonun retina morfolojisi ve retina fonksiyonları üzerine olumlu etkisinin olmuş olabileceğini göstermektedir. Sonuçlarımız ileri çalışmalarla desteklenmelidir.

Anahtar kelimeler: koroid kalınlığı; foveal kalınlık; böbrek yetmezliği; renal transplantasyon; retina sinir lifi tabakası kalınlığı.

INTRODUCTION

After the improvement of immunosuppressive drugs and the advancement of operation techniques, renal transplantation (RTx) has been a potent curing procedure for patients with end-stage renal disease (ESRD). After the RTx procedure, ocular disturbances are mostly caused by the primary renal disease, immunosuppressive therapy, metabolic variations, cytomegalovirus infection, or other postoperative infections[1–3]. Patients with ESRD usually have many accompanying diseases like hypertension (HT), diabetes mellitus (DM), or glaucoma. Furthermore, ESRD frequently exists in the older patients, in whom the vision has already started to deteriorate with aging because of cataract, macular or optic nerve diseases. That is why ophthalmological care in patients with RTx is essential to prevent the worsening of the preexisting ophthalmic disorder and the development of immunosuppressive drug–related side effects[1]. Vision deteriorations complained after RTx, are usulally caused by the condition of the eye before the transplantation so the ophthalmologist should check up the best corrected visual acuity (BCVA), intraocular pressure (IOP) and fundus of the patient regularly. Besides, fundus should be evaluated with Spectral-Domain Optical Coherence Tomography (SD-OCT)[1–3].

Recent modifications in enhanced depth imaging optical coherence tomography (EDI-OCT) allow viewing the choroid with clarity[4]. The blood flow per area in the choroid is greater than any tissue[5]. It has long been thought that opposite to the retinal blood flow, choroidal blood flow exhibits no autoregulation, but recent studies have shown it to autoregulate according to the fluctuations in systemic blood pressure. In addition to diurnal or circadian variations of IOP and anterior chamber depth,

diurnal variations of choroidal thickness (ChT) were demonstrated, which were associated with the alterations in systemic blood pressure[6].

In this study, we compared the OCT findings between CRF and RTx patients in order to investigate the effects of vascular variations of renal transplantation on OCT findings and to determine whether renal transplantation has a positive effect on retinal morphology and retinal function and to emphasize the multidisciplinary importance of renal transplantation.

METHODS

This retrospective, clinical study was directed at the Department of Ophthalmology, with the collaboration of the Department of Nephrology of a Training and Research Hospital. This study was built in compliance with the principles of the Statement of Helsinki, and the protocol was confirmed by Health Sciences University, İzmir Tepecik Training and Research Hospital ethics committee (2019/14-31, 09.10.2019). Informed consent was provided from all the patients. Sixty eyes of thirty patients with CRF, and 60 eyes of thirty patients with RTx were included in the study. Chronic renal disease is described as the existance of an aberrancy in the renal structure or renal function continuing for >3 months[6]. The CRF group was determined according to the laboratory results, and stage 2–3 patients with CRF were included. Patients with RTx who were followed up at least 6 months after the transplantation and who were using tacrolimus, mycophenolate mofetil/mycophenolate sodium, and prednisolone acetate treatment were included (4-8 ng/ml, 2000 mg and 5mg, respectively). Patients with HT, DM, stage 4 CRF, those using different immunosuppressive drugs and those who had acute rejection were excluded from both groups.

Patients who were diagnosed with CRF and RTx and referred for ophthalmic examination were evaluated retrospectively. Ocular examination including BCVA, IOP, anterior and posterior segment examination was performed. Patients with optic neuropathy, media opacities obscuring posterior segment visualization due to cataract or corneal disorder, glaucoma, retinal vascular disease, maculopathy, and weak qualification of SD-OCT images were excluded from the study. BCVA was evaluated with Snellen chart and the patients with spherical and cylindrical refractive errors between ±3 diopter (D) were included. IOP was evaluated with Goldman applanation tonometry. CCT measurement was performed with the noncontact infrared method (CT-1P; Topcon, Tokyo, Japan). Cup-to-disk (C/D) ratio, RNFLT, and foveal (FT) and choroid thickness (ChT) measurements were performed with SD-OCT (Heidelberg Engineering, Germany). After the pupil was dilated, fast optic disk and fast RNFL (Retinal Nerve Fiber Layer) scans (with quadrant distribution), automated FT, and subfoveal choroidal thickness (SFCT) measurements with EDI mode (Spectralis OCT), with the help of in-built caliper were performed. ChT scanning was performed at the subfoveal region using EDI mode SD-OCT software version 6.9. The horizontal division passing straight ahead the center of the fovea was used to measure the ChT. SFCT in the enhanced images was measured as the perpendicular distance between the outer portion of the hyperreflective line matching to the Retina Pigment Epithelium to the hyporeflective line matching to the choroidoscleral junction. The measurement of SFCT was made manually by a single qualified doctor. The C/D ratio was recorded after the optic disk analysis was achieved. To refrain the influence of diurnal and personal changes, all the RTx patients were examined at the same time in the morning and all the CRF patients were examined immediately after the second session

undergoing dialysis 3 sessions a week, at the same time in the morning, by the same doctor. SD-OCT measurements of both groups were also acquired at the same time in the morning, by the same doctor. For intraobserver reproducibility, SD-OCT measurements were performed for 3 times by the same doctor. SD-OCT scans were acquired without pupil dilation and only images with an imaging quality score of >20 were studied.

Statistics

All data were evaluated with IBM SPSS Statistics Standard Concurrent User version 25 (IBM Corp., Armonk, New York, USA) software. Descriptive statistics were presented as the number of units (n), percentage (%), mean (standard deviation (sd), standard error (se), median (M), first quartile (Q1) and third quartile (Q3) values. The normality of numerical data distributions was evaluated using the Shapiro–Wilk normality. The homogeneity of the variances was evaluated using the Levene test. Comparison between the groups in terms of sex and primary disease was evaluated with the Pearson chi-square test. Variables with a normal distribution (age) were crosschecked using independent-two samples t test, and those without a normal distribution with the Mann–Whitney U test. Analysis of covariance was used to crosscheck the eye and biochemical variables among the groups. In the analysis of covariance, a correction was made according to age and sex. P<0.05 was accepted statistically significant for all analyzes.

RESULTS

The study included 120 eyes of 60 patients: 30 (50%) with RTx and 30 (50%) with CRF. Of the 30 RTx patients, 14 (46.7%) were men and 16 (53.3%) were women; of the 30 CRF patients, 18 (60.0%) were men and 12 (40.0%) were women. The groups were statistically similar in terms of gender (p=0.301). The mean age of patients in the CRF group was statistically higher than that of the RTx group (57.5±10.6 and 44.4±11.9 years respectively, p<0.001). The median duration of the disease was 18.0 (9.5–75.0) months in the RTx group, while it was 36 (12.0–111.0) months in the CRF group, and the difference was not significant (p=0.390). Intraclass correlation coefficient (ICC) values for subfoveal ChT measurements ranged from 0.901 to 0.999 and were statistically significant.

Four (13.3%) RTx patients had chronic tubulointerstitial nephritis (TIN), four (13.3%) had Immunoglobulin A (IgA) nephropathy, two (6.7%) had chronic urinary tract infection, six (20.0%) had polycystic kidney disease, three (10.0%) had nephrolithiasis, and one (3.4%) had reflux nephropathy as primary disease; the primary disease of 10 (33.3%) was unknown. Of the 30 CRF patients, four (13.3%) had chronic tubulointerstitial nephritis (TIN), two (6.7%) had Ig A nephropathy, two (6.7%) had chronic urinary tract infection, five (16.6%) had polycystic kidney disease, two (6.7%) had reflux nephropathy, and six (20.0%) had nephrolithiasis; the primary disease of nine (30%) was unknown. The groups showed a similar distribution in terms of primary disease (p=0.921) (Table 1).

Table I: Primary disease distribution between the groups

PRIMARY DISEASE	GROUPS				Test Statistics*	
	RTx		CRF			
	n	%	*n*	%	χ^2	*p*
Chronic Tubulointerstitial Nephritis	4	13.3	4	13.3	2.144	0.921
IG A Nephropathy	4	13.3	2	6.7		
Chronic Urinary Tract Infection	2	6.7	2	6.7		
Primary Unknown	10	33.3	9	30.0		
Polycystic Renal Disease	6	20.0	5	16.6		
Reflux Nephropathy	1	3.4	2	6.7		
Nephrolithiasis	3	10.0	6	20.0		

The left eye temporal inferior (TI) RNFLT values were considerably higher in the RTx group than those of the CRF group (144.76±4.24µm and 135.09±3.91µm respectively, p=0.005), whereas the left eye global (G) RNFLT values were statistically similar between the groups (p=0.055). The left eye C/D ratio in the RTx group was significantly higher than that of the CRF group (0.401±0.031 and 0.342 ±0.027 respectively, p=0.035). Other variables were not significantly different among the groups (Table 2).

Table II: Comparison of ocular variables among the groups

	GROUPS				Test Statistics*	
	RTx		CRF			
	$\bar{x}$	sh	$\bar{x}$	sh	F	p
R BCVA	0.96	0.03	0.99	0.03	0.817	0.370
L BCVA	0.93	0.04	0.94	0.04	0.336	0.565
R IOP (mmHg)	17.12	0.70	18.11	0.65	0.080	0.779
L IOP (mmHg)	17.14	0.76	18.76	0.66	0.136	0.714
R CCT (µm)	510.71	8.36	525.50	7.38	0.176	0.676
L CCT (µm)	510.97	8.51	528.12	7.43	0.014	0.906
R RNFLT T (µm)	68.76	2.79	69.65	2.59	2.099	0.153
R RNFLT TS (µm)	132.09	4.38	139.07	4.07	0.006	0.941
R RNFLT TI (µm)	144.94	5.93	146.66	5.51	1.043	0.312
R RNFLT N (µm)	81.21	6.97	93.99	6.48	1.473	0.230
R RNFLT NS (µm)	114.62	5.75	111.81	5.34	0.001	0.994
R RNFLT NI (µm)	115.45	8.19	126.14	7.61	0.007	0.933
R RNFLT G (µm)	100.62	3.56	106.43	3.30	0.024	0.877
L RNFLT T (µm)	69.78	2.32	64.75	2.14	2.722	0.105
L RNFLT TS (µm)	132.67	4.82	133.95	4.43	1.811	0.184
L RNFLT TI (µm)	144.76	4.24	135.09	3.91	8.435	**0.005**
L RNFLT N (µm)	74.73	3.37	82.12	3.10	0.404	0.528
L RNFLT NS (µm)	113.23	5.43	118.79	5.01	3.445	0.069
L RNFLT NI (µm)	112.51	5.23	124.62	4.81	0.103	0.749
L RNFLT G (µm)	98.23	2.37	100.80	2.18	4.209	0.045
R FT (µm)	221.68	4.24	211.52	3.94	1.024	0.316
L FT (µm)	218.51	3.69	214.54	3.39	0.264	0.610
R ChT (µm)	285.47	8.54	259.79	7.93	0.198	0.658
L ChT (µm)	279.64	8.67	255.73	7.98	1.477	0.230
R C/D ratio	0.406	0.029	0.333	0.025	2.051	0.158
L C/D ratio	0.401	0.031	0.342	0.027	4.684	**0.035**

**Values corrected according to age and gender*

R: Right, L: Left, IOP: Intraocular Pressure, CCT: Central Corneal Thickness, BCVA: Best Corected Visual Acuity, RNFLT: Retinal Nerve Fiber Layer Thickness, T: Temporal, TS: Temporo-Superior, TI: Temporo-Inferior, N: Nasal, NI: Nasal-Inferior, NS: Nasal-Superior, G: Global, FT: Foveal Thickness, ChT: Choroid Thickness, C/D: Optic Nerve cup/disk ratio

DISCUSSION

Patients with ESRD who are treated with hemodialysis (HD) have many ocular complications such as refractive and corneal endothelial alterations, dry eye, and IOP changes[7]. Sudden changes in body fluids can affect choroidal volume and thickness during HD. Therefore, there have been many studies which have emphasized on the alterations in choroidal thickness after HD[8–9]. These studies have evaluated the choroidal thickness with the EDI technique of SD-OCT.

Abnormal ophthalmological findings after organ transplantations occur in more than half of the patients and are the consequence of both the preexisting disease and the immunosuppressive therapy[1–3]. After RTx, there are some drugs routinely used in the therapy such as immunosuppressive drugs, steroids (prednisone, prednisolone, or methylprednisolone), calcineurin inhibitors (cyclosporine A and tacrolimus), proliferation signal inhibitors (mTOR inhibitors, including sirolimus and everolimus), and inhibitors of cell division (azathioprine and mycophenolate mofetil/sodium (MMF/MPA). In some cases, polyclonal or monoclonal antibodies are being applied[10].

Many studies have evaluated OCT records before and after HD in patients with CRF and RTx. Hwang et al investigated the SD-OCT findings in patients with diabetic ESRD undergoing HD for the first time[11]. They found that macular edema and central subfield thickness significantly decreased after the initiation of HD without any ocular treatment, probably due to HD-related wellness of uremia and edema. Chang et al found alterations in body weight, serum osmolarity, and blood pressure during HD caused a decrease in ChT in and outside the macula after HD in patients with ESRD[12]. Regatieri et al investigated ChT in diabetic patients with SD-OCT[13]. They found that mean SFCT was lower in patients with diabetic macular edema or treated proliferative DR than in healthy individuals, but no difference was seen between the patients with nonproliferative diabetic retinopathy (DR) and healthy individuals. They stated that ChT was changed in DM and might have relation with the seriousness of retinopathy. Ishibazawa et al investigated the outcome of HD on the ChT in patients with and without DM who have ESRD and concluded that systemic volume overload had much more effect on the diabetic choroid in patients with ESRD, possibly because of damaging the choroid vessel structure[14]. Shin et al evaluated the outcome of HD on the ChT and the choroidal vascularity index in patients with ESRD by using swept-source OCT[15]. Choroidal thickness decreased considerably after HD in most subfields independent of the existance of DM. Ulaş et al used OCT to evaluate the outcomes of HD with a high ultrafiltration rate on the choroidal and retinal thickness of nondiabetic end-stage patients with CRF (ESRD)[9]. According to their study, HD with a high ultrafiltration volume did not change the retinal thickness but caused a significant choroidal thinning and an IOP decrease in nondiabetic end-stage patients with CRF. Since we excluded the patients with DM and HT in our study, we might not have found a difference in terms of retinal and choroidal thickness between the groups.

Many studies have analyzed RNFL before and after HD in patients with CRF. Atılgan et al evaluated the thicknesses of RNFL and macula by Fourier-domain (FD) OCT in patients without diabetes with ESRD undergoing HD[16]. Macular and RNFL thicknesses of patients undergoing HD were less than the normal population. Age did not affect these thicknesses, and the duration of HD affected more than sex. Paterson et al found that inner retinal thinning and retinal microvasculature changes were related with higher stages of CRF (stages 4 and 5), but not with stage 3 CRF and RNFL loss in

diabetic patients is often detected independent of DR as Kırıkkaya et al reported as well[17,23]. Jeon et al concluded that in younger patients with DM, autonomic dysfunction might be related with RNFL loss, but as the patient's age increases, arterial rigidity can increase vascular autoregulation and diabetic RNFL loss[18]. RNFL loss in DM might be correlated with systemic vascular conditions. Chen et al explored ocular changes during a single session HD in patients with CRF and found that after HD, ChT decreased significantly and that RNFLT and average retinal thickness increased[19]. Shin et al evaluated the relationship between RNFL defects and cardiovascular risk factors. They remarked that localized RNFL defects indicated the seriousness of glaucomatous damage but could also be sequelae of retinal vascular deficiency because of systemic vascular factors[20]. According to their study, RNFL defects were associated with systolic blood pressure, estimated glomerular filtration rate, and HbA1c levels.

Blood pressure changes, systemic vascular and microvascular structure changes, CRF and RTx, as well as the drugs used after RTx affect the ocular structures, leading to changes in RNFL, macular, and choroidal thickness[10–15]. Systemic diseases such as HT and DM also affect the retina, retinal nerve fiber layer, and choroid[7–10]. Therefore, we planned to compare SD-OCT findings in patients with CRF and RTx in a standard group without DM and HT.

In our study RTx group left eye RNFLT TI values were considerably higher than those in CRF group. This might be due to the statistically lower mean age of RTx group. Our study result is consistent with the previous studies which determine that RNFLT decreases with aging[17–18]. Studies by Rougier and Li have indicated that RNFLT decreases with aging in the CRF group[21–22]. Although we did not include patients with DM and HT in our study, there might have been slight microvascular changes even if in lower stage disease in CRF group, which might have caused a decrease in RNFLT, as Peterson and Jeon stated in their studies[17–8]. Therewithal, the improvement of retina functions in the microvascular level after renal transplantation might have caused higher RNFLT TI values. This shows that renal transplantation not only has a positive effect on renal functions, but also has a positive effect on retina functions. This is a very important data from a multidisciplinary perspective.

In our study, RTx group had significantly higher left eye C/D ratios than the CRF group; this might be due to the lower CCT values in RTx group, which increased the adjusted IOP values. Therefore chronic higher IOP values might have caused higher C/D ratios in RTx group. In CRF group; hypoalbuminemia decreases the plasma oncotic pressure and edema develops[19]. Therefore CCT might increase as a result of edema.

Other studies on CRF and RTx patients comparing OCT findings before and after HD reported a decrease in choroidal thickness and an increase in retinal thickness and RNFLT after the HD session[11–20]. In our study, foveal and choroidal thickness measurements were similar between the groups; however, left eye RNFLT TI values were better in RTx group. This might be due to the exclusion of the patients with HT and DM from the study and earlier stage of CRF group. Other studies have indicated that circulatory disorders, systemic blood pressure, and also microvascular changes might affect the retinal thickness, RNFLT, and choroidal thickness[11–20]. In our study population, there was no circulatory disorder barely visible, so the OCT findings were not statistically different between the groups except left eye RNFLT TI which was better in the RTx group. As a result our study results support the previous studies. (parantez ve içi tamamen çıkacak, devam eden cümle hatalı bir şekilde revizyon dosyasında kalmış.The findings of the study were

inadequately compared with the findings of the literature).

CONCLUSION

Our study is the unique study comparing the standardized RTx and CRF patients without HT and DM. RTx group left eye temporal inferior (TI) RNFLT values were significantly higher than those of the CRF group. This shows that renal transplantation not only has a positive effect on renal functions, but also might have a positive effect on retinal morphology and retina functions. This is a very important data from a multidisciplinary perspective. However our study has limitations. We did not include a healthy group in the study because post-transplant cases was planned as the control group, because it is assumed that post-transplant group is already close to the healthy group due to the normalization of post-transplant renal functions. We have limited number of standardized RTx and mild-moderate stage (stage 2-3) CRF patients. Since all renal transplantations were not performed in our center, we could not evaluate the SD-OCT findings of the same CRF group before and after transplantation either. A study in larger series, comparing the same CRF patients before and after RTx can provide more detailed and healthy information. Our results should be supported with further studies.

Ethical Committee Approval: This study was built in compliance with the principles of the Statement of Helsinki, and the protocol was confirmed by Health Sciences University, İzmir Tepecik Training and Research Hospital ethics committee (2019/14-31, 09.10.2019).

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