Periton Diyalizi Hastalarında Optik Koherens Tomografi Ölçümlerinin Değerlendirilmesi

Evalulation of Optical Coherence Tomography Measurements in Peritoneal Dialysis Patients

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ÖZ

GİRİŞ ve AMAÇ: *OCT(Optik koherens tomografi), günümüzde yaygın olarak kullanılan non-invaziv bir oküler görüntüleme tekniğidir. PD hastalarinda OCT bulgularinin değerlendirildiği sınırlı sayıda çalışma vardır. Bu calismada amacımız optik koherens tomografi (OKT) ile periton diyalizi (PD) hastalarının retina değişikliklerini sağlıklı kontrol grubu ile karşılaştırmak ve PD'nin yaş, cinsiyet ve süresinin bu parametrelere etkisinin araştırılmasıdır*

YÖNTEM ve GEREÇLER: *Bu kesitsel çalışmaya 32 hastanın sağ ve sol gözü ve 10 sağlıklı kontrolün yirmi sağ ve sol gözü değerlendirildi. Santral maküla kalınlığı (CMT), peripapiller retina sinir lifi tabakası (RSLT) kalınlığı ve koroid kalınlığı (EDI-OCT kullanılarak) ile detaylı oftalmolojik muayeneler ölçüldü. Makula kalınlığı beş farklı alanda ölçüldü: merkezi, üst, temporal, alt ve nazal. Peripapiller RSLT kalınlığı altı farklı alanda (temporal, inferotemporal, inferonasal, nazal, superiornasal ve superiortemporal) analiz edildi.*

BULGULAR: *Ortalama PD süresi 46,80 ay olan 32 hastanın (18 erkek, 14 kadın; 20-60 yaş, ortalama 48,67 ± 12,25 yıl) 64 gözü çalışmaya alındı. Kontroller ve PD hastaları arasında santral, temporal, nazal, inferior ve superior kadranlarda maküla kalınlığı açısından anlamlı farklılık vardı ($p < 0.05$). D3 vitamini takviyesi, santral, temporal, üst, nazal ve alt kadranlarda maküla kalınlığının azalması ile bağlantılı bulundu ($p < 0.05$). Rezidüel renal fonksiyon ile santral ve temporal kadranlarda maküla kalınlığı arasında pozitif korelasyon goruldu ($p = 0,006$, $p = 0,019$).*

TARTIŞMA ve SONUÇ: *PD hastalarında OCT tum kadranlarda retina kalınlığında incelme tespit edilmiştir.*

Anahtar Kelimeler: *Optik koherens tomografi, periton diyalizi, vitamin D*

ABSTRACT

INTRODUCTION: *Optical coherence tomography (OCT) is a non-invasive ocular imaging technique widely used nowadays. There are limited studies focusing on the OCT findings in PD patients. Our aim is to compare retinal changes of peritoneal dialysis (PD) patients with healthy control group by using OCT and investigate the effects of age, gender and duration of PD on these parameters.*

METHODS: *In this cross-sectional study right and left eyes of 32 patients and twenty right and left eyes of ten healthy controls were included. Detailed ophthalmological examinations with central macular thickness (CMT), peripapillary retinal nerve fiber layer (RNFL) thickness, and choroidal thickness (using EDI-OCT) were measured. Macular thickness was measured at five different areas: central,superior, temporal, inferior and nasal. The peripapillary RNFL thickness was analysed in six different areas: temporal, inferotemporal, inferonasal, nasal, superonasal and superotemporal.*

RESULTS: *Sixty-four eyes of 32 patients (18 males, 14 females; aged 20 to 60 years, mean 48.67±12.25 years) with a mean duration of PD of 46.80 months were included. There was a significant difference of macular thickness in the central, temporal, nasal, inferior and superior quadrants between controls and PD patients ($p < 0.05$). Vitamin D3 supplementation was linked to decreased macular thickness in central, temporal, superior, nasal and inferior quadrants ($p<0.05$). There was a positive correlation between macular thickness in central and temporal quadrants with residual renal function ($p=0.006$, $p=0.019$).*

DISCUSSION AND CONCLUSION: *OCT revealed a significant reduction of macular thickness in all quadrants in PD patients.*

Keywords: *Optical coherence tomography, peritoneal dialysis, vitamin D*

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INTRODUCTION

Measurements of macular thickness, retinal nerve fiber layer (RNFL) thickness and choroidal thickness are used in diagnosis and follow-up of various ocular diseases. Optical coherence tomography (OCT) is a non-invasive and objective ocular imaging method of the retina and optic nerve that has been widely used in recent years (1,2). It is an important diagnostic tool for various retinal diseases, glaucoma, other optic nerve diseases, retinal vascular disease and even corneal diseases. It is also used in measuring RNFL thickness that is a predictive of optic nerve health and enabling early detection of optic neuropathies (3), endothelial dysfunction in chronic kidney disease (CKD) (4) and diabetic retinopathy progression (5). It is a valuable method monitoring the progression of glaucoma as well (6).

The choroidal thickness changes with certain pathologies. Choroidal thickness measurement is more commonly used to assess these pathologies recently in clinics and research (7,8). Recent studies reported that the subfoveal choroidal thickness can be measured non-invasively by enhanced depth imaging optical coherence tomography (EDI- OCT) (1).

There are limited number of studies focusing on OCT findings in end stage renal disease (ESRD) and even less in peritoneal dialysis (PD) patients. According to these studies; findings like keratopathy, conjunctival calcifications, corneal pannus, keratoconjunctivitis, phacomorphic cataract due to uremia, fluctuations in intraocular pressure (IOP), retinal tear, hemorrhages, ischemic and uremic optic neuropathy can be seen in stage V CKD (9). Even the medications such as erythropoietin and vitamin D replacement can cause retinal changes in these patients (10-14). Optic neuropathy related with severe anemia, hypotensive and ischemic attacks, atherosclerosis, systemic diseases such as diabetes mellitus (DM) and hypertension is another well-defined complication in patients treated with dialysis (10,11,13). Thin retinal nerve fiber layer (RNFL) may be seen in these patients (15). Given the fact that ocular findings change with end stage disease and peritoneal dialysis, OCT can be used as diagnostic tool to find early ocular changes. We conducted this cross-sectional study to investigate the effects of age, gender, duration of PD, inflammation and malnutrition on macular, choroidal and RNFL thickness in peritoneal dialysis patients.

MATERIAL AND METHOD

This was a cross-sectional study conducted in Kocaeli University Hospital, Nephrology Department. Thirty-two patients on PD were included in the study . All procedures were carried out in adherence with the tenets of the Declaration of Helsinki and the study was approved by local ethics committee. Informed consent was obtained from all study participants. Thirthy two patients and ten healthy controls were examined in the study. The inclusion criteria were as follows: visual acuity 20/20 and spherical and/or cylindrical refractive errors between ±3 diopter ,OCT images with unremarkable media opacity. Exclusion criteria were as follows: the presence of medial opacity affecting optical clarity, macular diseases, such as macular hole, epiretinal membrane, macular scars, neovascular age-related macular degeneration and macular oedema, history of glaucoma, prior panretinal photocoagulation, diabetic retinopathy,cataract surgery and prior vitrectomy.

All subjects underwent ophthalmic evaluation, including assessment of distance best corrected visual acuity (BCVA) using Snellen charts, tonometry, slit lamp biomicroscopy and indirect fundus ophthalmoscopy, spectral domain optical coherence tomography (SD-OCT, Spectralis; Heidelberg Engineering, Heidelberg, Germany) with automated central macular thickness (CMT) measurements, customized high-resolution enhanced depth imaging (EDI) SD-OCT scans, and peripapillary RNFL thickness measurements with SD-OCT. All of the images were obtained with an eye-tracking system, and the same locations were scanned by the same operator.

To exclude diurnal variation of choroid thickness and IOP, PD patients were evaluated early in the morning between 09:00-12:00 am. All PD patients were having at least three exchanges a day. Total body weight and blood pressure (BP) was measured for each patient before the OCT recording.

The choroid layer thickness was measured from the outer portion of the hyper reflective line corresponding to the retinal pigment epithelium to the inner surface of the sclera. Measurements for retinal and choroidal thickness were made in the

central foveal segment. The CFT and peripapillary RNFL thickness parameters were automatically calculated with the SD-OCT. The peripapillary RNFL thickness was analysed in seven different areas: central, temporal, inferotemporal, inferonasal, nasal, superonasal and superotemporal. Central macular thickness was measured at five different areas as central, superior, temporal, inferior and nasal.

Statistical Analysis:

All statistical analyses were performed using IBM SPSS for Windows version 20.0 (SPSS, Chicago, IL, USA). Kolmogorov-Smirnov test was used to assess the assumption of normality. Normally distributed variables were expressed as mean ± standard deviation while the continuous variables that do not have normal distribution were expressed as median (25.percentile-75.percentile). Comparisons of normally distributed continuous variables between groups were performed using student's t test. For non-normally distributed continuous variables, differences between groups were tested using Mann Whitney U-test. Comparisons of paired variables were performed using the Paired Samples t test since the normality assumption was satisfied. Lastly, relationship between normally and non-normally distributed variables were evaluated by Pearson and Spearman Correlation Analyses, respectively. A two-sided p-value<0.05 was considered as statistically significant.

RESULTS

Sixty-four eyes in 32 patients (18 males, 14 females; aged 20 to 60 years, mean 48.67±12.25 years) were included in this study. The mean duration of PD was 46.80 ±28.91 months. The baseline characteristics of the patients and control group were presented in Table 1.

Laboratory findings of the patients are given in Table 2.

Table 1 Characteristics of patients and control group

Characteristics	Peritoneal dialysis	Control
Number of patients	32	10
Age,mean±SD (range)	48.67±12.25	50.90±12.15
Female / Male	14/18	5/5
Duration of PD (months), mean±SD (range)	46.80± 28.91	0
Mean Systolic/ Diastolic Blood Pressure (mmHg)	145.18±22.59/ 87.40±10.95	125.2±20.15/72±9.10

Table 2 Laboratory findings of the patients

VARIABLES	Patients (n=32)
Laboratory Data	
TC (mmol/l)	181.80±36.64
LDL (mmol/l)	105.42±34.98
Hb (gr/dl)	10.63±1.66
Creatinine (µmol/l)	8.85±3.75
eGFR (ml/min)	21.12±29.39
Ca (mg/dl)	8.97±0.87
P (mg/dl)	4.76±1.24
Ca x P	43.96±13.56
iPTH (pg/ml)	421.34±165.75
Uric acid (mg/dl)	5.48±1.13
CRP (mg/L)	0.81±1.08
Albumin (mg/dl)	3.46±0.32
Ferritin (ng/ml)	341.23±227.61

TC (total cholesterol) , LDL (low-density lipoprotein), Hb (Hemoglobin), e GFR (estimated glomerula filtration rate), Ca (Calcium), P (Phosphorus), iPTH (intact parathyroid hormone), CRP (C-reactive peptide

The mean value of systolic blood pressure was 145.18±22.59 mmHg and the diastolic blood pressure was 87.40±10.95 mmHg. The mean body weight of patients was 75.98 ± 11.93 kg. The mean residual renal volume was 975 ±698.74cc. Of the 32 patients, 25 were doing continuous ambulatory peritoneal dialysis (CAPD) and seven were doing automated peritoneal dialysis (APD). For the CAPD group, 36.5% the patients were doing four changes, 7.7% of them were doing five changes. The mean

volume of exchanges was 8576 cc. 38.5 % were using amino-acid and 28.8% were using icodextran containing peritoneal dialysis solutions while all of the patients were using glucose containing peritoneal dialysis solutions. The mean Kt/V value was 2.4804 ±1.23. And the mean of residuel eGFR value was 21.12 ± 29.39 ml/min/m2. The etiologies of ESRD in the 32 patients included chronic hypertensive nephrosclerosis (n =18), polycystic kidney disease (n = 6), diabetic nephropathy (n=5) and glomerulonephritis (n= 3).

The mean macular thickness was measured in the central, temporal, superior, nasal and inferior quadrants and given in detail in table 3.

Table 3 Peripapillary retinal nerve fiber layer (RNFL) and macular and choroidal thickness values of peritoeneal patients and control group (a : Independent samples t- test, b : Mann- Whitney U test)

Quadrants	Peritoneal (n=64)	Control (n=20)	p-value
Peripapillary RNFL	**Mean±SD**		**Mean±SD**
Central[b]	100±12.09	101.55±8.35	0.943
Temporal Superior[a]	136.93±22.60	139±16.18	0.727
Nasal Superior[a]	107.48±20.38	113.70±15.14	0.252
Nasal[a]	76.72±15.03	75.10±12.49	0.693
Nasal Inferior[a]	112.31±20.86	109.10±20.35	0.453
Temporal Inferior[b]	143.75±16.52	149.30±20.49	0.522
Temporal[a]	73.17±12.05	76.55±11.04	0.073
MACULAR THICKNESS			
Central[b]	263.64±34.60	273.65±36.66	**0.037**
Nasal[a]	327.25±26.21	342.30±18.65	**0.031**
Superior[b]	326.67±27.47	345.85±18.44	**0.010**
Inferior[b]	321.29±27.95	339.4±19.75	**0.010**
Temporal[b]	312.77±28.21	325.35±24.23	**0.043**
CHOROIDAL THICKNESS (EDI-OCT)[a]	316.70±60.64	303.35±64.03	**0.045**

The mean peripapillary RNFL thickness was not different in all quadrants between controls and PD patients. The mean central macular thickness was 263.64±34.60 µm in PD group and 273.65±36.66 µm in control group. The average peripapillary RNFL thickness was 100±12.09 µm in PD group and 101.55±8.35µm in control group. Mean choroidal thickness was significantly higher in in PD group (316.70±60.64 µm) than control group (303.35±64.03 µm) (p=0.045). There were significant negative correlations between age and choroidal thickness (p= 0.005, r:-0.494).

Vitamin D3 treatment was linked to decreased macular thickness in all quadrants (Table 4).

There was a positive correlation between central and temporal macular thickness with residual renal function(p:0.001). Higher urea (p:0.008) and lower LDL (p:0.031)concentrations were associated with increased central macular thickness (Table 5).While there was no correlation with malnutrition inflammation score (MIS), only positive correlation was found between high MIS values and nasal inferior peripapillary RNFL thickness.

DISCUSSION

Ocular involvement with specific findings is frequent in most of the systemic diseases. There is limited number of studies demonstrating this relationship in CKD in detail (4,16). In previous studies the acute effect of hemodialysis (HD) procedure on the central corneal and foveal retinal thickness was assessed along with chronic changes(15). There are a few studies done in PD; one of them is the study of Chong et al. (17) reporting that nocturnal intermitant PD causes reductions in IOP, mean arterial pressure (MAP) , body weight and serum osmolarity.

In our study we found that macular thickness was significantly reduced in PD patients compared to healthy controls. Thinning of the retina, especially a thinner retinal layers are related with neural apoptosis and damage in ganglion cells in diabetic retinopathy (18,19). In a recent study it has been demonstrated that loss of ganglion cell bodies are causing thinning of inner retinal layers (20) in diabetics prior to the abnormal vascular manifestations occur. Retinal and choroidal thickness and macular volüme were both reduced in CKD while RNFL thickness was not different compared with healthy population(4). Thin chorioretina was associated with renal inflammation and arterial stiffness(4). Therefore the reduced macular thickness can be considered as an earyl sign of neurodegeneration and ongoing inflammation in our patients.

Table 5:Correlation of Central Macular Thickness (a : Pearson Correlation, b : Spearman's Correlation) Residual renal volume

Correlation of Central Macular Thickness	R	p
Residuel urine volume [a]	+0.608	**0.001**
nPCR [b]	+0.487	**0.016**
Height [a]	+0.403	**0.037**
Weight [a]	-0.020	0.923
BMI [a]	-0.020	0.923
Ca[b]	+0.132	0.522
P[a]	+0.048	0.817
CaxP[a]	+0.118	0.567
Urea[a]	+0.507	**0.008**
Uric acid [b]	+0.522	**0.006**
LDL [a]	-0.424	**0.031**
TG [a]	+0.192	0.346
HDL [a]	-0.083	0.688
Total cholesterol [a]	-0,076	0,711
Kt/V [b]	+0.104	0.630
CRP [b]	-0.023	0.911
iPTH [b]	+0.010	0.962
Hb [b]	+0.045	0.827
MIS [b]	+0.089	0.654
BECK [a]	-0.236	0.202
Duration of PD [b]	+0.030	0.875

n PCR (Normalised protein catabolic rate), BMI (Body Mass Index), LDL (low-density lipoprotein), Hb (Hemoglobin), e GFR (estimated glomerula filtration rate), Ca (Calcium), P (Phosphorus), iPTH (intact parathyroid hormone), CRP (C-reactive peptide), TG (triglyceride), HDL (high density lipoprotein), MIS (malnutrion inflammation score), PD (peritoneal dialysis), BECK (Beck depression inventory)

Table 4 Vitamin D3 replacement and optical coherence tomography findings (22 of the 32 patients received active vitamin D3/Calcitriol Replacement) (a:Independent samples t-test, b : Mann- Whitney U test)

	Vitamin D_3 (Calcitriol) Treatment						
	Receiving (n=22)			Not Receiving (n=10)			
	Mean	±SD	Median	Mean	±SD	Median	p
RNFLCentral [b]	92,9	16,2	96	103,5	10,4	106	0,080
RNFL Temporal Superior[a]	127,8	27,3	137,5	137,8	21,4	138	0,332
RNFL Nasal Superior[b]	102,3	30,0	112	109,1	17,0	109,5	0,878
RNFL Nasal[a]	74,1	17,2	75,5	79,0	15,9	82	0,498
RNFLNasal Inferior[a]	102,8	25,5	99	119,5	18,8	123	0,081
RNFL Temporal Inferior[b]	130,1	36,0	139,5	152,4	22,2	148	0,133
RNFL Temporal [a]	66,0	10,1	61,5	75,9	13,0	73,5	0,071
Choroidal Thickness [a]	340,9	56,0	347	314,4	64,3	314	0,312
Macula Central [b]	255,4	34,4	259	272,2	37,8	270,5	**0,042**
Macula Superior[a]	311,0	20,5	319	336,1	30,9	343,5	**0,033**
Macula Nasal [a]	313,5	17,1	317	338,1	29,1	342,5	**0,024**
Macula Inferior [a]	307,4	24,0	316	330,9	29,8	337	**0,047**
Macula Temporal [b]	300,7	13,9	298	321,1	34,1	328,5	**0,004**

25-OH vitamin D inhibits angiogenesis (21,22) and regulates the renin–angiotensin system and causes endothelial cell–dependent vessel vasodilatation (21). Anti-angiogenic feature of vitamin D has been shown in cultured endothelial cells, animal retina model and ischemic retinopathy (23,24). Vitamin D (25,26) reduces the immune system proliferation and there is an inverse relationship between 25- OH vitamin D(27) and chronic inflammation. Vitamin D3 also affects intra-ocular pressure and ocular blood flow in diseases like: diabetes, hypertension and dyslipidemia (28).

Vitamin D is known to have role in ocular functioning with receptors found in retinal tissue (26,28). In patients with early age-related macular degeneration (AMD), serum 25-OH vitamin D levels were found to be low (22,27,30). Low 25-OH vitamin D concentrations are related with decreased neuroprotection and is linked with deteriorated visual acuity in older population (29). Vitamin D therapy was found to have a protective effect in preserving macular thickness and it reduces the risk of AMD (23,31) via anti-inflammatory properties. Uro et al. showed in their study that vitamin D deficiency was associated with reduced ganglion cell complex thickness in older patients (31). This finding can be a sign of early stage of optic nerve damage prior to RNFL loss. While vitamin D deficiency and replacement had no proved effect on the RNFL in our study similar to the previous studies, it was found to be related with marked differences on macular thickness. The patients who were taking vitamin D3 replacement had thinner macular thicknness regardless of the serum PTH and 25-OH vitamin D levels.

When evaluating patients with stage V CKD, who are started on HD or PD, ophthalmologists should think over the factors causing ocular pathological conditions (25) and the findings like thin macular thickness can be an early sign of non-optimal serum urea levels, bone mineral metabolism and a sign of vitamin D deficiency. Future studies are needed to evaluate the changes in PD patients.

CONCLUSION

Findings of OCT supported a significant reduction of macular thickness in PD patients. The reduction was significant in all quadrants. Choroidal thickness was also negatively correlated with the age of PD patients. No differences in RNFL measurements were found between PD and control groups.

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