• Letter to the Editor •

Long-term hemodialysis improved and stabilized diabetic macular edema: two case reports

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Dear Editor,

Diabetic macular edema (DME) is one of main sight-threatening conditions in patients with diabetic retinopathy (DR)[1]. Anti-vascular endothelial growth factor (VEGF) therapy, glucocorticoid therapy, laser photocoagulation, and vitrectomy are currently the main clinical treatments for DME[2]. In addition to ophthalmic interventions, management of systemic metabolic dysregulations, such as hyperglycemia, hypertension, hyperlipidemia *etc.*, are also important. Here, we described two patients who had refractory DME and obtained minimal beneficial effects of the aforementioned ophthalmic treatments. As their renal function became deteriorating, they were transferred to renal clinic and accepted hemodialysis. Their macular edematous changes were accidentally improved and maintained in normal shape for a long time without any other treatments. The principles outlined in the Declaration of Helsinki were followed. Written informed consents on publishing the clinical and laboratory data were obtained from the two patients.

The case one was a 32-year-old male patient with a history of type 2 diabetes for 10y accepted insulin treatment for hyperglycemia. In October 2013, he underwent binocular panretinal photocoagulation (PRP) treatment for severe non-proliferative DR in both eyes, and phacoemulsification with intraocular lens implantation was performed for bilateral cataracts. He was then diagnosed as bilateral neovascular glaucoma in February 2014. Fundus examination showed some old laser spots and retinal hemorrhage over the posterior pole and periphery in both eyes (Figure 1). Intraocular pressure was 45 mm Hg OD and 48 mm Hg OS. Macular edema was not observed in the optical coherence tomography (OCT) examination (Figure 2A). From February 2014 to July 2014, the patient firstly accepted once binocular ranibizumab intravitreal injections, and then twice binocular conbercept intravitreal injections. He also underwent retinal photocoagulation for three times, and trabeculectomy with mitomycin-C in the right eye. After the ophthalmic treatments, neovessels in the iris regressed with decreased intraocular pressure. However, the macular cystic edema was observed during the treatments and persisted with decreased visual acuity in both eyes (Figure 2B). Best corrected visual acuity (BCVA) was 0.02 OU. Intraocular pressure was 19 mm Hg OD and 22 mm Hg OS. As the patient's renal function was further deteriorated (Table 1), he discontinued ophthalmic treatments as well as follow-up investigations, and transferred to a local renal clinic. He then underwent hemodialysis three times a week for consecutive four years without any ophthalmic interventions. In July 2018, he came back for further ophthalmic investigations. Our examination results showed that his macular edema was ameliorated remained in healthy contour with 0.2 OU of BCVA (Figure 2C) and normal intraocular pressure.

The case two was a 49-year-old male patient，who had a history of type 2 diabetes and hypertension for 2y, used insulin

Table 1 Baseline and follow-up characteristics of the patient in case one

Characteristics	Baseline	6mo after ophthalmic treatments	4y after hemodialysis
BCVA (OD/OS)	0.1/0.2	0.02/0.02	0.2/0.2
HbA1c, %	6.2	5.4	6.4
BP, mm Hg	140/85	115/76	133/74
eGFR, mL/min	79	46	NA
Cre, μmol/L	157.3	305.7	NA
BUN, mmol/L	8.42	16.93	NA
24-hour urine protein, g	4.52	10.31	NA

BCVA: Best corrected visual acuity; HbA1c: Hemoglobin A1c; BP: Blood pressure; eGFR: Glomerular filtration rate; Cre: Serum creatinine; BUN: Blood urea nitrogen.

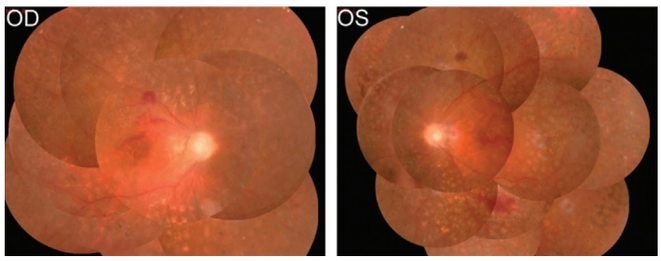

Figure 1 Baseline fundus photograph of the patient in case one.

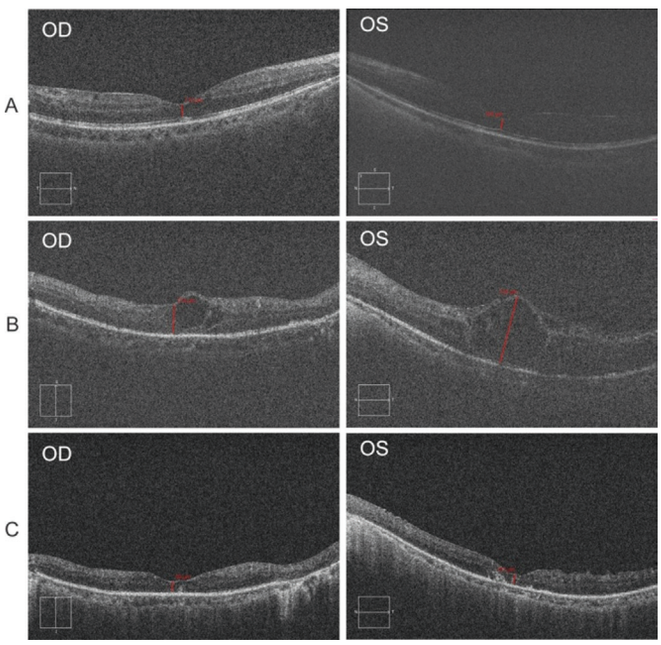

Figure 2 The patient did not present with macular edema in the OCT images at baseline (A), OCT revealed cystoid macular edema in both eyes after half a year's ophthalmic treatments (B), after four years' hemodialysis, macular edema was not found in the OCT images (C).

for blood glucose control and antihypertensive drugs for blood pressure control regularly. In 2012, he underwent binocular PRP treatment and pars plana vitrectomy (PPV) combined with intravitreal injection of triamcinolone acetonide (TA) for proliferative DR. In September 2012, he presented to our department with progressive blurry vision. BCVA was 0.2 OD and 0.5 OS. Fundus examination scattered old laser spots over the posterior pole and periphery in both eyes and hard exudates over the macular of the left eye (Figure 3). OCT examination showed thickening of the macular in both eyes (Figure 4A). From September 2012 to July 2014, the patient firstly underwent once macular grid laser treatment, and then three times intravitreal injections of ranibizumab and once intravitreal injections of conbercept. However, the macular edema was not ameliorated and even gradually became more severe (Figure 4B). BCVA decreased to 0.1 in both eyes. Due to deterioration of renal function (Table 2), the patient discontinued ophthalmic treatments and follow-up investigations, and transferred to renal clinic for hemodialysis

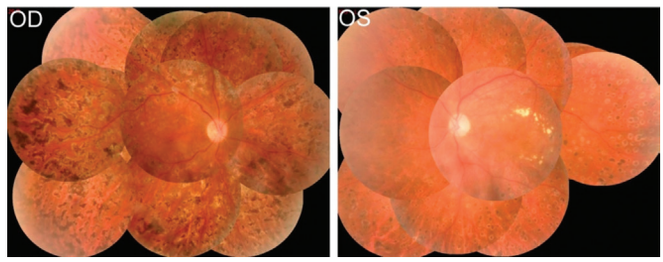

Figure 3 Baseline fundus photograph of the patient in case two.

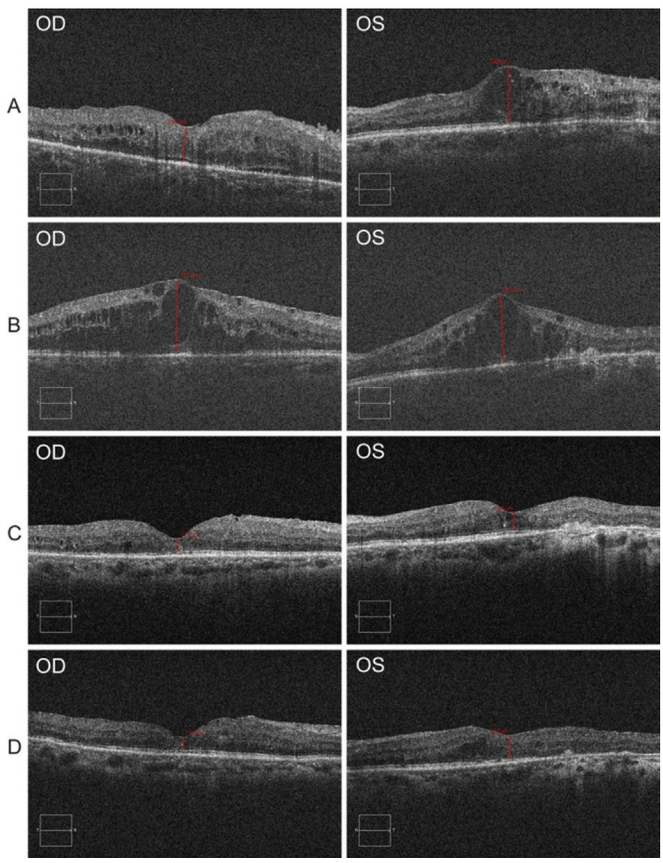

Figure 4 The patient presented with macular edema in the OCT images at baseline (A), OCT revealed significant bilateral cystoid macular edema after two years' ophthalmic treatments (B). After two years' hemodialysis, the thickness of macular was decreased in the OCT images (C). After four years' hemodialysis, OCT showed shape of the fovea remains stable (D).

three times a week without any ophthalmic interventions. In May 2016, his BCVA increased to 0.3 OU. OCT examination indicated the recovery of foveal shape and significant amelioration of the thickened macula (Figure 4C). In June 2018, the patient was reviewed again. BCVA increased to 0.4 OU. OCT examination showed normal shape of the fovea of the right eye and mild cystoids macular edema of the left eye. The thickness of bilateral foveas remained when compared with previous OCT results (Figure 4D). During the period from June 2014 to June 2018, the patient's macular edema was under control with gradually increased visual acuity by hemodialysis rather than ophthalmic interventions.

Table 2 Baseline and follow-up characteristics of the patient in case two

Characteristics	Baseline	6mo after ophthalmic treatments	2y after hemodialysis	4y after hemodialysis
BCVA (OD/OS)	0.2/0.5	0.1/0.1	0.3/0.3	0.4/0.4
HbA1c, %	8.2	6.2	5.8	6.0
BP, mm Hg	145/85	155/91	139/81	135/81
eGFR, mL/min	82	40.5	NA	NA
Cre, μmol/L	148	426.5	NA	NA
BUN, mmol/L	7.68	16.93	NA	NA
24-hour urine protein, g	0.04	11.41	NA	NA

BCVA: Best corrected visual acuity; HbA1c: Hemoglobin A1c; BP: Blood pressure; eGFR: Glomerular filtration rate; Cre: Serum creatinine; BUN: Blood urea nitrogen.

Diabetic nephropathy (DN) and DR are both the main microvascular complications of diabetes, and there is a close correlation between the two. The incidence of DN in patients with DR is 35.6%, and there is a strong correlation between the development of DN and DR[3]. Previous studies have found that chronic kidney disease, particularly the level of proteinuria, is a risk factor for the development and progression of DR[4-6]. Although DN is thought to closely relate to DR, the relationship between DN and DME is still uncertain. Some studies have suggested that levels of proteinuria are also associated with DME[6-7]. Deterioration of renal function was suggested to attenuate the absorption rate of subretinal fluid after anti-VEGF intravitreal injections in patients with DME[8]. However, in a five-year retrospective observational study, it was found that DN significantly increased the incidence of DR progression from severe non-proliferative DR to proliferative DR, but DN did not increase the incidence of DME development significantly[9]. What's more, lower level of glomerular filtration rate (eGFR) was found to associate with more severe DR rather than DME[10]. In the two cases, anti-VEGF therapy and other ophthalmic treatments did not stop the progression of DME. Renal function of both patients gradually deteriorated at the same time. In the case that blood glucose and blood pressure were controlled relatively stable, deteriorated renal function was thought to contribute to the development of DME and rendered the ophthalmic treatments less effective. When the patients interrupted ophthalmic treatments for hemodialysis, DME was accidentally improved. Similar cases have been reported previously. Mirza *et al*[11] reported that a 53-year-old DME patient delayed laser treatments for 4wk due to renal failure requiring hemodialysis. After 4 weeks' dialysis, her macular edema was relieved with improved vision and did not need laser treatment. Matsuo *et al*[12] reported casesabout a 63-year-old female and a 52-year-old male DME patient who required hemodialysis for renal failure. Their retinal exudates were attenuated after a half year's dialysis, but vision was not improved. Currently, there are few prospective clinical studies on the role of hemodialysis in the treatment of DME. Theodossiadis *et al*[13] observed the macular contours of 36 diabetic patients with end-stage renal disease with or without DME. OCT examination was performed before and immediately after dialysis treatment. Their results indicated that dialysis reduced the thickness of the edematous macula in patients with DME[13]. However, Azem *et al*[14] observed the changes of macular thickness in OCT images 30min after hemodialysis in 40 patients with end-stage renal failure with or without DME, and found that dialysis had no significant effect on retinal thickness in patients with and without DME. Tokuyama *et al*[15] observed the changes in fluorescence fundus angiography (FFA) post-dialysis in 22 diabetic patients with end-stage renal failure and DME, and also found that hemodialysis did not reduce vascular leakage in the macula[15]. As these studies only investigated the effects of short-term hemodialysis on DME, the role of long-term hemodialysis in the treatment of DME is not clear. In our two cases, patients underwent hemodialysis for consecutive 4y and had DME well controlled. Their macular edema as well as visual acuity was improved and remained stable during such a long period, suggesting that hemodialysis could improve DME and subsequent increase vision acuity, and the beneficial effects could last for years. However, it is not clear that the underlying mechanisms of the effects of hemodialysis on DME. Hemodialysis has been supposed to improve systemic problems caused by renal insufficiency, such as renal hypertension and sodium and water retention. It could also dialyze and purify certain toxic components or vasoactive substances in the blood, which in turns protect the function of blood retinal barrier.

In conclusion, through the two cases, it suggested that systemic conditions, particularly renal function, must be fully examined and treated accordingly. We observed that long-term hemodialysis could improve and stabilize edematous macula. However, due to the short of sample size, we could not perform statistical analysis. Effect of long-term hemodialysis on DME and its underlying mechanism is not fully understood and should be further investigated.

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