Original Article

Taiwan J Ophthalmol 2021;11: 367-371

Access this article online

Quick Response Code:

Website:
www.e-tjo.org

DOI:
10.4103/tjo.tjo_86_20

A study of effect of hemodialysis on macular thickness in patients with end-stage renal disease

Shwetha Suryakanth[1], H. N. Ravi Shankar[1], Mallikarjun M. Heralgi[2], Pradeep Sagar[1]*, V. Kavitha[3], S. Mahesha[4], N. Suresh Babu[1], Pradeep Tekade[1]

Abstract:

PURPOSE: The purpose was to study the effect of hemodialysis (HD) on macular thickness in patients with diabetic retinopathy (DR) and end-stage renal disease.

MATERIALS AND METHODS: In this prospective observational study, patients undergoing HD for diabetic nephropathy were recruited. None of the patients received treatment for DR *per se* during the study duration. Patients underwent ocular examination and optical coherence tomography before HD and were followed up on day 3 and day 30. At each visit, central subfield macular thickness (CSMT) and total macular volume (TMV) were measured and compared with baseline values using analysis of variance and *post hoc* test (Wilcoxon's matched-pairs signed-rank test).

RESULTS: Thirty-one eyes of 19 patients were recruited in the study. The mean CSMT decreased from baseline value of 278.93 ± 45.01 μ to 239.81 ± 40.54 μ at the end of 30 days ($P < 0.005$). The mean TMV decreased from baseline value of 8.14 ± 0.68 mm^3 to 7.80 ± 0.63 mm^3 on day 30 ($P < 0.005$).

CONCLUSION: There was a statistically significant reduction in CSMT and TMV after HD at 30 days as compared to baseline values. HD alone results in reduction of macular thickness over short term.

Keywords:

Diabetic nephropathy, diabetic retinopathy, hemodialysis, macular edema

Introduction

Diabetes mellitus (DM) is a chronic metabolic disease associated with significant morbidity and mortality. Chronic hyperglycemia is associated with long-term damage and failure of various organ systems, mainly affecting the eyes, nerves, kidneys, and the heart.[1] The pathological hallmark of DM is involvement of vasculature leading to both microvascular and macrovascular complications.[2] Diabetic retinopathy (DR) and nephropathy are major microvascular complications of DM.

DR is closely associated with the preclinical morphological changes of diabetic nephropathy (DN).[3] The inner retina and the glomerular filtration barrier have many similarities in terms of development[4] and structure.[5] Thickening of the basement membrane of the retinal and glomerular capillaries is reported in DR and DN,[6] suggesting that they share similar microvascular pathological pathways in cases of abnormal glucose metabolism.

It is reported that hemodialysis (HD) improves macular edema in patients with diabetes.[7,8] Few studies have evaluated the effects of HD on retinal thickness, and the results are conflicting. Some studies reported no change in macular thickness after HD,[9-11] while others reported a significant decrease in macular thickness after HD.[8,12-14]

Department of [1]Vitreo-Retina, [2]Cornea and Refractive Services, [3]Pediatric Ophthalmology and Strabismus and [4]Cataract and Trauma, Sankara Eye Hospital, Shimoga, Karnataka, India

***Address for correspondence:**
Dr. Pradeep Sagar, Department of Vitreo-Retina, Sankara Eye Hospital, Harakere, Thirthahalli Road, Shimoga - 577 202, Karnataka, India.
E-mail: pradeepsagarbk@gmail.com

Submission: 09-10-2020
Accepted: 25-11-2020
Published: 17-04-2021

How to cite this article: Suryakanth S, Shankar HN, Heralgi MM, Sagar P, Kavitha V, Mahesha S, *et al*. A study of effect of hemodialysis on macular thickness in patients with end-stage renal disease. Taiwan J Ophthalmol 2021;11:367-71.

Considering the conflicting results, we conducted this study to evaluate the effect of HD on the macular thickness in patients with end-stage renal disease (ESRD) due to DN in the absence of specific intervention for DR.

Materials and Methods

This is a hospital-based prospective observational study carried out at a tertiary care eye hospital in Karnataka between August 2017 and March 2019. The study was approved by the institutional review and ethical board (Sankara eye hospital, Shimoga Reg No- ECR/1296/Inst/KA/2019. IRB approval date: 16-6-2017) and adhered to the principles mentioned in the Declaration of Helsinki 2000.

All patients with DN requiring HD were recruited into the study from three hospitals. Cases with retinal photocoagulation or ocular surgery in the past 6 months and cases with hazy media and retinal abnormalities other than DR were excluded. Written informed consent was obtained from all the individuals. All the patients underwent a detailed clinical examination. Best-corrected visual acuity was measured at distance using Snellen's chart and at near using Roman chart. Intraocular pressure was measured using noncontact tonometry (Topcon CT-800). Dilated fundus examination was performed using +90D lens under slit-lamp biomicroscope and +20D lens with indirect ophthalmoscope. DR was graded as per proposed international clinical DR severity scales.[15] Optical coherence tomography (OCT) was performed using Topcon 3D OCT-2000 system. Two parameters, central subfield macular thickness (CSMT) and total macular volume (TMV), were obtained by high-definition images captured on spectral-domain OCT (3D OCT-2000 software edition version 4.0 x Topcon, Tokyo, Japan). CSMT was defined as the mean measurement of all A-scans within the 500 μm circle between internal limiting membrane (ILM) and outer segment/retinal pigment epithelium (RPE). TMV was defined as the volume between the ILM and RPE within 6 mm × 6 mm square centered on the fovea. This may be calculated as the sum of each subfield retinal thickness measurement multiplied by the subfield's surface area. Images with an image quality value of >50 which indicates a good scan quality sufficient enough to provide reliable analysis were included. Fundus fluorescein angiography was not performed in view of compromised renal function.

Patients underwent HD as per the nephrologist's orders within the next 24 h of initial OCT. All the recruited patients were on a twice-weekly HD regimen at the discretion of the treating nephrologist. All the patients were on low-flux dialysis, the dialysate consisting of a readily available acid concentrate and manually prepared base concentrate. The patients were followed up on day 3 and day 30, and the OCT parameters were recorded. The CSMT and TMV at baseline, 3rd-day follow-up, and 30th-day follow-up were compared.

The patients were not put on any topical medications, and no change was made in their systemic medications during the course of our study. Blood sugar control in the recruited patients could not be assessed or compared due to poor reliability of glycated hemoglobin values in patients on HD. Among patients with macular edema, asymptomatic patients were observed and the symptomatic ones were excluded from the study and treated with intravitreal anti-vascular endothelial growth factor (VEGF) injection.

Statistical analysis

The data were analyzed descriptively with mean and standard deviation. The analysis of variance (ANOVA) test was used to compare the CSMT and TMV values at baseline, 3 days, and 30 days. Whenever difference was noted between all three values, *post hoc* test (Wilcoxon's matched-pairs signed-rank test) was applied. In the analysis of groups not having a sufficient sample size to form a normal distribution curve, W value was calculated, and resultant P value was deduced. A two-sided $P < 0.05$ was considered to be statistically significant. Statistical analyses were carried out using the SPSS 25.0 version (SPSS, Chicago, IL, USA) software for Windows.

Results

During the study period, a total of 48 eyes of patients undergoing HD for DN were recruited. Considering the need for intervention in patients with advanced retinopathy, 3 eyes with symptomatic macular edema were excluded from the study and were treated with intravitreal anti-VEGF injection. Twelve eyes were lost to follow-up and 2 eyes were excluded from the study due to the death of a patient due to systemic condition before the completion of the study. A total of 31 eyes of 19 patients were included in the study, of which 63.15% were men. The mean age was 57.21 ± 7.48 years. 57.89% of the patients were known to be diabetic for more than 10 years (11/19 patients). 57.89% of the patients were on insulin therapy for control of DM (11 patients). Of the 31 eyes, 48.38% (15) of the eyes had proliferative diabetic retinopathy, 32.25% (10 eyes) had moderate nonproliferative diabetic retinopathy (NPDR), 9.67% (3 eyes) had severe NPDR, and 9.67% (3) of the eyes had mild NPDR.

The means and standard deviations of the CSMT and TMV at baseline, day 3, and day 30 are tabulated in Table 1.

Eight of the 31 eyes had cystoid or spongiform edema on OCT within 3 mm from the center of the fovea. In the group with macular edema, the mean CSMT value at baseline was 329.38 ± 47.76 µ. The mean CSMT value 3 days after HD was 310.50 ± 40.07 µ and 30 days after HD was 274.25 ± 43.40 µ. The average reduction in CSMT after 30 days was 55.13 µ. ANOVA test showed a statistically significant reduction in CSMT. On applying the *post hoc* test (Wilcoxon's matched-pairs signed-rank test), the reduction in CSMT was statistically significant between baseline and day 30 ($P < 0.05$, $W = 1$), baseline and day 3 ($P < 0.05$, $W = 0$), and between day 3 and day 30 ($P < 0.05$, $W = 1$). The decrease in CSMT on OCT is seen in Figure 1.

In the group without macular edema, the mean CSMT value at baseline was 261.39 ± 28.12 µ. The mean CSMT value 3 days after HD was 245.73 ± 33.62 µ and 30 days after HD was 227.83 ± 32.56 µ. The mean reduction in CSMT after 30 days was 33.56 µ. ANOVA test showed that there was a statistically significant reduction in CSMT ($F = 6.53$, $P = 0.0026$). On applying the *post hoc* test, the reduction in CSMT was significant between baseline and day 30 ($P = 0.003$), between baseline and day 3 ($P < 0.00001$), and between day 3 and day 30 also ($P = 0.00262$). The decrease in CSMT on OCT is seen in Figure 2. Overall, there was a statistically significant reduction in CSMT, as summarized in Table 2.

In the group with macular edema, the mean TMV value at baseline was 8.20 ± 0.89 mm^3. The mean TMV value after 3 days was 7.96 ± 0.93 mm^3 and after 30 days was 7.74 ± 0.48 mm^3. ANOVA test showed a reduction in TMV values. *Post hoc* test demonstrated reduction to be statistically significant between baseline and day 3 ($P < 0.05$, $W = 0$) and between baseline and day 30 ($P < 0.05$, $W = 0$). However, the reduction in TMV values from day 3 to day 30 was not statistically significant ($P > 0.05$, $W = 12$). The average decrease in TMV at the end of 30 days was 0.46 mm^3.

In the group without macular edema, the mean TMV value at baseline was 8.12 ± 0.62 mm^3. The mean TMV value on day 3 was 7.92 ± 0.68 mm^3 and on day 30 was 7.82 ± 0.68 mm^3. The average reduction in TMV after 30 days was 0.30 mm^3. ANOVA test showed that the reduction in TMV values was not statistically significant ($P = 0.299$).

Overall, there was a statistically significant reduction in TMV values after 3 days and 30 days from baseline. The data are depicted in Table 2.

Average thickness values on day 0, day 3, and day 30 were tabulated and analyzed, but the reduction was not statistically significant ($P = 0.32$). The thickness in each of the nine subfields of the Early Treatment Diabetic Retinopathy Study grid was tabulated on day 0, day 3, and day 30, and analysis was performed in both the groups with and without macular edema. However, except for the C_1 subfield which consists of the central 1 mm ring, none of the other subfields showed a statistically significant reduction in either group [Table 3].

Table 1: Central subfield macular thickness and total macular volume values

	Number of eyes	CSMT, mean (microns)±SD	TMV, mean (mm^3)±SD
Base	31	278.94±45.02	8.14±0.68
3 days	31	262.45±45.09	7.93±0.74
30 days	31	239.81±40.54	7.80±0.63

CSMT=Central subfield macular thickness, TMV=Total macular volume, SD=Standard deviation

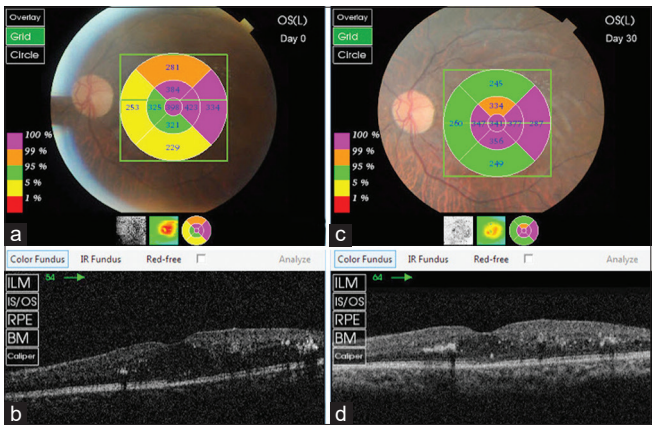

Figure 1: (a) Color photograph with Early Treatment Diabetic Retinopathy Study grid overlay of an eye with macular edema on day 0, before hemodialysis. (b) Corresponding optical coherence tomography-B-scan image of section shown in a. (c) Color photograph with Early Treatment Diabetic Retinopathy Study grid overlay of an eye with macular edema on day 30, after hemodialysis. (d) Corresponding optical coherence tomography-B-scan image of section shown in c

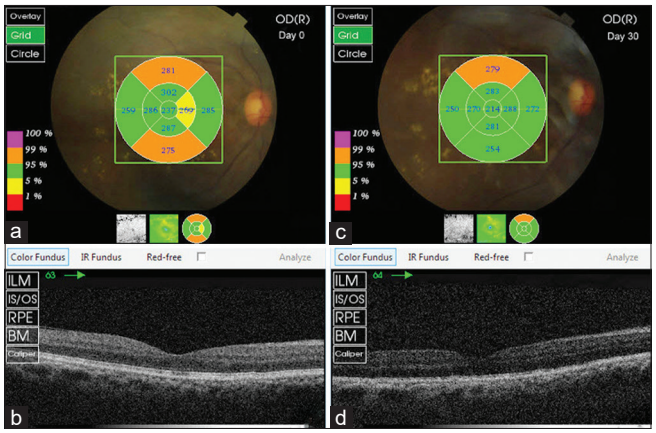

Figure 2: (a) Color photograph with Early Treatment Diabetic Retinopathy Study grid overlay of an eye without macular edema on day 0, before hemodialysis. (b) Corresponding optical coherence tomography-B-scan image of section shown in a. (c) Color photograph with Early Treatment Diabetic Retinopathy Study grid overlay of an eye without macular edema on day 30, after hemodialysis. (d) Corresponding optical coherence tomography-B-scan image of section shown in c

The changes in visual acuity following HD were analyzed and were not found to be statistically significant.

Discussion

We evaluated the effect of HD on macular thickness in patients with ESRD due to DN.

In our study, the reduction in CSMT at the end of 3 days after HD was statistically significant. Patients underwent HD twice a week, which indicates that the reduction in CSMT was significant even after one session of HD. This finding was similar to studies by Jung *et al*.[14] and Pahor D *et al*.,[16] who reported a significant reduction in macular thickness after one session of HD. However, studies by Emre *et al*.[10] in which OCT was performed immediately after HD and Azem *et al*. in which OCT was performed 30 min after HD[11] showed no reduction in macular thickness following one session of HD.

Table 2: Central subfield macular thickness and total macular volume values compared by *post hoc* test

Starting period (day)	Ending period (days)	*Z*	*P*
CSMT			
0	3	−4.6836	<0.00001*
0	30	−4.3308	<0.00001*
3	30	−3.8017	0.00014*
*Statistically significant at *P*<0.05. The *F*=29.3344. The *P*<0.00001. The result is significant at *P*<0.05			
TMV			
0	3	−3.5176	0.00044*
0	30	−3.8311	0.00012*
3	30	−1.7245	0.08544

*Statistically significant at *P*<0.05. The *F*=12.2245. The *P*=0.000035. The result is significant at *P*<0.05. CSMT=Central subfield macular thickness, TMV=Total macular volume

Table 3: Comparison of macular thickness in each subfield of Early Treatment Diabetic Retinopathy Study grid at baseline, day 3, and day 30

	Mean±SD (microns)			*P*
	Day 0	Day 3	Day 30	
Average thickness	280.95±27.98	273.67±29.75	270.16±28.25	0.32
C_1	268.42±42.21	252.52±43.97	230.84±38.42	0.002*
S_3	290.00±36.87	275.45±34.61	275.13±31.74	0.15
N_3	288.35±29.47	284.03±34.36	275.81±27.00	0.26
I_3	289.74±32.43	273.90±27.79	275.03±27.45	0.65
T_3	290.74±33.34	277.90±33.78	277.52±38.57	0.24
S_6	277.81±37.35	270.90±36.65	269.65±31.41	0.61
N_6	285.32±29.06	280.39±27.71	277.74±22.68	0.52
I_6	272.97±30.92	273.10±34.00	263.61±28.08	0.39
T_6	268.42±33.97	267.68±33.45	254.61±35.69	0.21

ETDRS=Early Treatment Diabetic Retinopathy Study, SD=Standard deviation, C_1=Central 1 mm, S_3=Superior subfield in inner ring, N_3=Nasal subfield in inner ring, I_3=Inferior subfield in inner ring, T_3=Temporal subfield in inner ring, S_6=Superior subfield in outer ring, N_6=Nasal subfield in outer ring, I_6=Inferior subfield in outer ring, T_6=Temporal subfield in outer ring. *Statistically significant at *P*<0.05

There was a significant reduction in CSMT at the end of 30 days after HD. Patients underwent 8 sessions of HD by 30 days. Hence, regular HD can result in reduction of macular thickness. None of the studies published in the literature have evaluated changes in macular thickness after multiple sessions of HD.

In our study, there was a statistically significant change in TMV following HD, measured at 3 days and 30 days. In a study by Theodossiadis *et al*.,[17] a significant reduction in central macular thickness (CMT) and TMV was noted immediately after HD and these changes were more pronounced in patients with macular edema. Similarly, in our study, the reduction in CSMT was more pronounced in patients with macular edema. The mean reduction in CSMT in the group with macular edema was 55.13 μ while it was 33.2 μ in the group without macular edema.

A comparison of our study with other similar studies is summarized in Table 4.

Diabetic macular edema (DME) in patients with Stage 5 CKD is attributed to systemic factors[18-20] such as increased blood volume, hypertension, and anemia. Massive changes in osmolarity caused by HD and the resulting homeostatic changes could be the underlying mechanism for a decrease in macular thickness. An improvement in macular edema, along with a decrease in blood pressure and blood volume, is reported to occur 1 month after initiation of peritoneal dialysis[7] or HD.[8] Hence, renal function replacement therapy would have an additive effect to local therapy in management of DME.

The limitations of our study are small sample size and shorter follow-up. Furthermore, in the group with macular edema, the number of eyes was 8, which was insufficient to obtain a normal distribution curve. The management protocols and parameters for HD did not vary significantly between the hospitals, however, there could be other confounding factors while recruiting patients from different hospitals.

Conclusion

HD results in a statistically significant reduction in the CMT and TMV 30 days after HD.

Acknowledgement of technical help

1. Dr. Anupama Y J, Consultant Nephrologist, Nanjappa Hospital, Shimoga
2. Dr. Praveen Malavade, Consultant Nephrologist, Vaatsalya Hospital, Shimoga
3. Dr. Ravi K R, Consultant Nephrologist, Sahyadri Narayana Multispeciality Hospital, Shimoga.

Table 4: Comparison of our study with various other studies on effect of hemodialysis on diabetic retinopathy

Author	Ethnicity	Number of eyes	Post-HD OCT	Number of follow-ups	Investigative modality	Reduction in CMT/macular leak	Reduction in TMV
Our study	South India	31	Day 3 and 30 after HD	2	OCT	Yes	Yes
Emre *et al.*[10]	Saudi	53	Immediately after HD	1	OCT	No	NA
Azem *et al.*[11]	Israel	40	30 min after HD	1	OCT	No	NA
Tokuyama *et al.*[9]	Japan	40	4 weeks after HD	1	FFA	No	NA
Pahor D *et al.*[16]	Slovenia	24	1 time measurement in patients on maintenance HD	0	OCT	Yes	NA
Jung *et al.*[14]	Korea	30	Immediately after HD	1	OCT	Yes	NA
Theodossiadis *et al.*[17]	Greece	72	Immediately after HD	1	OCT	Yes	Yes
Auyanet *et al.*[21]	Spain	25	Immediately after HD	1	OCT	No	NA
Chelala *et al.*[22]	Lebanon	49	Immediately after HD	1	OCT	No	NA

OCT=Optical coherence tomography, HD=Hemodialysis, TMV=Total macular volume, CMT=Central macular thickness, FFA=Fundus fluorescein angiography

Financial support and sponsorship

Nil.

Conflicts of interest

The authors declare that there are no conflicts of interests of this paper.

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