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WJO covers topics concerning optometry, ocular fundus diseases, cataract, glaucoma, keratopathy, ocular trauma, strabismus, and pediatric ocular diseases, blindness prevention, diagnostic imaging, evidence-based medicine, epidemiology and nursing. Priority publication will be given to articles concerning diagnosis and treatment of ophthalmological diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

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REVIEW

Pathogenesis, prevention, diagnosis and management of retinal vein occlusion

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Abstract

Retinal vein occlusion (RVO) is the second vascular retinal cause of visual loss and defined by the occlusion of a retinal vein. It is divided into branch retinal vein occlusion or central retinal vein occlusion, depending on the location of occlusion. RVO has severe medical, financial and social implications on the patients. The diagnosis of the disease is easier nowadays with the use of spectral domain optical coherence tomography and fluorescein angiography. The treatment options for RVO have changed dramatically over the past few years with the introduction of the intravitreal injections of dexamethasone (Ozurdex), bevacizumab (Avastin), ranibizumab (Lucentis) and aflibercept (EYLEA), along with the panretinal laser photocoagulation, abandoning former treatment modalities and surgical solution. This manuscript is a review of current literature about RVO with emphasize on the pathophysiology, risk factors and prevention, diagnosis and sub-group categorization and treatments including medical and surgical. Since no official guidelines are available for the treatment of RVO patients, and considering the latest developments in the treatment options, and the variety of follow-up and treatment modalities, this manuscript aims to provide tools and knowledge to guide the physician in treating RVO patients, based on the latest publications from the literature and on several of the patients characteristics.

Key words: Retinal vein occlusion; Pathophysiology; Prevention; Diagnosis; Treatment

Core tip: Retinal vein occlusion (RVO) is the second vascular retinal cause of visual loss and is defined by the occlusion of a retinal vein. The diagnosis of the disease is easier with the common use of spectral domain optical coherence tomography and fluorescein angiography. The treatment options for RVO, has changed over the past years with the introduction of the intravitreal injections of dexamethasone (Ozurdex), bevacizumab (Avastin), ranibizumab (Lucentis) and aflibercept (EYLEA). This manuscript is a review of current literature about RVO and provides tools and knowledge to guide the physician in treating patients.

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INTRODUCTION

Retinal vein occlusion (RVO) is a retinal vascular disorder. Its main characteristic is the (partial) occlusion of the central retinal vein (CRVO) or of a branch retinal vein (BRVO) followed by the associated veins becoming engorged and dilated, intraretinal haemorrhages and edema in the retina and mainly the macula. In some cases retinal ischemia is seen which consists of areas of non-perfusion of retinal capillary bed, more or less extensive,

in the periphery or in the macular area. The ischemia is associated with deep large hemorrhages and sometimes cotton wool spots (CWS)[1-7].

RVO is considered the second vascular retinal cause of visual loss, after diabetic retinopathy, and is responsible for up to 12% of severe visual loss[8-11]. RVO occurs most commonly in middle-aged and elderly individuals of age 50 and more. The incidence of RVO is 0.7% of the population between ages of 49 and 60, and rises to 4.6% above the age of 80, with about 15%-20% of patients having CRVO and the rest BRVO[12,13]. Hemiretinal vein occlusion involves the blockage of one of the two central retinal vein trunks, an extraordinary anatomical change found in up to 20% of the population, making it a less common RVO[14].

The pathogenesis of RVO is believed to be a compression, externally, on the wall of the retinal vein in the lamina cribrosa (CRVO) or at an arterio-venous crossing (BRVO) by the adjacent artery[15]. The type of RVO and clinical picture is the result of the location of interruption. In CRVO the whole venous system, in all 4 quadrants, is involved and characterized by optic disk edema, retinal veins in all 4 quadrants become dilated and torturous, CWS, and large areas of capillary nonperfusion. Haemorrhages are a significant clinical finding in CRVO, and are found in all four quadrants. CRVO can be further divided clinically into perfused (non-ischemic) or nonperfused (ischemic). The haemorrhages in CRVO can be divided into deep retinal haemorrhages in ischemic CRVO, and superficial dot and flame-shaped haemorrhages in non-ischemic CRVO.

BRVO consists of the same clinical findings in one major retinal vein and its quadrant.

Another subtle, less frequent finding is a macular venule occlusion, which does not involve any major arcade but only a small branch draining the macula, and is frequently missed[16].

PATHOGENESIS AND RISK FACTORS

Pathogenesis

The pathogenesis of RVO is not fully understood and it appears to be multifactorial and different for BRVO and CRVO. Both types however share an arterial disease as part of the etiology as part of a systemic cardiovascular risk profile[14].

BRVO occurs at a retinal arteriovenous crossing, where both artery and vein share a common adventitia[8]. The compression of the artery on the vein results in the formation of a turbulent flow which can be demonstrated by fluorescein angiography and can lead to thrombus formation[9].

CRVO is the result of arterial compression on the vein in the lamina cribrosa where both vessels share a common fibrous sleeve. The central retinal vein usually tends to narrow in aging eyes of otherwise healthy individuals in that location, and causing a disturbance to the normal laminar flow. This disturbance increases the chance of turbulent flow and thrombus formation[17].

Several factors such as blood dyscrasia, degenerative or inflammatory disease, hypotension and obstructive sleep apnea, were suggested to take part in the pathogenesis[17-20]. In young patients under the age of 50, a complete work up is warranted to find the cause for RVO.

Macular edema (ME) is the main complication in RVO patients and is a result of an increase in retinal and macular capillary permeability and leakage leading to hypoxic environment in the retina and changes, resulting in expression of many mediators of inflammation and later to BRB break down[21,22].

Inflammation plays a major role in macular edema development with many mediators having a role including: cytokines, interleukins, chemokines, angiotensin 2, vascular endothelial growth factor (VEGF), prostaglandins, P and E-selectins, vascular cell adhesion molecule 1 (VCAM-1), ICAM-1 and particularly activation of resident cells like microglia, macrophages and neutrophils[22]. Macular edema consists of accumulation of fluid with initial swelling of the Muller cells and intra retinal fluid accumulation in the outer plexiform and inner nuclear layers.

VEGF A (VEGF-A) is a very important regulator in angiogenesis and vascular permeability and has been shown to have a key part in the pathogenesis of neovascularisation (NV) and macular edema in RVO. VEGF-A is required, along with other mediators, for blood vessel growth in pathological angiogenesis[10].

Risk factors

Several risk factors have been implicated as having a role in RVO.

Glaucoma: Open angle glaucoma is an ocular risk factor which is most commonly connected to RVO patients and plays a role in RVO pathogenesis due to compromised venous flow and stasis induction in the face of high intraocular pressures (IOP)[23-27]. This process usually occurs in the lamina cribrosa and leads to CRVO formation and increase of severity[28]. History of glaucoma may be found in up to 4.5% of CRVO patients[29]. IOP lowering medications may improve perfusion in patients with CRVO and is considered as preventive treatment in the fellow eye, which has a 10% risk of developing RVO as reported in the Branch Vein Occlusion Study (BVOS)[14,30,31].

Hypertension, diabetes mellitus and cardiovascular disease: These conditions are found in over 64% of RVO patients over 50 years old. They tend to appear more in BRVO patients than in CRVO ones[23]. Hypertension is a significant risk factor and accelerates arterial stiffness[32]. In diabetic patients, the prevalence of CRVO is equal to that of the general population, but following CRVO, diabetic patients have more disc neovascularization and are more likely to require panretinal photocoagulation (PRP) laser treatment[33].

Hyperlipidemia and hypercholesterolemia: Hyperlipidemia and hypercholesterolemia are found in over 70% of RVO patients and more prominent in RVO patients

under the age of 50[24,34,35].

Obesity and smoking: These two risk factors are associated with RVO but in a lesser degree than the prior risk factors[34,36].

Thrombophilia: The findings of high levels of homocysteine in RVO patients led to the idea that thrombophilia has a role in the pathogenesis[8,12]. This role is particularly interesting in young RVO patients, in whom the pathogenesis of the disease may differ from patients with atherosclerosis, usually older[37]. A big meta-analysis of more than 500000 patient's files indicated a RR of nearly 2.5 times for CRVO in the presence of a hypercoagulable state including homocysteinemia[32].

Two other meta-analyses showed an increased risk for RVO by 50%-60% in patients carrying the factor V Laiden mutation. Other disorders such as disturbances in antithrombin, protein C or S or the G21201a mutation were not found to be in association with RVO[15].

The relation between other conditions such as lupus anticoagulant or anticardiolipin antibodies and RVO is still not clear[8,9,38-47]. Changes in platelets reactivity may be a predisposing factor.

In a recent study on the levels of intravitreal thrombin in RVO patients compared to control eyes, a significant elevated thrombin activity and VEGF levels were found in RVO patients compared to control eyes. Higher levels were found in CRVO patients compared to BRVO ones. This led Bertelman , 2014, to the conclusion that thrombin plays a role in RVO and direct treatment should be evaluated[48].

Inflammatory disease: Inflammatory diseases can cause retinal vasculitis or inflammation and may be associated with a nearby RVO. These diseases mostly affect younger individuals, under the age of 50, and include infectious diseases such as toxoplasmosis, syphilis and tuberculosis, systemic inflammatory diseases such as sarcoidosis, Behcet's disease and systemic lupus erythematosus, and vascular diseases such as polyarteritis nodosa, Wegner's granulomatosis and Goodpasture's syndrome[49]. Therefore in patients under the age of 50, a systemic investigation is warranted for these conditions, whereas is patients over 50 years arteriosclerosis is the main cause[49].

Other risk factors: Oral contraceptives and optic disc vasculitis are a debatable risk factors and evidence is available for both sides[49-53]. The risk for RVO is reduced by 70% in women in the post-menopausal period when treated with estrogen replacing therapy, consistent with reduced cardiovascular risk profile associated with this treatment[54].

Association to obstructive sleep apnea was also reported[55] and it may double the incidence of RVO[56]. Myeloprolipherative disorders are found in 1% of RVO patients[49,57]. No relation to gender was found in RVO[14], but ethnicity plays a role with a prevalence of 3.7 per 1000 population in whites, 3.9 in blacks, 5.7 in Asians and 6.9 in Hispanics[32,58].

BRVO

Natural history

Visual acuity: In BRVO patients the initial VA is generally found to be worse than 20/40 and although it tends to improve, a final VA better than 20/40 is seldom seen[59,60]. In most patients the improvement in VA was found to be up to 28 letters[59].

In the BVOS[30,31] a significant deterioration of vision was found in 20% of untreated eyes, and in 25% of cases final VA was worse than 20/200.

NV: The incidence is believed to be relatively low but there is no meaningful data on BRVO in relation to NV and neovascular glaucoma (NVG)[59].

It is believed that with severe and extensive area of ischemia of over one-third of the retina, there is a higher incidence of NV[15].

Macular edema: Macular edema in BRVO patients develops in 5%-15% of eyes in 12 mo[59]. The GENEVA clinical trial showed an improvement in both treatment and sham groups, although the treatment group had a bigger decrease in central retinal thickness of 208 μm compared to only 85 μm in the sham group. In a subanalysis, eyes with a shorter duration of ME had a better VA outcome after treatment[61].

Fellow-eye involvement: The BVOS reported bilateral involvement in 9%[30,31]. In several other studies, bilateral involvement was reported in 4.5%-6.5% of patients at baseline[2,38,62]. Some publications indicated a similar 5%-10% bilateral involvement[15].

Management

Two objectives are to be simultaneously managed by the physician in RVO patients: (1) identification and management of the risk factors leading to RVO; and (2) the diagnosis and treatment of sight-threatening complication associated with the disease, mainly macular edema and neovascularisation.

Risk factors management: The first goal in the management of RVO is the prevention of the disease and its complications by reducing and controlling systemic risk factors. Those risk factors mentioned above are to be treated and monitored closely. Management of these factors may diminish the severity of the disease and risk of complications including fellow eye involvement. (1) systemic risk factor management: When findings of RVO are clinically present [(engorgement and dilatation of retinal veins, hemorrhages and increased retinal circulation time on fluorescein angiography (FA)] in asymptomatic patients, initiation of treatment for systemic medical risk factors, may slow or even prevent the disease progression; (2) many studies including the CVOS have shown an association between arterial hypertension or glaucoma

and RVO. The physician should exclude those conditions, or if present, treat them. All though prompt treatment is recommended in these cases, no clear evidence was found regarding the benefits of the management of glaucoma and/or reduction of arterial hypertension in regard to the visual outcome in RVO patients[14]; (3) anticoagulants, antiplatelet medications and fibrinolytic medications: Though the use of such medication can help resolve RVO or lower complication rate, several studies using those drugs (Aspirin, Heparin, Streptokinase and Warfarin) showed little to no benefit, and in patients over 55 years, a greater tendency towards vascular adverse effects[63,64]. The use of Aspirin in the management of RVO is controversial and could only be suggested, yet no proven, in the prevention of cardiovascular events[15]; and (4) hemodilution: Hemodilution was suggested by several studies as a therapy in RVO. The rationale is to lower the blood viscosity thus preventing the slowdown of blood circulation and its developing complications. The studies showing benefits of Hemodilution were monocenter studies and conducted in the 1980s and 1990s but showed significant results.

A more recent multicenter, prospective study using the recent method of hemodilution, showed some limited but positive results, and recommended the use of hemodilution in the early stage of RVO. This was shown in cases when there were no contraindications such as ischemic CRVO requiring panretinal laser photocoagulation (PRP), cardiovascular conditions such as diabetes mellitus, uncontrolled hypertension and severe cardiac or renal failure, or haematological disease such as anemia or sickle cell disease[65].

The ophthalmological RVO management: The systemic investigation and treatments as mentioned above are identical for all types of RVO. Several types of management are available today for treating patients with RVO: The dexamethasone intravitreal implant (Ozurdex) that is based on the GENEVA trial, anti-VEGF treatments as with Ranibizumab, based on the Bravo and Cruise trials.

Management of BRVO is not that different from the management of CRVO regarding the systemic cardiovascular risk factors, but the differences are that in BRVO there is a limited risk of progression, conversion to ischemic type and neovascularization.

Several targets should be held by the physician in the management of a BRVO patient: (1) systemic risk factors management; (2) localization of the area of lesion (major or minor branch); (3) assessment of the degree of nonperfusion and ischemia of the macula; and (4) treatment according to eventual complications, mainly ME and NV.

Patients with BRVO, who has a good baseline vision acuity of 20/40 or better with perfused periphery, have a favourable prognosis yet monitoring should be maintained even without intervention. The follow-up should consist of a VA examination, biomicroscopy and optical coherence tomography (OCT) in order to detect the development of ME. If necessary or when in doubt, FA should be obtained.

The follow-up should begin with monthly visits for the first 3 mo, followed by a visit every other month for a year. Patients should be instructed to seek medical assistance if they notice a VA decline which may be an early sign of ME formation.

In patients with BRVO and a deterioration of vision, physician should initiate an assessment for the presence of ME. This assessment should be done with biomicroscopy and OCT. Treatment should be initiated promptly in cases of ME.

The BVOS, a prospective, randomized, controlled clinical trial on BRVO patients, set the criteria for the use of laser photocoagulation in BRVO in order to "stabilize VA", and included patients with VA of 20/40 or less, who had ME of 4 mo or more, and absorption of macular haemorrhages[30,31].

The SCORE study, a prospective double-masked, randomized trial, concluded that grid laser photocoagulation should be used in eyes with vision deterioration due to ME secondary to BRVO[66,67]. No difference in 12 mo for VA outcome between the laser treated group and the triamcinolone treated groups (4.2 letters compared to 5.7 and 4.0 letters respectively) was seen[10]. The proportion of patients with a $\geqslant$ 15 letters VA improvement was 28.9%, 25.6% and 27.2% in the standard care group and both treatment groups with a non significant difference[10]. To add was the fact that the 4 mg triamcinolone treated group had a worse safety profile (cataract and elevated IOP).

The use of paracentral laser coagulation may lead to paracentral scotomas which can cause visual field defect which may decrease the quality of vision. The central vision field was not tested in the SCORE BRVO study, thus the conclusions are still controversial[66,67]. The new navigated pattern laser (NAVILAS) and patterned scanning laser (PASCAL) systems allow for a more accurate and effective laser treatment with less pain and treatment time[68,69].

Nowadays it is custom by practitioners to use sectorial laser photocoagulation in cases of an extensive area of nonperfusion in the peripheral retina with the development of neovascularization.

Triamcinolone Acetonide is a known treatment, from several studies on RVO, and was shown to decrease edema and angiogenesis. The visual improvement is transient because of its limited duration of intraocular availability.

The SCORE clinical trial compared the efficacy and safety of intravitreal triamcinolone in two doses, 1 mg and 4 mg, to the standard of care (grid laser photocoagulation). The drug used in the SCORE trial was Trivaris which is a sterile preservative free, intravitreal injection. In the trial no difference was seen regarding VA after 12 mo between the standard care group and the treatment groups with gaining 15 letters or more in 28.9% of the standard care group compared to 25.6% and 27.2% in the treatment groups. However, more IOP elevations and higher percentage of cataract were found in the 4 mg treatment group with 35% and 33% respectively com-

pared to 8% and 18% in the standard care group[66,67].

The SCORE study suggested that grid laser photocoagulation should still act as the standard care for BRVO patients with VA deterioration due to ME.

Since the duration of ME is of great significance, in a subgroup analysis of the SCORE BRVO trial, it was shown that patients had greater benefit with classical treatment if disease duration was < 3 mo.

Of the patients with ME over 3 mo, a third showed a 15 letter or more gain in VA in the 4 mg treatment group compared to only 15% in the laser treatment group. These findings were not found to be statistically significant but indicated the importance of duration of ME in choosing treatment.

Dexamethasone is a corticosteroid that decreases inflammatory mediators which cause ME. Dexamethasone has a short half-life and is highly soluble therefore an intravitreal implant of dexamethasone (Ozurdex) was developed so it can deliver a sustained level of the drug during up to 6 mo. This drug was studied in the Ozurdex GENEVA study, a multicenter, masked, randomized, sham-controlled, clinical trial of RVO patients with ME[61]. A prefilled single use applicator, containing 0.7 mg of dexamethasone in a sustained-release biodegradable implant (Ozurdex) was used.

Patients in this trial were treated with a first masked treatment at baseline and another treatment in as needed after 180 d. In this prospective, multicenter study, two randomized, parallel groups of the same number of patients showed a statistically significant effect on VA which persisted up to 180 d and was maximal after 60 d. The second OZURDEX injection showed a better effectiveness than the first one. Adverse effects were low rates of cataract formation and elevations in IOP. No injection related adverse effects were noted.

The primary endpoint of the GENEVA study was set to be the time to achieve an improvement in best corrected VA (BCVA) of ≥ 15 letters, and secondary endpoints were BCVA over 180 d, and central retinal thickness as measured by OCT.

Duration of ME was similar in both study groups with 16.4% of patients with ME duration of under 3 mo, 51.3% with a duration of 3-6 mo and 32.3% with a duration of over 6 mo. An important fact to notice in comparison between trials related to RVO is that the proportion of patients with ME under 3 mo duration was 16.4%, in comparison with 50%-60% in the SCORE BRVO[67], the BRAVO[70] and the CRUISE[71] trials. This fact is thought to have affected the results and made it difficult to compare trials, since resolution is thought to be higher in patients with ME of shorter duration.

A significant larger percentage of patients achieving a VA improvement of ≥ 15 letters was seen in the 0.7 mg treatment group after 30 d and throughout day 90 rather than the sham group. The best response was at day 60 with 29.6% of the 0.7 mg treatment group achieving the desired improvement and only 12.5% in the sham treatment group. In achieving at least 10 letters improvement in VA from baseline the rates were 52% for the treatment group *vs* 29.4% in the sham group. By day 180, 41% of patients in the treatment group had an improvement of at least 10 letters from baseline compared to 33% in the sham treated group[61].

The differences in BCVA between the 0.7 mg treatment group and the sham group were significant for all time points throughout the study for patients with BRVO. Mean BCVA in the treatment group improved by 10 letters at 60 d, and then declined towards 180 d with only 7 letters improvement. In the sham treatment group mean VA improved by 5 letters by 60 d and did not change up to 180 d. Patients receiving sham at baseline demonstrated a lower improvement in VA even after receiving the open-label injection of dexamethasone than patients who were treated with the drug from the beginning.

At day 60 the percentage of patients in the treatment group which had an increased IOP peaked, was 2%-3% with an IOP over 35 mmHg, 15% with over 25 mmHg, and 15% with a rise of 10 mmHg and more. Patients returned to normal by day 180. After 12 mo of study and two injections only about 1% had a pressure lowering procedure, and only 0.9% had cataract surgery. All patients with adverse effects were in the 0.7 mg/0.7 mg treatment group.

A recent post-hoc study on the GENEVA results[61] showed that treatment of ME associated with BRVO of short duration is more effective than delaying treatment. The percentage of reduced odds of gaining 15 letters with treatment at day 180 was 54% in patients with ME duration of 6 mo, 32% for ME duration was 3 mo and only 12% for the duration of 1 mo.

Retreatment with Ozurdex was studied in several studies with special emphasize on the time frame between injections. In a multi-center retrospective study[72] of 128 patients, 70 of them (54.7%) with BRVO, the mean time between dexamethasone injections was 5.9 mo after the first injection and 8.7 mo after the second injection. A ≥ 15 letter gain was seen in 28% of eyes with a central macular thickness reduction of 214 μm. Some of the patients had decreases VA before 6 mo which leads to the conclusion that patients should be monitored for the chance of deterioration before the 6-mo period.

The SHASTA study[73], a retrospective study showed similar results with a mean reinjection interval of 5.6 mo and a significant improvement both in VA and central retinal thickness (CRT). Retreatment was also studied in several other studies with a mean time between injections of 4.7-5.3 mo, all with a favourable VA outcome[74-76].

The 0.7 mg dexamethasone implant (Ozurdex) is United States food and drug administration (FDA) and European Union (EU) approved for the treatment of BRVO patients with ME.

Ranibizumab is a pan-VEGF blocker (Lucentis) which its efficacy and safety were studied in the BRAVO trial. The trial was a multicenter, randomized, double-blinded, sham controlled, phase Ⅲ study on patients with ME secondary to BRVO.

The 3 parallel groups of the trial were: standard treat-

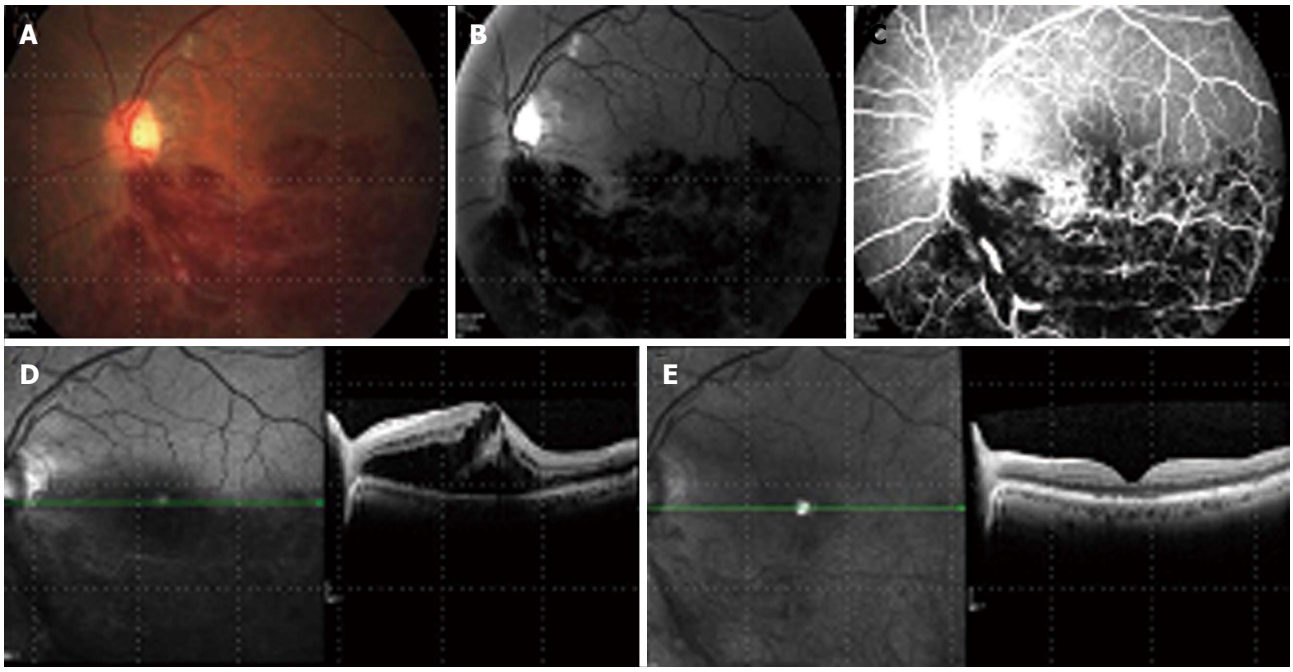

Figure 1 Left eye branch retinal vein occlusion with cystoid macular edema presented in color picture, red free and fluorescein angiography (A-C). A before treatment spectral domain optical coherence tomography (SD-OCT) of the macula (D) showing loss of foveal contour with increased central macular thickness due to many intraretinal large cystoids spaces and sub-retinal fluid accumulation. (E) SD-OCT 2 mo later, after 2 intravitreal bevacizumab injections, 1 mo apart. A normal foveal contour with some sub-foveal outer segment abnormalities. A decrease in retinal thickness back to normal and complete resolution of cystoid macular edema and sub-retinal fluid.

ment group with grid laser, 0.5 mg Ranibizumab, and a combination of grid laser and 0.3 mg or 0.5 mg Ranibizumab. According to the study's design, patients were injected on a monthly basis for the first 6 mo, followed by another 6 mo with treatment when needed. At 6 mo the treatment groups showed a better visual acuity recovery than the control group with an 18.3 letters gained in the 0.5 mg treatment group and 16.6 letters min the 0.3 mg group, compared to 7.3 letters in the sham group. This was achieved with an average of 5.7 injections. The proportion of patients achieving a ≥ 15 letters VA gain was 61.1% in the 0.5 mg group and 55% in the 0.3 mg group compared to 28.8% in the sham group[10].

In the second 6 mo period, patients were treated pro re nata (PRN), and visual improvement was maintained with an addition of only 2.7 injections. Though the change in VA was the largest in the treatment groups, the patients in the sham group also gained in VA. The BRAVO trial had ME of a short duration in about half of the patients (51.5%-53.8%)[70].

The recent RETAIN study followed the BRAVO patients in an open-label, single arm, multicenter long-term extension trial[77]. In a mean follow-up of 49.0 mo, 50% had edema resolution (no intraretinal fluid for 6 mo or more after last injection), with 76% receiving their last injection within 2 years of the first one. Final VA of 20/40 or better was seen in 80%. The mean central foveal thickness (CFT) remained under 200 μm with 88.5% with a CFT under 250 μm.

Ranibizumab 0.5 mg (Lucentis) is approved by the FDA and EU for the treatment of BRVO patients with ME.

A study conducted on Bevacizumab, in an off-label fashion off for the treatment of exudative age-related macular degeneration[78], made it commonly used medication for patients with RVO[79-85].

In a large open-label, single arm trial on the 2-year outcomes of Bevacizumab for the treatment of ME in eyes with BRVO, an improvement in VA of 0.31 logMAR was seen, with a decrease in foveal thickness of 361 μm. The response to Bevacizumab was fast and lasted throughout the year with a mean of 3.8 injections[86] (Figure 1).

No data is available on the use of pegaptanib in BRVO.

In patients with peripheral nonperfusion, assessment of the perfusion status of the macula must be done. If macula is well perfused, carrying out treatment should be as above mentioned, with grid laser photocoagulations for areas with extensive nonperfusion[60].

Even if macula is not perfused, still the treatment should be carried out in the same way, but the physician should inform the patient on the poor prognosis as related to VA.

In cases of BRVO with peripheral NV, a combined treatment of intravitreal therapy along with grid laser photocoagulation to the area of occluded vein should be promptly initiated[31].

Strategy of treatment

The randomized controlled studies on RVO have provided much information regarding treatment. An important lesson from those studies is that the duration of the disease before initiation of treatment is an important factor influencing outcome. Treatment is beneficial in any stage of the disease, including in the late stages. It has been shown that in patients with a shorter duration of

the disease, the rapid initiation of treatment may be more beneficial and the outcome is better.

Patients with BRVO should be primary screened for systemic and ocular risk factors and in case of any found, the family physician should be notified regarding the disease. The management and control of these risk factors should be fast and aggressive. Patients should be evaluated by vision assessment, biomicroscopy, measurements of IOP, and OCT. Examining the patient with FA should be done in order to find the location of the occlusive vein and to evaluate areas of nonperfusion in the periphery and the macular area. FA can also evaluate for the existence of ME or NV of the disk or retina. NV of iris or angle should be determined in a gonioscopy examination.

When periphery is perfused, and even in the face of a perfect vision, still a monthly evaluation is warranted, at least for the first 3 mo. In stable patients, the follow-up can be continued every 3 mo. All follow-up visits should include VA assessment, OCT and biomicroscopy.

In cases with decreased VA of 20/40 and under, the existence of ME should be evaluated. If ME is present, treatment should be initiated promptly. First line treatment should be with a properly approved drug, either Ozurdex with re-treatment decision according to follow-up, or with injections of an anti-VEGF drug every month for the first 3-6 mo, with additional injections depending on the progression or regression of ME.

Several characteristics of the patient may help the physician in deciding on the initial treatment. Mobility of the patient is of importance due to the necessity of a monthly visit for injections if treated with anti-VEGF. The socioeconomic status should be considered for the cost of the treatments. Pseudophakic patients can be treated with steroids with less concern. The presence of glaucoma can exclude steroids as first line treatment. Patients after vitrectomy are better treated with steroids due to their pharmacokinetics, non-compliant patients are better treated with steroids because of the need or less office visits. Younger patients should be considered for anti-VEGF because of the lens status. Patients with systemic disease such as MI or stroke are to be handled carefully with anti-VEGF. Adding to that is the physician's experience and treatment availability of the various treatments which are factors to consider.

The ongoing COMO trial is an interventional, randomized, single blind, comparison of Ozurdex *vs* ranibizumab for the treatment of BRVO. Patients with ME secondary to BRVO are randomized 1:1 to receive one of the drugs with assessments at day 7 and monthly for the first year. The hypothesis is that the effect of Ozurdex is non-inferior to that of ranibizumab in BRVO patients as assessed by change in BCVA after 1 year.

When there is non-perfusion of the periphery, and if ME is present, a rapid initiation of treatment is mandatory. First line treatment should be with an approved drug, with Ozurdex and decision about re-treatment according to follow-up, or with injections of an anti-VEGF drug every month for 3-6 mo, with additional injections based on the progression or regression of ME.

Laser treatment can still be considered for the ischemic areas in the periphery. In cases of macular ischemia the prognosis for VA improvement is generally poor even in cases of prompt treatment and ME resolution.

The development of neovascularization anywhere in the posterior or anterior chamber, no matter at what point during follow-up, should prompt the immediate treatment with sectorial laser photocoagulation to the ischemic areas. The addition of an intravitreal drug, steroids or anti-VEGF should be considered, although not proven in the trials available.

CRVO

Natural history

Visual acuity: Several studies including the Central Vein Occlusion Study (CVOS) show a poor visual outcome in patients with CRVO[7,29]. Baseline VA for CRVO is usually less than 20/40 and in most ischemic CRVO (10 disk areas or more of capillary non-perfusion), it is less than 20/200[87].

VA loss is usually more accentuated in ischemic CRVO, although VA is also poor in the non-ischemic type with more than 60% of non-ischemic CRVO patients had VA of less than 20/40 in the CVOS[6,87]. In the Ozurdex GENEVA study 92.5% of the observation group had no improvement or mild improvement (< 15 letters) after 30 d[61]. The SCORE study (Standard Care *vs* Corticosteroid for Retinal Vein Occlusion) reported 75% of CRVO eyes (both types) in the observation group with a final VA of 20/40 or worse after 12 mo[66,87].

In most studies the mean decline in VA ranged from 1 to 75 letters, although a mean improvement in VA of 1.5-12.5 letters was seen in several studies. No studies showed an improvement above 20/40[87]. In a meta-analysis of over 50 studies, the mean decrease in VA was 10 letters from baseline in 6 mo and 3 letters from baseline in 1 year for non-ischemic CRVO. In the ischemic group the decrease was of 15 letters and 35 letters accordingly[87].

In many prospective studies such as the GENEVA, CRUISE, COPERNICUS, GALILEO and others, the use of treatment for macular edema improved visual outcome largely, mainly in the non-ischemic type and changed the visual outcome of the disease in a large scale[61,71,88,89].

Alternative blood drainage formation: In BRVO, the process of venous collaterals formation is a way to facilitate the flow of blood from the vein which was obstructed to a close-by vein which is open and have normal flow. The collateral formation is the result of pressure and flow changes within the retinal veins after the obstruction[90]. Collateral formation allows reversibility of the circulation interruption and inflammation formation, and was correlated to better visual outcome. In one study VA improved from 0.22 logMAR to 0.59 in patients with collateral formation compared to an improvement from 0.24 log of the minimum angle of resolution (logMAR) to only 0.31 in eyes with no collateral formation[91].

In regards to CRVO, retino-choroidal collateral veins,

also known as optico-ciliary veins tend to develop on the optic disc. They act as an alternative drainage route for retinal blood. Some researchers believe these shunts are formatted de novo, while others hypothesise that the vessels only enlarge in the face of CRVO[92]. In a study regarding the formation of those shunts, the mean time to develop them was 6.7 mo, and most patients with those shunts did not develop anterior segment NV. The conclusion of Fuller *et al*[92] (2003), was that optico-ciliary veins are protective in CRVO patients from the development of anterior segment NV.

Conversion from well perfused to ischemic CRVO: The recognition of well perfused (non ischemic) retina and ischemic areas is best done by FA.

Conversion rates were reported in several studies to be up to 27%[87,93,94] in CRVO, after up to a 13 mo period. The ischemic conversion was described in the CVOS[6] where a total of 34% of patients converted to ischemia in the 3 year follow-up period. Of them 15% converted in the first 4 mo since disease developed[87]. Since conversion to the ischemic type can occur in up to third of CRVO patients in up to 3 years time, a long-duration, close follow-up is warranted in these cases with high clinical suspicion and performing FA and initiating treatment when conversion is suspected.

NV: NV of retina or disk secondary to an initially non-ischemic CRVO was found in up to 33% over a period of up to 15 mo[87]. As for ischemic CRVO, the incidence of NV was up to 20% over a period of 9 mo[87,95]. In some studies with no sub-division, NV was seen in up to 50% of patients after a 6 mo period[87].

The strongest predictors for NV of iris or angle were found to be visual acuity and extend of ischemic areas as seen on FA. 35% of ischemic eyes in the CVOS, developed NV of the iris or angle, compared to only 10% developing anterior chamber NV in non-ischemic eyes[29].

Ischemic CRVO is associated with neovascular glaucoma in 23%-60% of cases, and is first detected by gonioscopy. The primary finding is of a vascular network located in the trabecular meshwork and causing blockage[87]. Gonioscopy is useful and should be part of the examination regularly in all CRVO patients, but mostly in the patients with the ischemic subtype, in order to detect NV of the angle as soon as possible and allow immediate treatment with PRP for the prevention of neovascular glaucoma as proposed by the CVOS[7].

Macular edema: Most studies on CRVO enrolled patients already diagnosed with having ME at baseline. Only 2 studies reported the development of ME over time but both had only 3 eyes[87]. ME is a major complication of CRVO and associated with poor visual prognosis without treatment. Early treatment is essential since the longer the edema exists, the worse is the structural damage to the fovea[87], but even late treatment could improve VA.

In cases of ischemic CRVO resolution of ME ranged up to 73% in up to 15 mo, compared to the non-ischemic type where the corresponding proportion was about 30% by 15 mo[96,97].

Fellow-eye involvement: Systemic risk factors of CRVO patient make the fellow eye as vulnerable as the effected eye. Both eyes involvement at baseline was described in 9 studies and showed a rate of 0.4%-43% of CRVO cases[87]. 5%-10% of CRVO cases will develop RVO of any type in the fellow eye in a 3 year period[87,98-100].

Vitreous haemorrhage: The incidence of vitreous hemorrhage (VH): in CRVO patients was described in one study and was 10% in a 9 mo follow-up[87].

Management

Two objectives are to be simultaneously managed by the physician in RVO patients: (1) identification and management of the risk factors leading to RVO; and (2) the diagnosis and treatment of sight-threatening complication associated with the disease, mainly macular edema and neovascularisation.

Risk factors management: The first goal in the management of RVO is the prevention of the disease and its complications by reducing and controlling systemic risk factors. Those risk factors are to be treated and monitored closely. The management of these factors may diminish the severity of the disease and risk of complications including fellow eye involvement.

When findings of RVO are clinically present (engorgement and dilatation of retinal veins, hemorrhages, increased retinal circulation time on FA) in asymptomatic patients, initiation of treatment for systemic medical risk factors, may slow or even prevent the disease progression.

Many studies including the CVOS have shown an association between arterial hypertension or glaucoma and RVO. The physician should exclude those conditions, or if present, treat them. All though prompt treatment is recommended in these cases, no clear evidence was found regarding the benefits of the management of glaucoma and/or reduction of arterial hypertension in regard to the visual outcome in RVO patients[14].

Though the use of such medication can help resolve RVO or lower complication rate, several studies using those drugs (Aspirin, Heparin, Streptokinase and Warfarin) showed little to no benefit, and in patients over 55 years, a greater tendency towards vascular adverse effects[63,64].

The use of Aspirin in the management of RVO is controversial and could only be suggested, yet no proven, in the prevention of cardio vascular events[15].

Hemodilution was suggested by several studies as a therapy in RVO. The rationale is to lower the blood viscosity thus preventing the slowdown of blood circulation and its developing complications. The studies showing benefits of Hemodilution were mono-center studies and conducted in the 1980's and 1990's but showed significant results.

A more recent multicenter, prospective study using

the recent method of hemodilution, showed some limited but positive results, and recommended the use of hemodilution in the early stage of RVO. This was shown in cases when there were no contraindications such as ischemic CRVO requiring panretinal laser photocoagulation, cardiovascular conditions such as diabetes mellitus, uncontrolled hypertension and severe cardiac or renal failure, or haematological disease such as anemia or sickle cell disease[65].

Ophthalmological management of CRVO: The systemic investigation and treatments as mentioned above are identical for all RVO patients. The ophthalmological management differs between BRVO and CRVO. Several types of management are available today for the treatment of RVO: The dexamethasone intravitreal implant (Ozurdex) that is based on the GENEVA trial, anti-VEGF treatments as with Ranibizumab, based on the BRAVO and CRUISE trials, the recent Aflibercept, based on the COPERNICUS and GALILEO trials, and the laser treatments in specific indications.

When managing a CRVO patient it is crucial to classify it into well perfused (or non-ischemic) or non-perfused (ischemic). This classification is based upon the evaluation of capillary non-perfusion areas both at the posterior pole and at the periphery of the retina by fluorescein angiography. This classification is the basis for the treatment indications of sight-threatening complications.

In the well perfused, non-ischemic CRVO, the major sight-threatening complications are ME and the conversion into the ischemic subtype.

In the non-perfused, ischemic CRVO the major sight-threatening complications are again macular edema, usually in a more severe way, but also and mainly, neovascularization of the posterior pole [neovascularization of disc (NVD) or elsewhere (NVE)], or of the anterior segment of the eye [iris or angle neovascularization (NVI or NVA accordingly)].

The differentiation between ischemic and non ischemic CRVO subtypes can be difficult, especially at an early stage of the disease[3,5,7,29,38]. There are several clinical and functional findings that are typically found more in ischemic CRVO: acute onset of the disease, a very poor baseline VA, relative afferent papillary defect, the presence of deep and extensive intraretinal hemorrhages, the rapid formation of multiple cotton wool spots, and, as seen on FA, an extensive retinal capillary non-perfusion (more than 10 disc areas) both in the periphery and the macular region. The enlargement on FA of the foveal avascular zone is an indication of macular ischemia, and those patients usually carry a less favourable VA outcome[7].

Electroretinogram is another clinical tool to aid differentiate ischemic to non-ischemic CRVO as showed by Hayreh in 1989. In Ischemic CRVO a subnormal b-wave amplitude of < 60% of the mean value for normal individuals, or < 64%-69% of the patient's normal eye amplitude is usually found[101].

The use of spectral domain optical coherence tomography (SD-OCT) is essential in the evaluation and quantification of the amount of cystoid macular edema in RVO patients. It also provides further information regarding the location and amount of fluid in the retinal layers or in the sub-retinal space. SD-OCT showing hyper-reflective dots, especially in the outer layers of the retina, is suggestive of an inflammatory reaction and may represent disease activity[11].

Following absorption of fluid, severe ischemia is shown on SD-OCT by a decrease in retinal thickness, atrophy of the macular area and disruption of the outer retinal layers (external limiting membrane, Ellipsoid zone and photoreceptors)[11].

The integrity of several of the retinal layers, including the external limiting membrane as well as the inner segment and outer segment of the photoreceptors, is indicative of the visual prognosis. The existence of the ischemic component is shown by thinning of the retinal nerve fiber layer that can be discovered during follow up[102].

Patients with non-ischemic CRVO which have a favourable baseline VA (better than 20/40) have a good prognosis and observation only policy is acceptable. No ophthalmological treatment is compulsory, due to the lack of complications. Yet this situation does warrant a systemic investigation for hypertension, hyperlipidemia and diabetes mellitus, with risk factor management, in order to decrease the likelihood for complications such as ischemic conversion, or fellow eye involvement. Ophthalmological risk factors such as glaucoma should be ruled out or treated. Close and prolonged follow up must be suggested in order to detect progression to the ischemic subtype as early as possible[25,27].

Monitoring these patients closely with OCT, VA assessments and biomicroscopy is essential for early identification of ME and/or conversion to ischemic CRVO. An addition of FA is warranted when progression cannot be assessed properly, or it is doubtful, and when the physician needs to assess the amount of retinal ischemia.

Monitoring these patients is suggested be done every month for the first 3 mo, followed by every other month for the first year. Gonioscopy has been suggested during this follow-up. Patients should be informed to be aware of their vision, and return promptly for an examination with every deterioration of visual acuity, which may be a sign of macular edema.

In patients with non-ischemic CRVO and poor VA, physician should assess the macula for the presence of ME, and in case of its presence, an immediate treatment should be initiated.

Treatment nowadays is indicated in eyes with non-ischemic CRVO with macular edema and a VA of 20/40 or worse[38].

The CVOS showed that no statistically significant VA benefit was seen with laser photocoagulation treatment, though improvement of the macular edema was seen. This finding was with the exception of the younger patient population[103]. Because of these findings, grid laser photocoagulation is no longer indicated for that purpose.

Corticosteroids are used in CRVO with ME due to

their ability to decrease capillary permeability and inhibit inflammatory reaction and expression of inflammatory mediators, and affect the metabolism of most of inflammatory mediators including VEGF.

Triamcinolone Acetonide in a corticosteroid preparation containing benzyl alcohol and was used to treat CRVO patients in an off label fashion (Kenalog*; Squibb). Several studies have showed the benefits of Kenalog for the treatment of patients with ME secondary to non-ischemic CRVO[104]. Kenalog* is known to have some side effects including cataract development and progression and raised IOP. The benzyl alcohol component in the preparation was also associated with sterile endophthalmitis.

The multicenter SCORE CRVO study[67] showed the beneficial effects of a preparation of preservative free intravitreal triamcinolone acetonide, (Trivaris; Allergan), for the treatment of patients with ME secondary to non-ischemic CRVO[105]. This study showed that the odds of reaching a ⩾ 15 letters gain in VA, were 5 times better in both the 1 mg dosage group and the 4 mg dosage group than the observational arm (26.5%, 25.6% and 6.8% respectively)[10]. No difference was seen between both treatment groups. The 1 mg regiment had a better safety profile rather than the 4 mg group in regards to cataract formation, IOP elevation, disease progression and the necessity for surgery. Trivaris is nowadays FDA approved.

The use of Triamcinolone acetonide is rare nowadays as newer better treatments are available.

Dexamethasone is a potent corticosteroid that is known to decrease the expression of inflammatory mediators exhibited in ME including VEGF. Dexamethasone is intravitrealy injected as a slow release, biodegradable implant (Ozurdex; Allergan), allowing up to 6 mo of medication in the vitreous. The use of an implant is mainly due to dexamethasone being highly soluble and with a short half-life when in the vitreous. The effect of Ozurdex on RVO with ME was studied in a multicenter, randomized, sham-controlled clinical trial (the GENEVA study)[61]. A disposable applicator prefilled with 0.7 mg of dexamethasone in a polyglycolate-acetate implant to induce slow release of the drug, is used for the insertion of the drug into the vitreous cavity.

The GENEVA study was a prospective, multicenter, sham-controlled study which included 3 identical, randomized, parallel groups treated with either 0.35 mg or 0.7 mg dexamethasone or sham treatment (needless applicator). In the second 6 mo of the study, the open-label treatment (second injection), all patients eligible for treatment received the 0.7 mg implant. The primary endpoint of the study was the time to achieve a ⩾ 15 letter improvement on BCVA. The secondary endpoints of the study included the BCVA over the whole 6-mo period, the central retinal thickness and the safety profile of both dosages.

The study resulted in that the 0.7 mg dexamethasone implant (Ozurdex) showed an improvement in VA with a peak effect after 60 d, followed by a decline towards the baseline VA after 180 d. After 60 d the proportion of patients achieving the primary endpoint was 29.3% and 28.5% in the 0.7 mg and 0.35 mg treatment groups, compared to only 11.3% in the sham treatment group. At 180 d the proportions were 26.4%, 19.4% and 17.0% respectively. Over a 1 year follow-up, VA improvement was achieved with a second injection after 180 d. OCT demonstrated an anatomical improvement in macular edema[61].

In regards to safety issues cataract rate was low with 7.3% in the treatment group, and so was the rate of IOP increases, 4% with a peak over 2 mo. In all cases pressure declined throughout the follow-up period, especially if treated with anti-glaucomatous topical treatment. Treatment, if given, was ceased by 180 d after implant injection. No adverse effects, regarding the injection, were noted[61].

A major conclusion from the GENEVA study was that early treatment of ME is much better than delayed treatment in regards to vision improvement. A retrospective review of the study groups has shown that eyes treated within 3 mo from onset of ME showed a better improvement of VA than eyes treated after more than 90 d[15].

A more recent post-hoc analysis of the GENEVA study, regarding the onset and duration of BCVA improvement in eyes treated with Ozurdex, showed an improvement of ⩾ 15 letters in 10% of the treatment group as soon as 7 d post treatment. The duration of a ⩾ 3 lines improvement was 60-90 d[106].

Retreatment with Ozurdex was studied in several studies with special emphasize on the time frame between injections. In a multi-center retrospective study[72] of 128 patients, 58 of them (45.2%) with CRVO, mean interval between Ozurdex injections was 5.9 mo following the first injection and 8.7 mo following the second injection. A ⩾ 15 letter gain was seen in 48.8% of eyes with a central macular thickness reduction of 355 μm. Some of the patients had decreases VA before 6 mo which leads to the conclusion that patients should be monitored closely for the chance of deterioration before the 6-mo period.

The SHASTA study[73], a retrospective study showed similar results with a mean reinjection interval of 5.6 mo and a significant improvement both in VA and CRT. Retreatment was also investigated in several other small studies with a mean time between injections of 4.7-5.3 mo, all with a favourable VA outcome[74,75].

A retrospective study on 15 eyes with ME secondary to CRVO compared the efficacy of Ozurdex treatment in vitrectomized *vs* non-vitrectomized eyes[107]. The study demonstrated both groups had a significant improvement with no significant difference between groups in regards to VA improvement and CMT reduction. Conclusion is to be made that Ozurdex is effective in both vitrectomized and non-vitrectomized eyes, and the absence of vitreous does not alter the pharmacodynamics of the drug, therefore making it suitable even in eyes after pars plana vitrectomy.

Ozurdex has the FDA and EU approval and is licensed for the treatment of patients with ME secondary to non-ischemic CRVO. The GENEVA study suggests

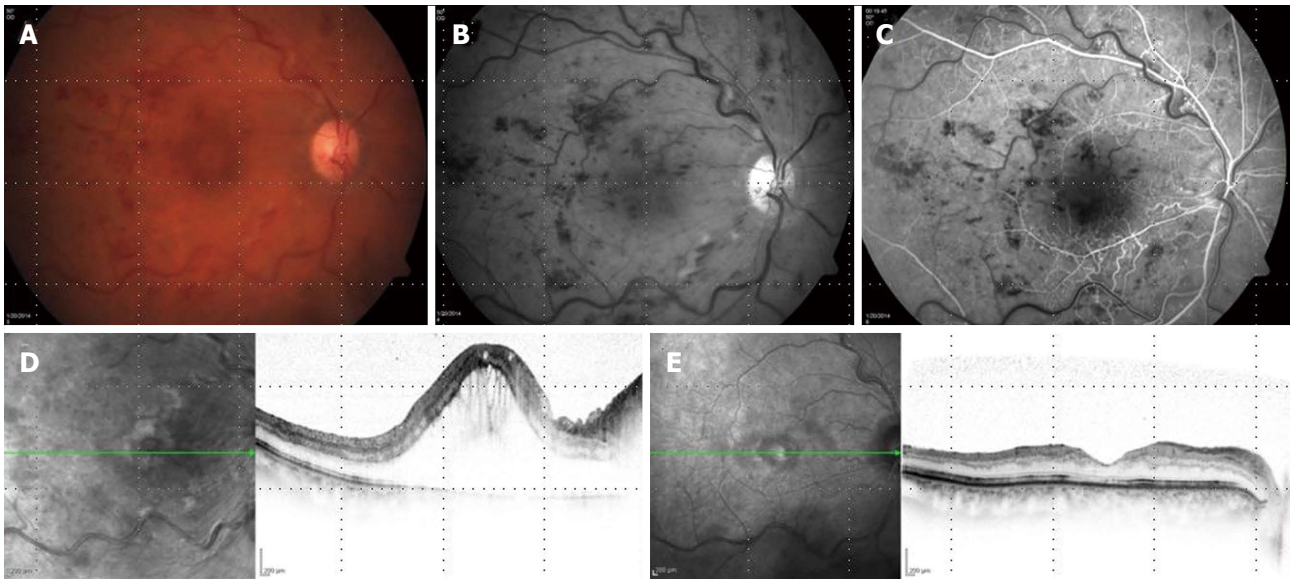

Figure 2 A non-ischemic right eye central retinal vein occlusion with cystoid macular edema in color picture, red free and fluorescein angiography (A-C). A before treatment spectral domain optical coherence tomography (SD-OCT) of the macula (D) showing loss of foveal contour with increased central macular thickness due to many intra-retinal large cystoids spaces and sub-retinal fluid accumulation. (E) SD-OCT 3 mo later, after 3 intravitreal bevacizumab injections, 1 mo apart, showing normal foveal contour with a decrease in retinal thickness to normal and complete resolution of cystoid macular edema and sub-retinal fluid.

that the implant may be considered a first-line choice in the treatment of ME secondary to CRVO.

Ranibizumab is a pan-VEGF blocker (Lucentis; Novartis) which showed effectiveness in patients with ME secondary to CRVO in the CRUISE trial[71]. In the first 6 mo of the study, ranibizumab was injected every month in two doses (0.3 and 0.5 mg) and yielded a VA gain of 12.7 and 14.9 letters, respectively, compared to 0.8 letters gained in the sham injections group. The proportion of patients achieving a ≥ 15 letters VA gain was 47.7% in the 0.5 mg group compared to 16.9% in the sham group. The effect of ranibizumab was noticed as soon as 7 d post first injection with a 9 letter improvement in the treatment group which was significantly better than the sham group[65]. In relation to the anatomical change mean CFT was significantly reduced at 6 mo in 433-452 μm in the treatment groups compared to only 162 μm in the sham group[71].

Following treatment in the first 6 mo, all patients continued in an extension for another 6 mo of monitoring and therapy PRN. The 12 mo results of the study concluded that the VA improvement showed in the first 6 mo could be maintained. Earlier treatment after ME diagnosis may bring a better functional improvement in retinal thickness than delayed therapy.

The recent RETAIN study followed the CRUISE patients in an open-label, single arm, multicenter long-term extension trial[77]. In a mean follow-up of 49.7 mo, 44% had edema resolution (no intraretinal fluid for 6 mo or more after last injection), with 71% receiving their last injection within 2 years of the first one. VA improved in 15 letters or more in 53.1%, with 43.8% having a final VA of 20/40 or better. The CMT remained as it was in the end of the CRUISE trial with a mean of 420 μm reduction.

Ranibizumab is FDA and EU approved for the treatment of ME in patients with CRVO.

Bevacizumab is a pan-VEGF blocker (Avastin; Roche) which is not licensed for intraocular use. A prospective, randomized, double-masked clinical study on Bevacizumab compared to sham in patients with ME secondary to CRVO was conducted on 60 eyes with a 1:1 randomization[108]. At the 6-mo follow-up time 60% of the study group gained ≥ 15 letters compared to only 20% in the sham group. The BCVA improved by 14.1 letters compared to a decrease in 2 letters in the sham group and the decrease in CRT was 426 μm compared to 102 μm. No residual edema was found in 86.7% of the treatment group compared to 20% in the sham group. No rubeosis was developed in the treatment group and no safety concerns were detected.

In a 6 mo extension of the study all patients received Bevacizumab every 6 wk. The percentage of patients with a ≥ 15 letters gain did not change in the primary treatment group, but in the sham group it rose to 33%. The mean VA improved in both groups to 16 letters in the treatment group compared to 4.6 letters in the sham group. In the latter, a further decrease in CRT was noticed to a total reduction of 404 μm. No rubeosis or safety issues were found in both groups in the extension trial[109].

Many other uncontrolled studies have reported that the intravitreal injection of bevacizumab may lead to VA improvement and regression of ME[110,111]. Long term outcomes and safety data is non-conclusive because of the variations in treatment regiments between those studies. Bevacizumab is less expensive than other anti-VEGF treatments making is widely used (Figure 2).

Pegaptanib is a selective anti-VEGF blocker (MACUGEN; Pfizer) which was investigated in a multicenter randomized study as treatment in RVO. Patients with ME

associated with CRVO were randomized to receive either a sham injection or 0.3 mg or 1 mg of pegaptanib sodium. The phase Ⅱ trial showed that 0.3 mg pegaptanib administered every 6 wk caused an improvement in VA of 7 letters, over a 6 mo follow-up[112]. Due to the vast use of bevacizumab and ranibizumab, pegaptanib is not frequently used.

Aflibercept is a VEGF Trap-Eye (Eylea; Regeneron) protein comprising of the second domain of VEGF receptor 1 and the third domain of the VEGF receptor 2 fused to the Fc domain of immunoglobulin G1. Its binding affinity for VEGF is greater than that of either Ranibizumab or Bevacizumab.

Aflibercept was studied in the COPERNICUS which is a 2-year, phase 3, prospective, randomized, double-masked, multi-center study of aflibercept compared to sham injection[88]. Patients were assigned randomly in a 3:2 ratio to receive aflibercept 2 mg or sham injection every 4 wk for a 24 wk period. Between weeks 24 and 52 patients were treated according to specific retreatment criteria based on VA and CRT on OCT. The second year treatment was PRN based.

VA outcome was significantly better in the treatment group with 56.1% of eyes treated achieving a ≥ 15 letter VA improvement compared to 12.3% in the sham group. 93.9% of treated eyes gained 10 letters or more compared to 52.1% in the sham group.

The improvement in VA was seen in the treatment group as soon as 4 wk post first injection. By week 24 treated eyes had a mean improvement of 17 letters compared to a loss of 4 letters in the sham group. BCVA improved steadily from week 4 to week 24 in the treatment group. A sub-group analysis of perfused and non-perfused eyes showed a significant better VA improvement in both groups in the treated eyes.

Reduction in CRT was noticed even after 4 wk with a 457 μm reduction in the treatment group compared to a 144 μm reduction in the sham group. Reduction in CRT was significantly better in treated eyes both in perfused and non-perfused sub-groups.

No progression to NV was seen in the treatment group compared to 6.8% in the sham group. Regarding nonperfusion, at week 12 the proportion was similar whereas at week 24 there was much less non-perfused eyes in the treatment group.

The 1-year results of the COPERNICUS trial[113] were similar. Patients were treated with 2 mg aflibercept as needed (PRN). At week 52, 55.3% of the primary treated group gained ≥ 15 letters in VA compared to only 30.1% in the primary sham group. The mean VA gain was 16.2 letters *vs* 3.8 letters in both groups. No adverse events were noted in the second treatment period.

The improvement in VA was significant in both perfused and non-perfused eyes compared to the sham group even after PRN treatment. Regarding CRT the reduction observed at week 24 in the treatment group was maintained in the PRN regiment. The sham treatment group showed great reduction in CRT during weeks 24-52 and in the end of the 1 year study both groups showed a similar reduction of CRT, around 400 μm.

During a second year follow-up on the COPERNICUS patients VA continued to be superior in the primary treatment group, but CRT reduction which was similar at week 52, continued to be similar at week 100 with a mean of 3 injections for both groups[114].

Another phase 3 randomized, double-masked, multicenter clinical study of aflibercept for CRVO, conducted in Europe, is the GALILEO[89]. The randomization was 3:2 to monthly intravitreal 2 mg aflibercept injections *vs* sham injections.

Results were similar to COPERNICUS with VA improvement of ≥ 15 letters at 6 mo 60.2% in the treatment group compared to 22.1% in the sham group. The mean change was 18 letters compared to 3.3. An important note is that the change between the treatment and sham groups was greater among patients with disease duration of up to 2 mo. The proportion of patients reaching the 15 letter gain endpoint at 6 mo among the treatment group was 70.9% among patients with disease duration of fewer than 2 mo and 50% in patients with disease duration of over 2 mo.

The anatomical outcome was also similar to that of the COPERNICUS with a different of 279 μm between treatment group and sham group in the CRT reduction. No significant ocular or non-ocular adverse events were noticed.

In the second year of the GALILEO study[115] the treatment group continued the 2 mg aflibercept treatment PRN and the sham group continued receiving sham injections. After 52 wk the percentage of patients with at least 15 letters VA improvement was 60.2% in the treatment group compared to 32.4% in the sham group. The VA improvement was of 16.9 letters compared to 3.8 letters and CRT reduction was of 423 μm compared to 219 μm in the sham group. The average in the PRN treatment was 2.5 injections during the second 6 mo.

The drug was found to be safe with no difference found in ocular and non-ocular adverse events between the two groups. Aflibercept is approved both by the FDA and EU for the treatment of ME secondary to CRVO.

Follow-up after the recommended treatment in the initial 6 mo as seen in the above mentioned studies is dependent on the treatment which was initiated for ME (corticosteroids or anti-VEGF). Follow-up is usually advised for up to 2 years, even in cases with no sight-threatening complications. Close monitoring should be held especially to detect conversion to ischemic CRVO and the occurrence or reoccurrence of ME. Development of collaterals of the optic disk or resolution of ME should bring the physician to lower the frequency of follow-up[15].

The recurrence or a persistent ME, diagnosed by means of decreased VA, biomicroscopy and OCT examination, should lead the physician to a decision to reinject. The use of laser photocoagulation is to be suggested for several populations such as non-responders or partially responders, or patients who are non-compliant with multiple injections.

Ischemic CRVO is characterized by a peripheral area

of non perfusion, initially defined in the CVOS Study, as greater than 10 disk diameters, as evaluated by FA, but more recently to a more extensive area as used in the ischemic index method, with the use of wide field retinal imaging[116].

In patients with ischemic CRVO, physician should primarily evaluate and asses both peripheral area of non perfusion and macular perfusion, the presence of ME and the existence of NV.

In a patient with ME, with FA that shows a relatively good perfusion to the macular area, treatment should be as outlined above as for non-ischemic CRVO. In cases where the macula is not perfused, the VA prognosis is very poor, yet immediate treatment with dexamethasone implants is reported to be effective.

In patients with a large non perfusion area, defined as more than 10 disc areas, an early and immediate PRP treatment is strongly suggested as an attempt to prevent the development of ocular NV, associated simultaneously with anti-VEGF intra vitreous injection[7].

In cases with less severe non perfusion, without any neovascularization (including on gonioscopy), scatter laser treatment aimed at the non perfused area may suffice with a very close monitoring and follow-up. Patients who pose a great difficulty to treat are noncompliant patients[31].

Patients with ischemic CRVO and (moderate) area of peripheral ischemia, and no ME nor NV should still be monitored monthly with a VA check, biomicroscopy, OCT and FA. In addition, the iris and corneal angle should be assessed regularly with gonioscopy[29].

Evidence nowadays supports the immediate PRP whenever an anterior segment NV (iris or angle) is found. An anterior segment NV which necessitates treatment is any degree of angle NV and/or iris NV in an area of 2 clock hours[7].

The complete PRP treatment can be carried out in one session or be divided into several sessions. The aim is to treat the retina completely from the periphery to the main vascular arcades. Typically the treatment in done on a slit lamp and consists of 1500-2000 burns (but usually more to 3000), 500 micron each, 0.1 seconds burn, and the space between burns should be 1 burn width. The burns should be in an energy level enough to produce a white burn in the retinal layers. PRP should begin in the inferior quadrants with avoidance of areas with retinal hemorrhages. Repeating treatment can be done whenever anterior segment NV does not regress. Today with the NAVILAS and PASCAL a great degree of accuracy is seen with lesser variations between burn size and a more uniform burn shape[117].

A treatment combination of PRP and anti-VEGF injection has not been tried in a randomized clinical trial, but has been suggested with favourable results in some publications and seems reasonable to attempt, in order to achieve faster regression of anterior segment NV and/or at least limit the evolution, hemorrhage and pain associated to NVG along with IOP reduction[68,118,119]. No indication in the studies mentioned about the timing of bevacizumab injection related to the PRP. Since those were all retrospective studies, the decision regarding timing is reserved to the physician as suited to each patient.

Posterior segment NV of the retina or disc can appear alone or along with anterior segment NV and needs to be actively detected during monitoring due to the risk of vitreous hemorrhages. In cases of posterior segment NV an immediate and non delayed PRP treatment is in order.

Anti-VEGF mono-therapy can only lead to a transient regression of NV[118,119]. No clinical data is available about the efficacy of anti-VEGF mono-therapy to stop NV, but repeated injections may be required to stop NV progression, probably without complete cessation.

A PRP treatment in conjunction with anti-VEGF may prove to be more effective even if still not tried in controlled studies.

In cases of severe NV, especially with vitreous hemorrhage, early PRP is strongly indicated (in all areas accessible). In these cases anti-VEGF injection may help in controlling the development of NV until the resolution of the vitreous hemorrhage allowing better visualization for complete PRP treatment.

In patients with neovascular glaucoma, the intravitreal injection of anti VEGF has been shown regress iris NV and improve the level of obstruction of the angle[120]. Some case series has shown that anti VEGF (Bevacizumab) with PRP induced a faster regression of iris NV than PRP alone[68].

Juvenile CRVO, defined as CRVO in patients under the age of 50, should be differentiated from the traditional CRVO because of a different pathogenesis and clinical course. In some patients the CRVO is related to a systemic disease and patients should be evaluated with a complete systemic workup for the underlying cause.

Juvenile CRVO could often present as benign, well perfused, with limited or no risk factors. Sometimes Juvenile CRVO could be preceded by inflammation as evident by cells in the vitreous[50]. The visual prognosis is usually better than the traditional CRVO, though the risk of complication may become the same, after one or more recurrence.

There is evidence showing that steroids treatment in a systemic administration can hasten the resolution of symptoms. It is custom to treat such patients that have ME with intraocular steroids, especially Ozurdex though little evidence exist.

Strategy of treatment

The randomized controlled studies on RVO have provided much information regarding treatment. An important lesson from those studies is that the duration of the disease before initiation of treatment is an important factor influencing outcome. Treatment is beneficial in any stage of the disease, including in the late stages. It has been shown that in patients with a shorter duration of the disease, the rapid initiation of treatment may be more beneficial and the outcome is better.

Patients with CRVO should be first screened for known risk factors and in case any, the family physician should be notified regarding the disease. The manage-

ment and control of the risk factors mentioned earlier should be fast and aggressive. The patient is evaluated by VA assessment, biomicroscopy, measurements of intra ocular pressure, and OCT. Examining the patient with fluorescein angiography should be done in order to evaluate areas of ischemia in the periphery and the macular area. FA can also evaluate for the existence of ME or NV of the disk or retina. NV of iris or angle should be determined in a gonioscopy examination. Distinguishing the subtype of CRVO should be done according to the extent of ischemia as seen on FA.

In cases of preserved VA of 20/40 and better, observation in a monthly fashion is advised, at least for the first 3 mo. If no sight-threatening complications are detected, the follow-up may be continued every other month for at least 1 year. All follow-up visits should include VA assessment, OCT and biomicroscopy and FA when needed.

In cases of decreased VA of less than 20/40, the physician should assess for the presence of ME. In the presence of ME, treatment should be initiated promptly. First line treatment should be with a properly approved drug, with Ozurdex and re-treatment decision based on the follow-up, or with injections of an anti-VEGF drug every month for 3-6 mo, with additional injections based on the progression of ME. As for BRVO, same considerations should be taken to account in deciding the first line treatment.

In cases of nonperfused CRVO, in the presence of ME, treatment is still warranted, but the prognosis is poor. First line treatment should be with a properly approved drug, with Ozurdex and re-treatment decision based on the follow-up, or with injections of an anti-VEGF drug every month for 3-6 mo, with additional injections based on the progression of ME. The addition of PRP treatment directed at areas of non-perfusion should also be considered by the physician in order to prevent NV. In cases of macular ischemia the prognosis for VA improvement is generally poor even in cases of prompt treatment and ME resolution. As mentioned before, same considerations should be taken in deciding the first line treatment.

At any visit during follow-up, the identification of neovascularization anywhere in the posterior or anterior chamber should prompt the treatment with scatter laser photocoagulation to the ischemic areas, guided by FA. The addition of an intravitreal drug, steroids or anti-VEGF should be considered, although not proven in the trials available.

GENERAL ASPECTS OF MEDICAL TREATMENT

The treatment of RVO patients has a long course. Multiple visits with examinations and intravitreal injections are the main course of action today. The common use of intravitreal injections is a burden on the patient and may cause further morbidity.

When treating patients with Ozurdex, a close monitoring should be advised and a reinjection should be done in cases of VA deterioration due to recurrence of ME usually after 5-6 mo.

When treating with anti-VEGF treatments, usually initiating treatment with Ranibizumab or Bevacizumab, two main methods can be employed. The first method is the monthly injection of anti-VEGF for the first 3 mo followed by a PRN approach. The patient is examined every month for the first 6 mo followed by an exam every other month for the rest of the first year. Injection is carried out only if recurrence is noted by VA worsening and ME presence on OCT.

The second method is rising among practitioners and is the treat and extend. After the primary 3 injections the patient is being injected in every visit until macula is dry. Since achieving a dry macula, the patient is evaluated by VA exam, biomicroscopy and OCT and is being injected in every visit. If macula is considered dry in the examination, the follow-up time increases by 2 wk and so on after every visit with no ME. If ME is presence in one of the visits, the follow-up decreases by 2 wk. This method allows the practitioner to discover the precise amount of time between injections for the individual patient with close enough monitoring and less injections than other methods.

In a review of intravitreal therapy for ME secondary to RVO, all anti-VEGF treatments showed a better improvement in VA than steroid treatment at month 12. The greatest gain in VA in CRVO patients after 12 mo was shown with the use of aflibercept and Bevacizumab with a gain of 16 letters compared to Ranibizumab with 14 letters improvement. In BRVO patients Ranibizumab showed to bring the greatest gain of 18.3 letters compared to Bevacizumab with 15 letter gain[121].

The use of longer-acting dexamethasone implant (Ozurdex) in conjunction with anti-VEGF therapy was examined in a small prospective, non comparative trial. VA gains were achieved up to 6 mo 14 letters, with 29% showing a $\geqslant$ 15 letters gain. CMT decreased by 200 μm. The mean time to re-treatment was 125.9 d, but it was unnecessary in 18.6% of patients[122]. The study demonstrated the synergy between both drugs with increasing VA and prolonging time between injections compared to each drug alone.

A recent prospective study on the effects of multiple anti-VEGF injections on IOP resulted in the conclusion that multiple injections were not found to be a risk factor for elevation in intra ocular pressure[123].

SURGICAL APPROACHES IN RVO TREATMENT

Few surgical approaches are utilized today in the treatment of RVO. These treatments target the vein occlusion itself or the macular edema. Most surgical treatments are abandoned and not in use nowadays due to the new and

effective pharmacological treatments.

Radial optic neurotomy

Radial optic neurotomy (RON) was used in the past for the treatment of CRVO[124]. However the benefit effect has not been studied enough and is still questionable[125]. In most places this technique is not used.

The surgical approach relied on the assumption that the radial incision will decompress the pressure on the vein.

Optic neuropathy leads to the development of optociliary venous anastamosis (or retino-choroidal shunts), which increase the retinal venous outflow[126-130]. Incisions are made on the nasal side of the optic nerve, radial to the optic nerve itself and parallel to the nerve fiber layer. A study conducted on 11 CRVO patients, 73% had improved vision with an average gain of 5 lines.

Hayreh[125] raised the concerns about the location of the incision close to the central retinal artery which can cause optic nerve head ischemia and complete vision loss. RON was associated with some serious complications in more than 71% including damaging central retinal artery, central retinal vein, optic nerve fiber, globe perforation, retinal detachment, cataract, choroidal neovascularization and anterior segment neovascularization[124,130,131].

Patient selection is important with more benefit for patients with CRVO of under 90 d and a pronounced peripapillary swelling[127].

RON is a very questionable procedure with controversial benefits and serious possible adverse events. Nowadays it is generally abandoned except for selected cases.

Chorioretinal venous anastamosis

In this procedure, in order to bypass the occluded vein, a shunt is made between a retinal vein and the choroid. This procedure creates another route to for the retinal outflow and relieves the obstruction. The anastamosis can be induced by laser or surgery[132-134].

A successful anastamosis was first reported in 33% with various degrees of VA improvement[132]. However complications were described in several studies and included posterior vitreous detachment, hemorrhages, retinal fibrosis, NV of the choroid, retinal ischemia and retinal detachment[129,132,134].

The anastamosis, in all the techniques, does not reperfuse areas of nonperfusion, however it leads to better perfusion of the perifoveal and parafoveal areas, reduce ischemia, increase venous return, decrease macular edema and improve VA.

This technique also is generally abandoned and not in use.

Pars plana vitrectomy

Pars plana vitrectomy (PPV) with ILM peeling can bring resolution of retinal damage and ME in CRVO patients[135-137]. The exact mechanism is unknown but 70% of RVO patients have shown decreases retinal thickness and increased VA after this operation[136,137], with an effect of up to 5 years[138].

This procedure is reserved to patients where other treatments, especially intravitreal injection have failed in achieving improvement, and the blood perfusion of the macula is sufficient to allows improvement of VA[136,139-146].

Successful results after PPV without ILM peeling have been described. PPV itself removes VEGF and other mediators from the vitreous and allows better oxygenation of the retina[147]. PPV with gas/air tamponade for ME showed a statistically significant improvement in BRVO patients[148,149]. In CRVO patients the benefit is questionable[150]. This procedure can also be combined with intravitreal injection of steroids which permits a more rapid and lasting action.

PPV is hardly used in most clinics for the purpose of RVO treatment.

Injection of t-PA through retinal vein cannulation

A need for direct tissue type plasminogen activator (t-PA) injection had followed some unsuccessful attempts to treat RVO patients with t-PA systemically or intravitrealy[151]. The surgery includes PPV with removal of the posterior hyaloid, and injection of 200 μg/mL t-PA to the optic nerve head through a cannulation of a peripapillary retinal vein.

This technique is favourable because: (1) t-PA is delivered directly to the site; (2) Allows the visualization of the drug reaching the thrombus; (3) Very small dose provides sufficient concentration near the thrombus; and (4) The injection can dislodge the thrombus and induce dilatation of the central retinal vein. VA was increased in about 50% of the CRVO patients. However in another study the results were poor with high complication rate[152].

This technique can cause some complications like vitreous hemorrhage, retinal tears or detachment, NVG formation, endophthalmitis and phthisis bulbi. Only retrospective data is at hand. This technique is also hardly ever used.

Arteriovenous sheathotomy

The surgical procedure, first introduces in 1988, included PPV with posterior hyaloids detachment and the opening of the adventitial sheath at the location of the arteriovenous block in BRVO patients and resulted in improved visual acuity[153]. The endpoint was the separation of arteriole from the venule. More recently, better results were seen using a bimanual technique followed by intravitreal recombinant t-PA[13].

Most studies regarding this surgical procedure failed to show an outcome justifying the risk of the surgery in BRVO patients[127,154]. In a study comparing this technique with intravitreal triamcinolone acetonide in BRVO patients, authors showed similar anatomical and functional improvement after 6 mo[155].

A recent match-control study compared 45 eyes with BRVO who underwent arteriovenous sheathotomy to 45 naïve eyes with BRVO. Improvement in VA was 0.42 logMAR in the treatment group compared to 0.22 logMAR in the control group. The mean postoperative CMT was

significantly thinner than the control group at 1 mo, but not at 3, 6 and 12 mo[156]. This technique is not actually utilized in most clinics.

Endovascular cannulation with a microneedle

This is a new surgical treatment in which a retinal endovascular cannulation using a microneedle is done in eyes with CRVO, in order to flush the thrombus out of the central retinal vein and through the lamina cribrosa. Seventy-five percent of patients had a VA improvement of 15 letters or more 24 wk post surgery, mean BCVA improved by 16.3 letters and CFT decreased by 271 μm. No adverse events were noted[157].

This technique is not actually utilized in most clinics.

PREVENTION

The prevention of recurrent RVO in the same eye, or fellow eye involvement has been discussed in several studies without any benefit shown, including in the use of anti-aggregates or anticoagulants[54,158].

The only available data about recurrence supports the medical treatment of underlying cardiovascular and other systemic and ocular risk factors as mentioned above.

BURDON OF RVO

Studies estimate that there are about 500 new RVO patients per million population[38], which can be divided to 85% BRVO and 15% CRVO.

Despite the large numbers, only 40%-50% require intervention, as the others have good vision not necessitating ophthalmological intervention[7,38].

CONCLUSION

RVO is a common disease and responsible for a large percentage of ocular morbidity and decreased vision. The modern imaging techniques allow fast diagnosis with detection of the ischemic forms if presence, and the complications, mainly macular edema with OCT and neovascularisation with biomicroscopy and gonioscopy. Studies have shown that fast diagnosis and treatment initiation brings better outcome in terms of visual acuity.

The treatment modalities have evolved over the last few years with the introduction of Ozurdex, anti-VEGF treatments including bevacizumab and ranibizumab and the new and promising aflibercept. The diversity allows the physician to switch between drugs according to patients characteristics and reaction to treatment. The recent extension studies for the large trials suggest benefit of both CS and anti-VEGF treatment after 36-48 mo. The ongoing COMO study will shed more light on the first choice for treatment in the comparison between Ozurdex and ranibizumab.

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REVIEW

What is new in central serous chorioretinopathy?

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Abstract

Central serous chorioretinopathy (CSCR) is considered a benign, self-limiting disease. However, as many as third of the patients have recurrent episodes or chronic disease that may cause significant functional impairment. New diagnostic tools and new treatment modalities are emerging in order to improve the functional outcomes of these patients. Spectral domain optical coherence tomography (SD-OCT) has the ability to image individual layers of the retina and choroid. SD-OCT images in CSCR patients have demonstrated increased subfoveal thickness measurements, high reflective deposits in areas of subretinal precipitates and changes in the Retinal pigment epithelium layers of the asymptomatic eyes of patients with supposedly unilateral CSCR. A positive correlation was found between the level of distribution to the layer of inner segment/outer segment junction of the photoreceptors and the visual impairment. Fundus autoflouresence images show a wide variety during different stages of the disease in CSCR patients. Minimal abnormalities during the early stages are followed by hyperautofluoresence in the detached area in later stages, often in a manner of inferior gravitation and at the borders of the detachments. The chronic phase is characterized by varying degrees of atrophy and areas of decreased autofluorescence surrounding areas of chronic leaks. These changes help differentiate an active disease from an inactive state. Multifocal electroretinography (mfERG) has the ability to demonstrate a persistent depression despite the resolution of subretinal detachments. It is therefore being investigated as a follow up tool for patients with chronic CSCR. An excellent correlation was found between changes in mfERG and visual function. Macular microperimetry, measuring retinal sensitivity within the central visual field, is intended to compensate for the underestimation of visual impairment in patients with macular diseases. Reduced retinal sensitivity was found in areas of previous subretinal fluids in CSCR patients. The device can also serve as a follow up tool in these patients. Regarding treatment in CSCR patients, focal argon laser photocoagulation treatment may be applied to small extrafoveal leaks. However, the main purpose of this treatment is to shorten disease duration, with no advantage over observation regarding final visual outcome, rate of progression to chronic CSCR or number of recurrences. Photodynamic therapy (PDT) with verteporfin has been shown to completely resolve serous detachment in 60%-80% of patients and to have a partial affect in the remaining patients. Reduced-fluence treatment is replacing full-fluence therapy in order to minimize side effects with no accompanying reduced effectiveness. Visual acuity is also improved following reduced-fluence PDT compared to placebo. It has also been found that patients with intense hyperfluorescence are more likely to show resolution of accumulating fluid compared to patients with mild or no leakage observed on indocyanine-green angiography prior to treatment. Regarding newer treatment modalities, intravitreal injections of anti-vascular endothelial growth factor agents have a limited effect in patients with CSCR. Recent reports have not demonstrated an advantage for this treatment in regards to anatomic and functional outcome. Micropulse diode laser was not proven to be safer or more effective than argon laser or PDT. Corticosteroid antagonists, not tested in controlled trials, may have a beneficial effect in patients with CSCR. Aspirin may also play a role in treating these patients, with rapid recovery of visual acuity and reduced number of recurrences observed. In

conclusion, imaging is evolving rapidly while the clinical implications of these new imaging modalities are less clear. Large randomized trials investigating different treatment modalities are still lacking.

Key words: Central serous chorioretinopathy; Optical coherence tomography; Fundus autoflouresence; Multifocal electroretinography; Macular microperimetry

Core tip: (1) New diagnostic tools and therapies may improve the prognosis of patients with chronic or recurrent central serous chorioretinopathy; (2) Changes in fundus autoflouresence images help differentiate an active disease from an inactive state; (3) Multifocal electroretinography and macular microperimetry may serve as follow up tools due to their ability to measure macular visual function; (4) Focal argon laser photocoagulation shortens disease duration but does not affect final prognosis; (5) Reduced-fluence photodynamic therapy improves visual acuity and resolves serous detachments; and (6) The role of anti-vascular endothelial growth factor agents, micropulse diode laser, corticosteroid antagonists, aspirin, anti-viral or Helicobacter pylori treatment is still being investigated.

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INTRODUCTION

Central serous chorioretinopathy (CSCR) was first described by Albrecht von Graefe in 1866 as a relapsing central luetic retinitis[1]. The various terms later used to describe the disease, including the current acceptable term CSCR first used by Gass[2] in 1967, have omitted the relapsing characteristic from the term. However, relapsing serous detachments of the neurosensory retina are known to occur in as many as third of the patients[3]. Moreover, the recurrent and chronic nature of CSCR may result in severe and irreversible visual loss in these patients[4]. Therefore, in order to improve patients outcome, there is an ongoing search for new diagnostic tools, shedding more light on disease pathophysiology, and for new treatments and different treatment protocols.

PATHOPHYSIOLOGY

The typical presentation of CSCR is serous detachment of the neurosensory retina, but the source of the accumulating subretinal fluid is still not completely understood[2-13]. Retinal pigment epithelium (RPE) dysfunction has been hypothesized as the primary pathologic mechanism in CSCR, in part due to images obtained using fluorescein angiography (FA)[4-6]. These images show characteristic single or multiple leaks from the RPE, implicating the RPE as a major factor in the pathophysiology, as can be seen in Figure 1. However, different investigative tools led investigators to challenge this hypothesis. According to some reports, the choroid seems to be primarily affected, with the retinal changes seen with FA representing a later stage in the mechanism of the disease progression[7].

In order to further understand the role of the choroid in the disease, indocyanine-green angiography (ICGA) images were investigated. The congestion and dilatation of choroidal capillaries and veins, the choroidal staining and the leakage into the interstitial space all prove the choroid plays a major role in the accumulation of fluid in CSCR[12,13]. These changes in ICGA images are demonstrated in Figure 2. However, ICGA was found to have some limitations as a tool for diagnosis and follow up of patients. Previous studies on cross-sectional optical coherence tomography (OCT) images of eyes with chronic CSCR reported increased choroidal thickness observed, with no corresponding hyperflouresence observed on ICGA[14]. Moreover, ICGA gives a 2-dimensional scans, which means that all choroidal layers overlap in the angiogram.

NEW INSIGHTS ON PATHOPHYSIOLOGY FROM NEW IMAGING AND EXAMINATION MODALITIES

Spectral domain optical coherence tomography

The introduction of spectral domain optical coherence tomography (SD-OCT) as a more accurate imaging tool, with its ability to characterize individual layers of the retina and choroid and its noninvasive characteristic, has led to important observations regarding CSCR. The subfoveal thickness was found to be increased by 50%-80% in CSCR patients compared to normal eyes in different reports, when measured by enhanced depth imaging OCT[14-17].

Another measurement that can be performed with SD-OCT is the thickness of the outer nuclear layer (ONL). In one study, ONL thickness was found to be correlated with visual acuity in patients with resolving CSCR[18]. In that study, the mean ONL thickness measured in patients with resolved CSC was 74.6 μm in patients with visual acuity worse than 20/20 compared to 103 μm in patients with visual acuity of 20/20 or better[18]. That same group of researchers also showed elongation of photoreceptors outer segments and decreased thickness of the outer nuclear layer in CSCR, as a possible sign for photoreceptors apoptosis[19].

SD-OCT has also shed some light on the multiple, dot-like, yellow precipitates and subretinal yellow material within the area of a serous retinal detachment in patients with CSCR. These deposits correlate with high reflective deposits on SD-OCT[20,21] (Figure 3). Different hypothesis regarding these substances has been proposed, including the accumulation of shed photoreceptor outer segments, fibrin or lipids, or macrophages clearing the subretinal

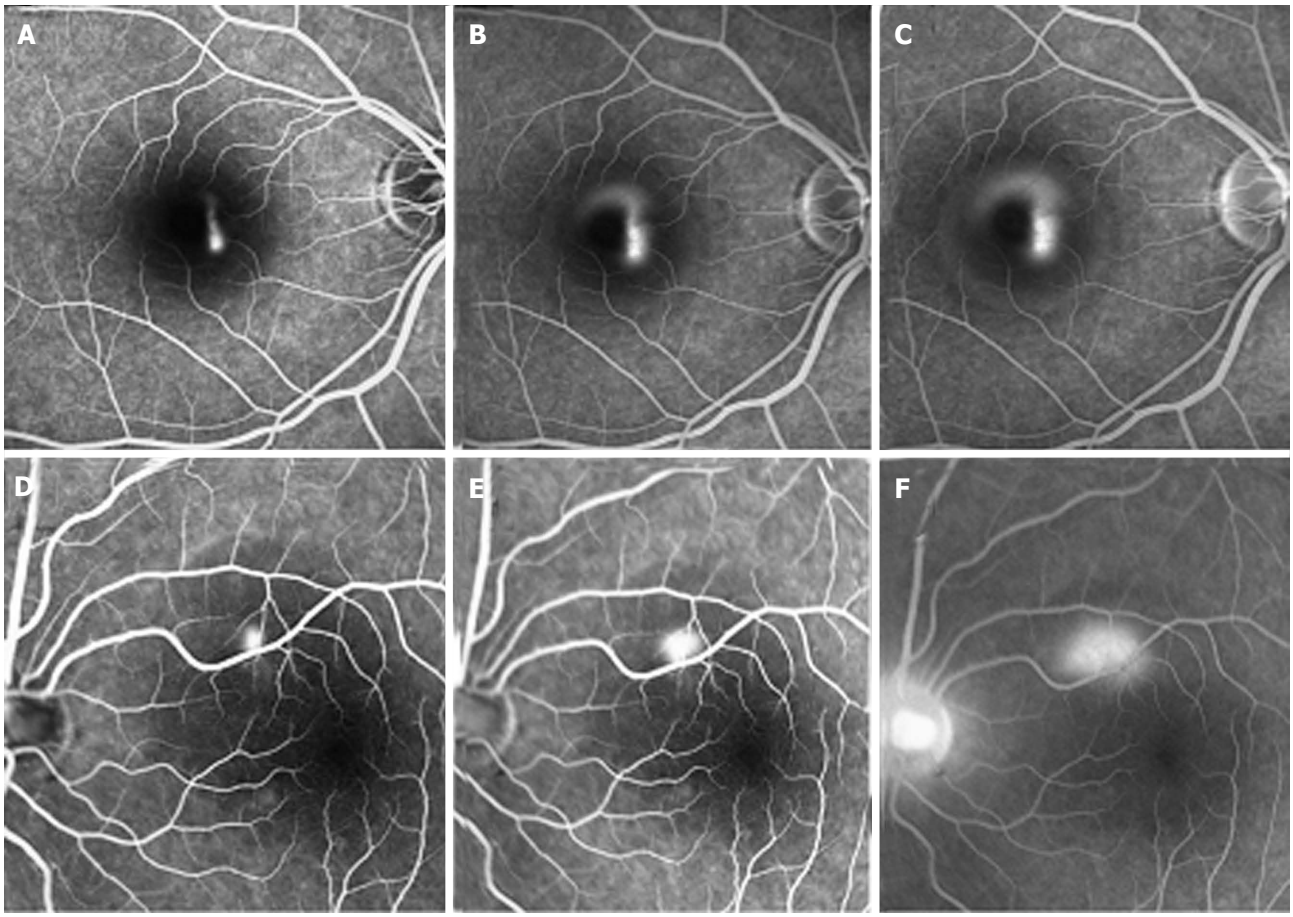

Figure 1 Two different patterns of hyperfluorescent dye leakage on fluorescein angiogram in acute central serous chorioretinopathy; Smokestack pattern of leakage (A, B and C) and inkblot pattern of dye leakage (D, E and F).

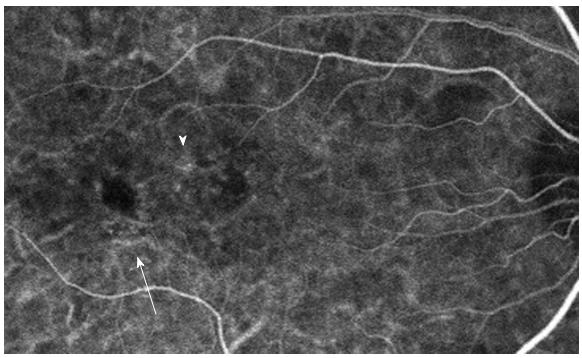

Figure 2 Indocyanine green angiography in a patient with chronic central serous chorioretinopathy. Note congestion and dilatation of choroidal capillaries and veins (arrow) and choroidal staining (arrowhead).

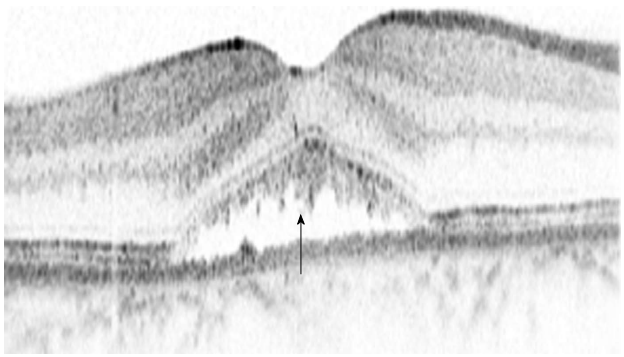

Figure 3 Spectral domain optical coherence tomography of acute central serous chorioretinopathy. Note high reflective subretinal deposits within the area of a serous retinal detachment (arrow).

space. However, the exact nature of these deposits and their origin is yet to be determined[21].

The bilateral nature of CSCR was also demonstrated by SD-OCT, even in eyes with supposedly unilateral disease[22]. Changes in the RPE cells layer has been previously shown in patients with CSCR, specifically around areas of a demonstrated leakage on FA[23]. This study investigated these RPE changes in the asymptomatic eyes of patients with CSCR in the other eye, using 3 dimensional single-layer RPE analyses. Presence of RPE bumps was observed in 94% of eyes and pigment epithelium detachment (PED) in 11.8% of eyes, compared to 8% of eyes with RPE bumps and no PED observed in normal control eyes[23].

Special attention has been addressed to the layer of inner segment/outer segment (IS/OS) junction in different retinal disorders. The level of disruption to this layer in different retinal disorders has an excellent correlation with visual acuity[24-27]. That correlation is also maintained in patients with CSCR[18,28-30]. The length of IS/OS dis-

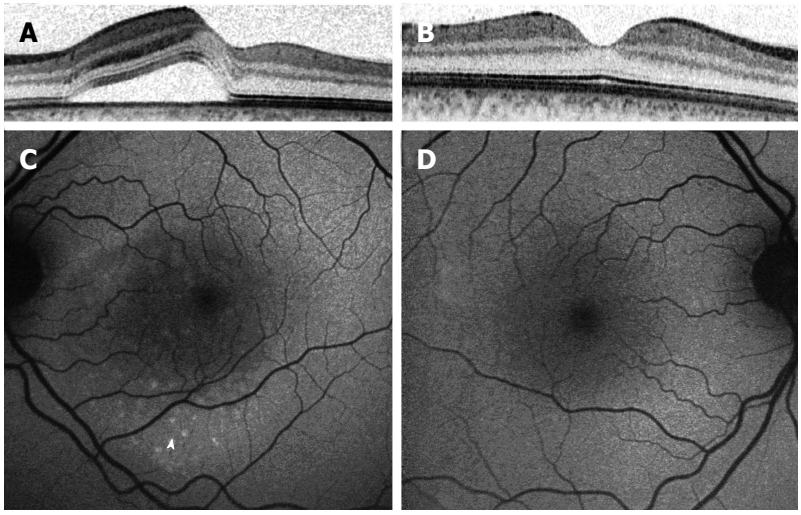

Figure 4 Imaging of a 38-year-old patient with central serous chorioretinopathy, one month following the beginning of his symptoms. Comparison of left (A) and right (B) eyes imaged with spectral domain optical coherence tomography shows a serous retinal detachment in his left eye. Minimal changes are seen with fundus autofluorescence imaging (C), consisting of a granular pattern of increased autofluorescence in the area of retinal detachment (arrowhead), compared to images of the right eye (D).

ruption, loss of foveal IS/OS and the level of integrity of the external limiting membrane layer were also found to be significantly correlated with visual acuity[31].

A newer generation of SD-OCT, swept-source OCT (SS-OCT), has also been investigated in patients with CSCR[32,33]. Ferrara *et al*[32] investigated the images of 15 eyes with chronic CSCR using SS-OCT. They documented PEDs in all eyes, as well as morphologic changes in the choroid underneath observed RPE changes and beyond these changes. They also observed focal and diffuse vascular dilation at the level of the choriocapillaris in half of the enrolled eyes, and at the level of Sattler's and Haller's layers in all eyes[32].

Fundus autoflouresence

Fundus autoflouresence (FAF) images were also shown to have an added value in the understanding of CSCR pathophysiology. Images of patients through different stages of the disease show a variety of autoflouresence phenomena, implying an ongoing damage to the RPE and photoreceptors. While Patients imaged within the first month following diagnosis have minimal abnormalities seen in their FAF photography (Figure 4), the next months are characterized by an increased hyperautofluorescent in the detached area of retina[34-36]. Some hyperautoflouresence appears as a granulated process, in correspondence to pinpoint subretinal precipitates[37]. The material often gravitates inferiorly or is shown to be collected in deposits at the border of the detachment[34]. These patterns are demonstrated in Figure 5. After resolution of subretinal fluid, the hyperautofluorescence of the fundus abates, suggesting that the accumulated material could be cleared with time. The chronic phase of the disease is characterized by varying degrees of atrophy, including areas of geographic atrophy and areas within fluid tracts descending inferiorly[34] (Figure 6). Areas of chronic leaks can have decreased autofluorescence surrounding them. These areas of hypoautofluorescence appear to expand in size with increasing chronicity of the disease[38]. In chronic CSCR eyes, inactive disease can be differentiated from an active disease by the lack of hyperautoflouresence, with only the atrophic component remaining as areas of hypo-autofluorescence[34] (Figure 7).

Multifocal electroretinography

The main advantage of multifocal electroretinography (mfERG) is the ability to demonstrate a persistent depression despite the resolution of the accumulating subretinal fluids. Hence, it has been investigated as a follow up tool for patients with chronic or recurrent CSCR as well as for examination of the seemingly healthy fellow eye[39]. It has been argued whether the pathologic findings in mfERG correspond with and are limited to the clinically observed areas of detachments or extend beyond these areas[39-41]. Excellent correlation was observed between changes in mfERG and function[42]. In a cross-sectional observational study by Lai and colleagues on 45 eyes with acute CSCR, it has been demonstrated that despite the fact that the outer retinal dysfunction is mostly localized to the central macula, a more widespread impairment in the more peripheral macula exists in the inner layers of the retina[43].

Macular microperimetry

Visual function evaluated only by the measurement of visual acuity may underestimate the level of impairment in patients with macular diseases[44-49]. Macular microperimetry was designed to detect more subtle defects in visual function in these patients by measuring retinal sensitivity within the central visual field[50,51]. The device can also serve as a follow up tool due to its image-registration facility. Reduced retinal sensitivity is observed in areas with previous subretinal fluids[28]. This reduced sensitivity also corresponds with RPE irregularities found on OCT[52].

NEW INSIGHTS ON TREATMENT MODALITIES FOR PATIENTS WITH CSCR

Acute CSCR is a self-limited disease in the majority of cases, with good final visual outcomes. The common management of acute CSCR still remains observation

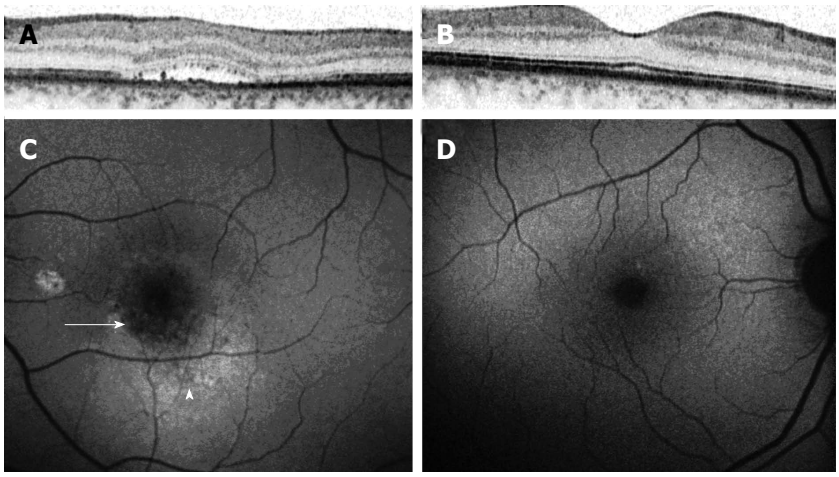

Figure 5 A 36-year-old patient with central serous chorioretinopathy, six months following the beginning of his symptoms. Comparison of left (A) and right (B) eyes imaged with spectral domain optical coherence tomography shows a serous retinal detachment in his left eye. In fundus autofluorescence imaging of the left eye (C) note the hyperautofluorescent in the detached area (arrow) beginning to form the manner of inferior gravitation (arrowhead), compared to images of the right eye (D).

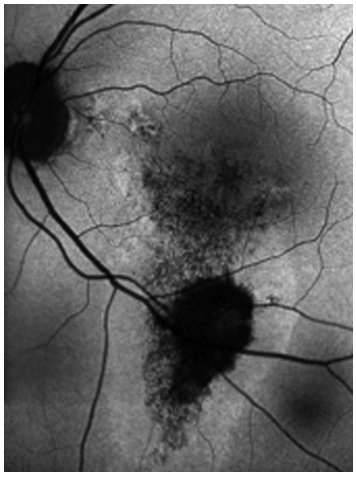

Figure 6 Fundus autofluorescence of a patient with chronic central serous chorioretinopathy showing inferior gravitational tracks and areas of decreased autofluorescence corresponding to areas of atrophy.

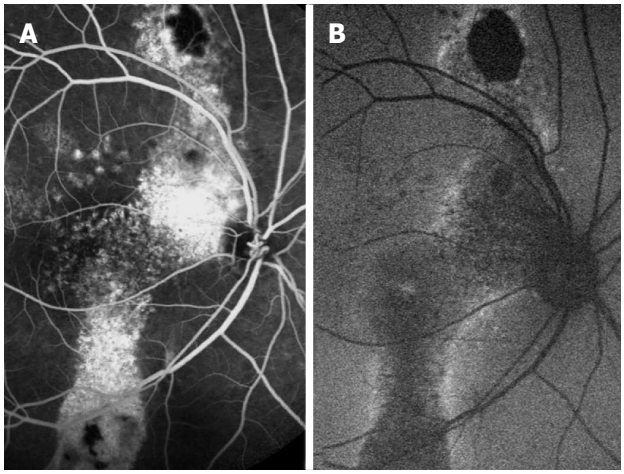

Figure 7 Chronic central serous chorioretinopathy; imaging from the same eye. Fluorescein angiography (A) with extensive hyperfluorescent areas, corresponding to areas of atrophy, seen as areas of decreased autofluorescence (B). Note the inferior gravitation pattern in both images.

and risk modification, with the exception of certain indications prompting immediate medical management. The common indications for the initiation of treatment are non-resolved subretinal fluid for 3 mo, decreased visual acuity from CSCR in the fellow eye or the need for immediate visual acuity rehabilitation. However, chronic CSCR as well as frequent recurrences of serous detachments may lead to RPE atrophy and other changes in the neurosensory retina leaving the patient with impairment of visual function[53]. Therefore, earlier treatment in selected patients may improve the final outcome and even prevent further damage.

Focal argon laser photocoagulation

Treatment with argon laser may be applied to small extrafoveal leaks on FA, mainly to shorten disease duration. Long term follow up results for argon laser treatment demonstrate no advantage over observation regarding final visual outcome, rate of progression to chronic CSCR or number of recurrences[54-56]. The main disadvantages of this treatment are the limited ability to affect final prognosis, the need for specific extrafoveal lesions to perform the procedure and possible side effects including the growth of new choroidal neovascularization (CNV)[56].

Photodynamic therapy with verteporfin

Standard dose photodynamic therapy (PDT) with injection of verteporfin has been shown to completely resolve serous detachment in 60%-80% of patients and to have a partial affect in the remaining patients[57-60]. However, serious side effects such as sudden visual loss, new CNV and atrophy of the RPE, had led to reduced-fluence treatment development[61,62].

Randomized and non-randomized trials on reduced-fluence PDT have found this treatment to be as effective as full-fluence therapy in regards to fluid resolution and functional outcome. Chan and colleagues performed a double masked randomized controlled trial on 63 eyes with acute CSCR treated with either half-dose PDT or placebo[63]. One year following treatment, approximately 95% of eyes in the PDT group compared to 58% in the placebo group had no subretinal fluid on OCT. Visual acuity at one year follow up was improved or stabilized in all patients in the PDT group compared to approximately 79% of patients in the placebo group[63]. Wu and

colleagues observed an improvement in mfERG in 24 eyes with acute CSCR, compared with 10 eyes in placebo group[64]. New imaging modalities, such as microperimetry, demonstrated the efficacy of PDT, beyond improvement in visual acuity[65-67].

There is still an ongoing search for the best way to reduce PDT dose, either by decreasing the laser therapy time, lowering the laser energy, altering the time interval between injections of verteporfin or lowering the dose of verteporfin. Zhao *et al*[68] conducted a research testing different doses of verteporfin for CSCR patients. Their conclusion was that 30% of the standard dose was optimal both for achieving fluid resolution and for avoiding adverse events[68].

In order to compare half-dose PDT to argon laser, Lim and colleagues prospectively assessed 26 eyes with CSCR[69]. Their results showed an earlier anatomic and functional resolution after treatment with half-dose PDT compared to laser. These differences, however, were no longer noted 3 mo following treatment[69].

Clinical response for this treatment has been linked to the level of hyperfluorescence observed on ICGA[70]. Patients with intense hyperfluorescence were more likely to show resolution of the serous detachment compared to patients with mild or no leaks observed on ICGA prior to treatment[70]. A recent report by Kim *et al*[71] evaluated the efficacy of half-dose PDT targeting the focal leakage point on FA for acute CSCR. In this retrospective trial, all 10 eyes treated in this manner had complete resolution of subretinal fluid compared to 27.3% of eyes receiving no treatment. These differences were minimized at 12 mo follow up; with 90% of PDT group and 63.6% of observation group showing no subretinal fluid. No differences were noted in final visual acuity or recurrence rates between the two groups[71]. Therefore, this treatment protocol may serve as a substitute for focal argon laser treatment for hastening absorption of subretinal fluid.

Other treatment modalities

Anti-vascular endothelial growth factor agents: Intravitreal injections of anti-vascular endothelial growth factor (VEGF) agents have dramatically changed the anatomical and functional prognosis of patients with retinal and choroidal diseases[72-74]. However, in patients with CSCR, improvement in prognosis following injections is more questionable, and anti-VEGF agents are not considered first line treatment. Despite the fact that VEGF levels were not found to be elevated in the aqueous humor of eyes with CSCR, many uncontrolled studies reported favorable results for anti-VEGF agents[75-84]. The largest series to date published by Lim *et al*[75] included 40 eyes in a prospective interventional case series. In their study, following one or two injections, 82.5% of patients achieved resolution of subretinal fluid at 4 mo follow up. However, they only included patients with acute CSCR, known to have a better prognosis; with no comparison arm for this study, and a relatively short follow up period[75].

A recent prospective, randomized study by Bae and colleagues compared ranibizumab injections to low-fluence PDT in 16 eyes with chronic CSCR[85]. Their conclusion was that the effect of ranibizumab was not promising compared with that of low-fluence PDT, in terms of anatomic outcomes. An important observation was that 50% of eyes in the ranibizumab group accomplished complete resolution only after they underwent additional low-fluence PDT[85].

A meta-analysis, conducted by Chung *et al*[86], identified four clinical controlled studies evaluating the effects of intravitreal bevacizumab injection in CSCR. In their data analysis, no significant differences in BCVA or central macular thickness (CMT) were found at 6 mo after injection between the bevacizumab group and the observation group. Another important issue they raised was that no report assessed severe complications or side effects of these intravitreal injections in patients with CSCR[86].

Micropulse diode laser

The main advantage of diode laser over argon laser is deeper penetration, reaching the choroid, mainly implicated as the pathologic origin of the subretinal fluid[87]. That sets the theoretical basis for the trials investigating the role of this laser in CSCR, as an attractive replacement for focal argon laser treatment. Verma and colleagues conducted a small randomized trial comparing the results of these two types of lasers in patients with acute CSCR[88]. Despite the fact that visual acuity was better in the diode laser treatment group 4 wk following the procedure, this difference was no longer observed 4 wk later[88]. Micropulse diode laser is considered less damaging to the RPE and photoreceptors, by applying short multiple pulses of energy instead of continuous energy. However, unlike the argon laser, the micropulse diode laser is less widely available and does not cause retinal bleaching guiding the operator when to stop laser application. In addition, micropulse diode laser was not proven to be safer or more effective than argon laser or PDT, and still requires a focal leak as seen on FA to guide treatment[89]. Therefore, the role of this laser as a substitute for conventional laser is still questionable.

Corticosteroid antagonists

The basis for corticosteroid antagonists administration for CSCR is the association found between the development of the disease and endogenous hypercortisolism (Cushing's syndrome)[90]. The hypothesis is that if this association exists with other hypercortisolemic states, than blocking the effect of corticosteroids may play a role in treating CSCR[91]. That hypothesis is further supported by the elevated serum cortisol levels commonly found in patients with CSCR[92-94]. The proposed medications, including ketoconazole, mifepristone (RU486), finasteride, rifampin, and anti-adrenergics, have not been tested in randomized, controlled trials.

Ketoconazole, an adrenocorticoid agent, has been investigated by two groups for the treatment of CSCR. In a prospective, case control study, Golshahi and colleagues

treated 15 patients with new onset subretinal fluid with 200 mg of ketoconazole per day for 4 wk[95]. No statistically significant benefit was found for that dosage[95]. An increased dose of 600 mg per day for 4 wk was later adminstered by Meyerle *et al*[96]. The results of this prospective, uncontrolled pilot study on 5 patients with chronic CSCR showed reduced serum cortisol levels, stable visual acuity, and anatomic improvement at 8 wk. They suggested larger, controlled trials to test the efficiency of ketoconazole in CSC patients[96].

Nielsen and colleagues treated 16 chronic CSCR patients with mifepristone (RU486), an active anti-glucocorticosteroid and anti-progesterone agent[97]. Favorable response was seen, with seven subjects gaining five or more letters of vision and seven subjects with improved OCT findings. Despite the fact that treatment was well tolerated without serious adverse effects in these patients, main obstetric concerns regarding this drug still limit its use[97].

Anti-adrenic agents, proposed to cause reduction of the adrenergic drive induced by stress, were also investigated for the treatment of CSCR. In his monkey model for experimental CSCR, Yoshioka suggested that inhibition of adrenergic receptors, particularly alpha receptors, may be beneficial[98]. Later studies investigating beta-blocking agents have shown partial improvement in CSCR patients, with no difference found between selective and non-selective agents[99-102]. However, none of the studies were controlled or randomized, and significant systemic side effects further limit the use of these agents.

Aspirin

The hypothesis that hypercoagulability plays a role in the pathogenesis of CSCR was based on a previous work showing increased levels of plasminogen activator inhibitor in patients with CSCR, compared to controls[103,104]. Caccavale and colleagues treated 107 CSCR patients with 100 mg acetyl salicylic acid (aspirin) once daily for one month and then every other day for five months[105]. A rapid recovery of visual acuity was observed after the first week of therapy, with low recurrence rate[105].

Anti-bacterial and anti-viral therapy

The hypothesis that an inflammatory damaging process has a role in the pathogenesis of CSCR is based on the characteristic of the disease. The proceeding stress as well the recurrent episodes of the disease have led investigators to consider a viral or a bacterial etiology.

The most investigated infectious association to CSCR is between the disease and *Helicobacter pylori* (*H. pylori*) infection[106-110]. Some investigators have noted a beneficial effect for *H. pylori* treatment in patients with CSCR[111,112]. In a randomized, controlled trial, twenty-five *H. pylori*- infected acute CSCR patients were treated with an anti-*H. pylori* treatment; another twenty-five patients with the same clinical presentations served as the control[112]. Subretinal fluid reabsorption time was significantly reduced in the treatment group, with no beneficial effect observed for final visual acuity[112]. Larger studies to confirm the association between H. pylori and CSCR are warranted.

Regarding a viral etiology, no large studies to establish the association between CSCR and any virus were published. Rathschuler *et al*[113] reported two cases of acute CSCR immediately started with an antiviral therapy (Acycloguanosine), with immediate regression of symptoms accompanied by an anatomic resolution of the leakage and the detachment. Larger studies to confirm the association between *H. pylori* or a viral etiology and CSCR are warranted.

CONCLUSION

CSCR is a common cause of visual impairment, especially in the middle aged population. Despite the fact that most patients will have spontaneous recovery, those with recurrent episodes or chronic disease may remain with significant functional impairment. The exact pathophysiology leading to subretinal fluid accumulation remains undetermined, but it is probably a combination of choroidal and RPE pathology. While imaging is evolving rapidly, the clinical implications of all these new imaging modalities are less clear. Treatment is still a subject of dispute, regarding indications, proper initiation time and type of treatment for both acute and choronic CSCR. That is mainly due to the fact that large randomized trials are still lacking.

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MINIREVIEWS

Retinal emboli

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Abstract

Retinal emboli are opacities identified in retinal arterioles and are often incidental findings on ophthalmic examination. They are generally composed of cholesterol, platelet-fibrin, or calcium and are thought to arise from carotid arteries, coronary arteries, or cardiac valves. In the general population, the estimated prevalence is 0.2% to 1.3%, and the estimated incidence is 0.9% to 2.9%. The transient nature of retinal emboli likely explains the variations between and within these reported figures. The strongest risk factor for retinal emboli is smoking, which has been reported consistently across many studies. Other likely risk factors include older age, hypertension, male sex, total cholesterol, coronary artery disease, and history of coronary artery bypass grafting. The presence of multiple risk factors, as is common in many patients, confers a higher risk for retinal emboli. Several studies suggest that retinal emboli predict an increase in stroke-related, all-cause, and possibly cardiovascular mortality. Due to these sequelae, patients often undergo further workup, most commonly carotid ultrasonography. However, given the low prevalence of significant carotid disease in patients with retinal emboli, further workup, such as carotid ultrasound, should be reserved for those with risk factors for carotid disease. All patients would benefit from medical optimization and coordinated care with the primary care physician.

Key words: Retinal emboli; Hollenhorst plaque; Stroke; Carotid disease; Cardiovascular disease

Core tip: Retinal emboli occur in up to 3% of the population and predict an increase in stroke-related, all-cause, and possibly cardiovascular mortality. The strongest risk factor for retinal emboli is smoking, which has been reported consistently across many studies. Other likely risk factors include older age, hypertension, male sex, total cholesterol, coronary artery disease, and history of coronary artery bypass grafting. Because many patients with retinal emboli have multiple co-morbidities, they would benefit from medical optimization and coordinated care with the primary care physician. Further workup, such as carotid ultrasound, should be reserved for those with risk factors for carotid disease.

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INTRODUCTION

As early as 1862, retinal emboli were identified as discrete opacities in retinal arterioles. Many more accounts of these emboli have since surfaced, including a large case series by Hollenhorst that identified an association with carotid disease[1]. He described 3 main constituents of retinal emboli - cholesterol, platelet-fibrin, and calcium – which have been confirmed in histopathology reports[2-5]. Cholesterol emboli are the most common and are characteristically bright orange-yellow, highly reflective, migrate frequently, and are thought to originate from ulcerated atherosclerotic lesions on cardiac valves or from aortic and carotid endothelium[1,6,7]. Coronary arteries may also

Table 1 Prevalence and basic demographic features of patients found to have retinal emboli in large population-based studies

Ref.	Prevalence	No of participants	% male	Average age	Ethnicity
Wong *et al*[18]	0.2%	15466	44%	63	Mixed (21% black, 79% white)
Hoki *et al*[15]	0.4%	5959	42%	55	Latino
Cheung *et al*[14]	0.6%	3265	52%	59	Asian Malays
Klein *et al*[16]	1.3%	4926	44%	62	White
Mitchell *et al*[17]	1.4%	3654	43%	66	White

be a source, supported by the observation that coronary angiography can liberate cholesterol emboli into retinal arterioles[8-10]. Another less common source is an atherosclerotic lesion in renal arteries[11]. Cholesterol emboli are generally asymptomatic because their thin, flat shape usually does not result in an occlusion[7,12]. Platelet-fibrin emboli are creamy-white, irregularly shaped, immobile, and are postulated to arise from mural thrombus formation in carotid or coronary arteries[1,4,6]. Lastly, an "extremely white," irregular embolus represents calcium likely originating from calcified cardiac valves[1,13]. Given these likely sources, retinal emboli are thought to be indicators of cerebrovascular and cardiovascular disease. The remainder of this review will thus focus on the incidence, risk factors, outcomes, and management of retinal emboli.

PREVALENCE AND INCIDENCE

Several studies in asymptomatic subjects in the general population have identified the prevalence and incidence of retinal emboli. Among 5 modern population-based studies (The Beaver Dam Eye Study, The Blue Mountains Eye Study, The Los Angeles Latino Eye Study, The Singapore Malay Eye Study, and The Atherosclerosis Risk in Communities and Cardiovascular Health Studies), the prevalence of retinal emboli has been reported to range from 0.2% to 1.3%[14-18]. The difference in the reported prevalence among these studies could possibly be explained by the variations in basic demographic characteristics between the study populations (Table 1).

Only 2 studies have reported the incidence of retinal emboli. The Blue Mountains Eye Study identified the 10-year incidence to be 2.9%[19], which is higher than the 1.4% prevalence reported in the same study group in their earlier study[17]. In the Beaver Dam Eye Study, the 5-year incidence was reported as 0.9%[16] and the 10-year incidence was calculated to be 1.5%[20], as compared to the 1.3% prevalence reported in the initial report[16].

Of the 3 different types of retinal emboli - cholesterol, platelet-fibrin, and calcium - the most common is cholesterol. An estimated 46%-80% of all retinal emboli are composed of cholesterol, followed by 6%-32% platelet-fibrin and 6%-16% calcific[14,17,19,21,22]. Since the majority of retinal emboli are of the mobile cholesterol type, it is not surprising then, that many studies report dynamic changes in the presence of retinal emboli on subsequent exams. Hollenhorst[1] reported such changes in 39% of his cases at a subsequent visit, Schwarcz *et al*[23] in 84% of cases, and The Blue Mountains Eye Study and The Beaver Dam Eye Study in 87%-90% of cases[16,19,20]. While the distal migration of emboli is the most commonly accepted theory, another proposed mechanism for the disappearance of these retinal emboli is through autophagy, in which the endothelium engulf the embolus and lead to its extravasation into perivascular spaces[24]. Whatever the mechanism, the transient nature of retinal emboli thus makes it difficult to identify their true prevalence and likely contributes to the variations between different studies and the apparent discrepancies between the incidence and prevalence even within the same study group.

RISK FACTORS

Given the likely sources of retinal emboli, it has been postulated that the risk factors for retinal emboli are similar to the risk factors for vascular disease. However, the definite risk factors for retinal emboli are difficult to assess due to the transient nature of retinal emboli, the presence of multiple co-morbidities, differing demographics across reported studies, and a survivor effect wherein subjects who may be at highest risk are not included in the cohort. Although there are some inconsistent results across the different studies (Table 2)[14-20,25], some generalizations can still be made. Smoking appears to be the strongest risk factor and has been consistently associated with the presence of retinal emboli in all studies reviewed here. Most of the traditional vascular risk factors appear to be significantly associated with retinal emboli with the exception of diabetes, which has fairly consistently been shown not to confer increased risk. Indeed, the incidental finding of retinal emboli has been reported in 0.9%-1.9% of patients who undergo screening for diabetic retinopathy[21,26], which is within the range of the prevalence and incidence of retinal emboli reported in the general population.

As is the case with patients afflicted by other vascular diseases, patients with retinal emboli often have multiple risk factors. The additive effect of multiple co-morbidities was demonstrated in The Blue Mountains Eye Study, which found that the presence of 2 or more risk factors conferred a greater risk of having retinal emboli as compared to none or 1 factor[27]. The combination of hypertension and current smoking conferred the highest risk of retinal emboli with an odds ratio of 6.0 in subjects under age 70[27]. Any 2 or more of hypertension, current smoking, history of vascular event, and history of vascular surgery also led to an increased risk with an odds ratio of 4.6[27].

OUTCOMES

The presence of retinal emboli may be a harbinger of future vascular events and has been associated with increased mortality. In a 7-year follow-up study of 208 patients by Hollenhorst[28] and Pfaffenbach *et al*[29], the

Table 2 Risk factors for retinal emboli

Probable risk factors	Unlikely risk factors	Insufficient data
Smoking (8/8)	History of angina (2/5)	Elevated pulse pressure (2/2)
History of coronary artery bypass graft (3/3)	History of myocardial infarction (2/5)	Known carotid artery plaque (2/2)
Hypertension (5/7)	Body mass index/obesity (1/7)	LDL cholesterol (1/1)
Older age (4/6)	Diabetes (1/7)	Mean arterial blood pressure (1/1)
Coronary artery disease (2/3)	Aspirin use (1/3)	Previous vascular surgery (1/1)
Serum fibrinogen (2/3)	History of stroke (0/6)	Serum lipoprotein (1/1)
Systolic blood pressure (3/5)	Diastolic blood pressure (0/4)	Congestive heart failure (0/1)
Male sex (3/6)	Alcohol use (0/3)	Hemoglobin A1C (0/1)
Total cholesterol (3/6)	Hematocrit (0/3)	Hormone replacement therapy (0/1)
	Platelet count (0/3)	Serum triglycerides (0/1)
		Carotid artery bypass surgery (0/2)
		Serum glucose (0/2)

The numbers in parentheses indicate the fraction of studies reviewed in this article that report a statistically significant association with retinal emboli. A potential risk factor was considered to have insufficient data if there were fewer than 3 studies investigating its relationship to retinal emboli.

all-cause mortality rates were 8% at 3 mo, 15% at 1 year, 29% at 3 years, and 54% at 7 years in patients with a median age of 64 years at initial embolus detection. The most common cause of death was coronary artery disease (42% of deaths), followed by stroke (10% of deaths), other atherosclerotic vascular disease (10% of deaths), and ruptured aortic aneurysm (8% of deaths). Savino *et al*[30] reported the overall mortality as 28% during a 9-year follow-up period, with the largest proportion of deaths similarly attributable to cardiovascular disease (46% of deaths). The next largest cause of death was stroke (29% of deaths), which corresponded to a 4 to 5-fold annual increased stroke-related mortality compared to an age and sex-matched population. Howard *et al*[31] reported a 2.3-fold increased risk of death and 12-fold risk of fatal stroke as compared to age and sex-matched controls during a 6-year follow-up period. The Beaver Dam Eye Study[20] similarly reported a 2.4-fold increased stroke-related mortality and no statistically significant association with ischemic heart disease.

To achieve greater statistical power, a study was performed pooling mortality data from The Blue Mountains Eye Study and The Beaver Dam Eye Study. When adjusted for age and sex, there was a mild increase in cardiovascular mortality (HR = 1.46, 95%CI: 1.03-2.06), a moderate increase in stroke-related mortality (HR = 2.33, 95%CI: 1.34-4.07), and a mild increase in all-cause mortality (HR = 1.52, 95%CI: 1.18-1.96)[32]. After adjusting for multiple systemic factors, such as body mass index, hypertension, diabetes, current smoking, total cholesterol, high-density lipoprotein cholesterol, history of stroke, history of angina, history of acute myocardial infarction, retinal emboli were still significantly associated with increased stroke-related mortality (HR = 2.02, 95%CI: 1.07-3.81) and all-cause mortality (HR = 1.34, 95%CI: 1.02-1.76), although at a lesser magnitude. The risk of cardiovascular mortality became statistically insignificant (HR = 1.18, 95%CI: 0.80-1.73). These findings suggest that the presence of retinal emboli may be an independent risk factor for all-cause and stroke-related mortality. In reality, most patients do tend to have multiple systemic risk factors, which further increases mortality risk.

While associated mortality has been published in many studies, less commonly reported are morbidities linked to the presence of retinal emboli. Due to significant impact of disabilities on quality of life, these morbidities should not be ignored. The most common morbidity is non-fatal cerebrovascular infarction. In a study of 70 men with asymptomatic retinal emboli seen at the Albuquerque Veterans Affairs Medical Center, Bruno[12] reported an 8.5% annual rate of non-fatal stroke, which corresponds to a 10-fold increased risk of cerebral infarction as compared to controls matched for age and vascular risk factors. More specialized brain imaging techniques like diffusion weighted imaging has allowed the detection of subclinical strokes, with a study by Helenius *et al*[33] reporting that 20% of patients whose sole presenting complaint was acute monocular vision loss were found to have brain infarcts on the ipsilateral side. Other morbidities reported by Pfaffenbach *et al*[29] include claudication (9% of patients), angina or abnormal electrocardiogram (7% of patients), transient ischemic attack (3% of patients), and amaurosis fugax (1% of patients). However, the lack of statistical analyses provided for these sequelae make it difficult to ascertain whether the presence of retinal emboli confers an increased risk for these phenomena or whether these are related to the patients' other comorbidities and underlying vascular disease.

Because of the increased stroke mortality and morbidity in patients with retinal emboli, carotid ultrasonography and angiography are sometimes performed. However, data reported in the literature vary widely, not only with regards to the prevalence of carotid disease, but also in the way results are reported and how "significant" disease is defined. Among studies that do not specify the degree of carotid stenosis, as low as 23% and as high as 95% of patients with retinal emboli are estimated to have some carotid disease[18,25,31,34]. Significant carotid artery stenosis defined as at least greater than 50% was present in 17%-22% of patients with asymptomatic retinal emboli[25,34,35]. Other studies that defined significant carotid stenosis as greater than 70% reported a prevalence of

9%-22% in asymptomatic patients[21,26,36]. Lastly, when significant stenosis was defined as greater than 75%, a prevalence of 20% was reported[22]. Despite stroke-related mortality being most commonly reported sequela of retinal emboli, it should be noted that carotid disease, especially high grade stenosis, is still only found in a minority of these patients.

It has been postulated that the presence of visual symptoms could be an indicator of carotid disease. Bunt[37] reported that 17% of asymptomatic patients, 73% of patients with amaurosis fugax, and 100% of those with focal visual loss had significant stenosis. Bakri *et al*[36] found that there was a significant difference in the proportion of symptomatic and asymptomatic patients (25% *vs* 9%) when stenosis was defined as > 69% but not when defined as > 40%. This study also suggests that asymptomatic patients with a carotid bruit are more likely to have carotid stenosis. These findings may seem intuitive, but are not replicated in all studies. For example, O'Donnell *et al*[22] reported a similar proportion of carotid disease in symptomatic (21%) and asymptomatic patients (18%).

Since most patients with asymptomatic retinal emboli do not have significant carotid disease, only a small proportion undergoes carotid endarterectomy. Hadley *et al*[21] reported that 25 of 190 patients with retinal emboli (13%) had significant stenosis between 70%-99%, and only 10 of these patients underwent ipsilateral carotid endarterectomy. By the end of the study period (up to 7 years of follow-up), 4 of these 10 in the surgical group had died, but none from a stroke. Of the 15 who did not have surgery, 5 died during the follow-up period, none from a stroke although one patient did experience a non-fatal stroke. In Bunt's study[37], 28% of patients with asymptomatic retinal emboli underwent carotid endarterectomy, and no patients in either the non-surgical group or any of the surgical groups developed any subsequent symptoms of vision loss or cerebral ischemia during an 18-mo follow-up period. Schwarcz *et al*[23] reported that whether patients underwent carotid endarterectomy or not, both groups experienced recurrent retinal emboli and subsequent transient ischemic attacks. These reports seem to suggest that perhaps carotid endarterectomy for these patients does not affect mortality. However, the effect on long-term outcomes is limited in these studies due to short follow-up, small sample sizes, lack of data on medical interventions that were provided concurrently to the surgical group, and lack of data on medical interventions done to the non-surgical group.

Other less commonly used workup for retinal emboli include transcranial Doppler and echocardiogram. The incidence of cardiac pathology, such as valvular disease and wall motion abnormalities, was reported in 8%-43%[26,27,35]. It is unknown how many of these patients underwent cardiac surgery as a result. Ultimately, it is estimated that up to 45% of patients will have no identifiable cause despite extensive evaluation[35], suggesting that maximal extensive workup is neither cost-effective nor informative.

MANAGEMENT

The increased morbidity and mortality rates suggest a need for additional interventions in patients found to have retinal emboli. Given the coexistence of multiple medical problems, the presence of retinal emboli may simply be a marker of their underlying metabolic and vascular disease. Medical therapy should be the mainstay of management and should emphasize risk factor modification, such as stricter blood pressure control, the initiation of cholesterol-lowering medication, counseling for smoking cessation, encouragement of weight loss, diabetes management, the initiation of antiplatelet therapy, and monitoring through carotid auscultation[15,16,21,26,27,36,38].

The current guidelines[39] for the use of carotid ultrasonography in asymptomatic patients list the following indications: suspected of having carotid disease; have a carotid bruit; have symptomatic coronary artery disease, peripheral arterial disease, or atherosclerotic aortic aneurysm; or have at least 2 associated risk factors (hypertension, hyperlipidemia, tobacco smoking, a family history of a 1st degree relative with manifestations of atherosclerosis before age 60, or family history of stroke). The routine screening of the general population is not recommended. It has been suggested that carotid ultrasonography should be offered to all patients with retinal emboli[40], but given the low prevalence of significant carotid disease in these patients, it may be more reasonable to reserve carotid ultrasonography for patients who meet the aforementioned indications. Other imaging modalities like echocardiogram and transcranial Doppler are low yield and have not been recommended in the literature.

The currently established indications[39] provide strongest evidence for the use of carotid endarterectomy in symptomatic patients with at least 70% stenosis on carotid ultrasound (or at least 50% on catheter angiography) with low or average surgical risk and low anticipated perioperative mortality; and asymptomatic patients with greater than 70% stenosis and low perioperative risk of stroke, myocardial infarction, or death. Ideally, surgery should be performed within 2 wk of the index event. Surgery in asymptomatic patients with retinal emboli who are subsequently found to have significant carotid stenosis is more controversial[41], since carotid endarterectomy is an invasive procedure that itself carries a significant risk of perioperative mortality and postoperative stroke[39,42,43]. As previously discussed, small studies of the short-term outcomes of carotid endarterectomy are not suggestive of a mortality benefit of surgical management. Therefore, this subset of patients may benefit from referral to a vascular surgeon, during which it should be carefully considered whether the benefits of stroke prevention would outweigh the perioperative risks, taking into account the patient's comorbidities, individual risk factors, life expectancy, and complication rates of the surgical center. Large, prospective, randomized, controlled studies addressing the effects of carotid endarterectomy in this unique patient population will determine the out-

comes of this proposed algorithm.

CONCLUSION

Retinal emboli occur in up to 3% of the general population, particularly in those with risk factors similar to that of other vascular diseases. As such, there is significant overlap in patients with retinal emboli and other metabolic and vascular conditions. Therefore, management should involve working with the primary care physician to maximally control the underlying comorbidities and risk factors, such as smoking cessation, control of blood pressure, and lowering of serum cholesterol.

Carotid ultrasound has a low-yield for detecting significant carotid disease in patients with retinal emboli, suggesting that it should not be done routinely in this population but instead reserved for those who meet an established indication. Those who would benefit most from surgery are patients with significant stenosis > 70% and symptoms of an impending cerebrovascular event, such as unilateral weakness, unilateral sensory loss, aphasia, sudden monocular vision loss, or homonymous hemianopsia. The subset of asymptomatic patients with significant stenosis should be referred to a vascular surgeon for consideration of the risks and benefits of this invasive procedure.

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MINIREVIEWS

Age-related macular degeneration treatment in the era of molecular medicine

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Abstract

Age-related macular degeneration (AMD) is the leading cause of irreversible blindness in the developed world. The quality of life of both patients and families is impacted by this prevalent disease. Previously, macular degeneration had no known effective treatment. Today, vitamins for non-exudative AMD and intravitreal injection of medications for its exudative form are primary forms of current treatment. Modern advances in molecular science give rise to new possibilities of disease management. In the year 2003 the sequencing of the entire human genome was completed. Since that time, genes such as complement factor H, high-temperature requirement factor A1, and age-relateed maculopathy susceptibility 2 have been discovered and associated with a higher risk of AMD. A patient's genetic make-up may dictate the effectiveness of current or future therapeutic options. In addition, utilizing genetic data and incorporating it into new treatments (such as viral vectors) may lead to longer-lasting (or permanent) VEGF blockade and specific targeting of complement related genes. There have also been considerable advances in stem cell directed treatment of AMD. Retinal pigment epithelial (RPE) cells can be derived from human embryonic stem cells, induced pluripotent stem cells, or adult human RPE stem cells. Utilizing animal models of RPE and retinal degeneration, stem cell-derived RPE cells have been successfully implanted into the subretinal space. They have been injected as a cell mass or as a pre-prepared monolayer on a thin membrane. Visual recovery has been demonstrated in a retinal dystrophic rat model. Preliminary data on 2 human subjects also demonstrates possible early visual benefit from transplantation of stem cell-derived RPE. As more data is published, and as differentiation and implantation techniques are optimized, the stabilization and possible improvement of vision in individuals with non-exudative macular becomes a real possibility. We conclude that the technologic advances that continue to unfold in both genetic and stem cell research offer optimism in the future treatment of AMD.

Key words: Age-related macular degeneration; Stem cell therapy; Anti-vascular endothelial growth factor; Gene therapy; Complement factor H; High-temperature requirement factor A1; Age-relateed maculopathy susceptibility 2; Pharmacogenomics; Genetics

Core tip: New therapies for age-related macular degeneration (AMD) such as stem cell transplantation and viral vector delivery are currently under intense investigation. Possible new treatments for both non-exudative and exudative AMD are on the horizon. Human embryonic stem cell derived retinal pigment epithelial cells have been transplanted into the subretinal space in human subjects. Viral vectors that encode proteins with a strong affinity for vascular endothelial growth factor are in clinical trials. In light of these exciting advances in both genetic and stem cell therapy, the future of AMD treatment shows substantial promise.

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INTRODUCTION

Age-related macular degeneration (AMD) is the leading cause of blindness in the developed world, surpassing cataracts which were the leading cause in 1990[1]. In the United States, current prevalence of advanced AMD defined as geographic atrophy or exudative macular degeneration is estimated to be at 1.75 million. By 2020, it is predicted that 3 million patients will suffer from advanced AMD[2]. At present, there are effective treatments for the exudative form of AMD[3-7], however, when faced with advanced non-exudative AMD visual loss there is little to offer. Research efforts focused on the biological mechanisms of the disease, utilization of stems cells, and genetically based treatments are currently underway to develop novel human therapies.

RISK FACTORS

AMD is a disease that presents with a wide spectrum of severity - from early small drusen with no visual impact to geographic atrophy or choroidal neovascular membrane formation causing severe visual impairment. Multiple non-modifiable and modifiable risk factors have been implicated.

Age

AMD increases significantly in prevalence, incidence, and progression with increasing age. The Beaver Dam eye studies found that by age 75, 7.1% of patients had late AMD compared to 0.1% in those aged 43-54 and 0.6% in age group 55-64[8,9]. Another, more recent study demonstrated that 57.4% of patients over age 85 had signs of AMD[10].

Genetic risk

One study found that 14% of patients with AMD reported a parental history and 21% reported a sibling history of AMD compared to 1% and 2% respectively in control patients. Examined siblings of affected patients showed a 16% prevalence of intermediate disease and a 23% prevalence of advanced disease[11].

Inflammation

Several studies have shown the presence of complement factor byproducts and complement regulatory proteins in drusen and juxtaposed RPE cells. In one study, RPE cells adjacent to drusen exhibited a phenotype consistent with cellular response to complement attack[12]. The role of the complement pathway has been strengthened by the discovery of complement factor gene associations with AMD[13,14].

Oxidative stress

Retinal pigment epithelium (RPE) cells are prone to damage from oxidative stress due to toxin or light exposure[15-17]. The decreased risk of progression with antioxidant supplementation as seen in the AREDS studies yields further evidence of this important mechanism[18,19].

Other risk factors

Some additional non-modifiable risk factors include female sex, hyperopia, and Caucasian race[8,20,21]. Modifiable risk factors include smoking, elevated HDL cholesterol, atherosclerosis, and obesity[10,22].

HUMAN GENOME PROJECT

In April 2003, at an estimated cost of 2.7 billion dollars, the sequencing of the human genome was completed. The project mapped 3 billion base pairs and is estimated to contain approximately 20500 genes. These genes only make-up 1%-2% of the entire sequence. Human to human variation is approximately 0.1% and is more commonly found in non-coding DNA. The past 10 years have led to numerous discoveries including the identification of about 5000 disease producing genes. With technological advances in gene sequencing, today's cost to sequence the human genome has dropped considerably to approximately 1000 dollars (as compared to 2.7 billion 10 years ago). In addition, what used to take years to decades of collaboration among institutions to discover one gene can be completed by one lab within days to weeks[23].

Genome-wide association studies

Genome-wide association studies (GWAS) involve analyzing variations in single nucleotide polymorphisms (SNPs) in patients with a particular disease compared to controls[24]. Coupled with the International HapMap project[25,26] that is responsible for mapping SNP's, GWAS studies today can evaluate a growing number of genetic loci. The overall goal of GWAS is to identify at risk genetic markers for individuals with multifactorial diseases in which a familial component has been identified. Accurate mapping may provide information about disease phenotype, predict genetic markers associated with disease progression, and lead to tailored risk reduction techniques and treatment options. Some limitations of GWAS include: the discovery of many SNPs that are not related to disease, expense, and the requirement of large studies in order to identify a modest risk association[24,27].

AMD GENETICS DISCOVERY

Complement factor H

In 2005, the first GWAS for AMD was published in which a major susceptibility locus was identified. A SNP rs1061170 in the complement factor H (*CFH*) gene in chromosome 1 was shown to have a high association with AMD. SNP rs1061170 encodes a tyrosine to histidine change at the 402 position of the gene (*Y402H*). Complement Factor H inhibits the conversion of C3 to its C3a/C3b components and competes with Factor B to prevent activation of C3b to C3bB[13,14]. A meta-analysis

of eight studies showed that a single allele (heterozygous for risk *Y402H* allele, CT genotype) confers a 2.5-fold increased risk of AMD, while those homozygous for the risk allele (CC) had a 6 fold increased risk. Predicted population attributable risk (PAR) in the same meta-analysis for the risk genotype (CC or CT) was 58.9%[28]. Meta analyses in Asian and Chinese subjects demonstrated a similar increase in risk of AMD per C allele, but a lower PAR[29,30].

OTHER ASSOCIATED GENES

In a meta-analysis in 2005, Fisher *et al*[31] showed a significant link between the locus 10q26 and AMD. Age-related maculopathy susceptibility 2 (*ARMS2*), and high-temperature requirement factor A1 (*HTRA1*) are genes in this locus (10q26) and variations confer a significant risk for AMD that may be higher than with CFH[32,33]. Conversely, polymorphisms of the genes for complement factor B and complement component 2 seem to confer a protective effect to the development of AMD[34-36].

POTENTIAL IMPACT ON MANAGEMENT

Commercial AMD genetic testing has been available for screening at risk patients for several years. However, the value of screening is limited due to the lack of understanding of the association between genetic mutations, modifiable risk factors, and the current therapeutic options. It would be useful to target specific lifestyle modifications in patients depending on their genetic make-up. In addition, if disease progression could be predicted by analyzing the genetic profile of an individual, decisions about the frequency of monitoring and the institution of early intervention could be tailored accordingly[37]. The data however remain conflicting and limited.

GENETIC IMPACT ON CERTAIN RISK FACTORS

Smoking

Several studies show a strong association between smoking and advanced AMD in patients with at risk genes. DeAngelis *et al*[38] showed 144 fold increased risk of CNV in patients who had a 10 pack-year smoking history and were homozygous for the at risk CFH variant compared to individuals who smoked less than 10 pack-years and were heterozygous for the at risk variant, or those who carried the non-risk gene[38]. Similar results were noted for patients with variant at the 10q26 locus[39,40]. Since smoking is an independent risk factor for progression of disease, the effect of smoking in individuals with the risk genotype yields a multiplicative effect[38].

Obesity

AREDS showed a body mass index > 25 did not increase the risk of AMD in patients with a non-risk CFH genotype, however, those who were heterozygous or homozygous for the risk variant showed increased risk with an odds ratio of 2.2 and 5.9 respectively[41].

Genetic impact on risk of progression

The Beaver Dam Eye study patient cohort looked into the association of the CFH and ARMS2 risk alleles and the natural history of AMD. Persons aged 45 years with no evidence of AMD who had low, intermediate, and high AMD genetic risk groups were estimated to develop early AMD at 33.0%, 39.9%, and 46.5% by age 80 years. Late AMD was estimated at rates of 1.4%, 5.2%, and 15.3%, respectively, for these same groups[42]. In addition, a Spanish study showed significant associations of the rate of progression and growth of geographic atrophy with genetic polymorphisms *CFH Y402H*, *CFH-62Ile* and *CFB-32Gln*[43]. Several other studies showed underlying genotype was associated with development of geographic atrophy but had no implication on progression of disease[44,45].

Pharmacogenomics: Targeting/Tailoring treatment

Therapeutic interventions available for the treatment of macular degeneration have been limited to risk modification, anti-oxidants, laser, photodynamic therapy (PDT) and anti-vascular endothelial growth factor (VEGF) agents. With the discovery of the anti-VEGF agents for the treatment of exudative AMD, choices of regimen, dosing, and frequency have been largely dictated by medication cost, physician preference, and large studies that leave a lot to interpretation by the prescribing physician. Tailoring and targeting treatment to individual patients based on calculated susceptibility of the disease to specific intervention(s) is certainly in the future for medicine. Knowing which anti-VEGF medication would be most effective, ideal injection frequency, and the individual risk of complications (such as drug toxicity or RPE tears) prior to initiating treatment would revolutionize our current approach to anti-VEGF treatment and may reduce unnecessary costs[46].

Genetic studies in AMD therapeutic responses have mixed results thus far.

Antioxidants

Klein *et al*[47] studied 876 patients from the AREDS trial who had category 3 and 4 AMD and showed that AREDS vitamin supplementation resulted in a 68% reduction in the rate of progression in the subgroup with the homozygous non-risk genotype compared to a reduction of only 11% in the subgroup with the homozygous risk genotype of *CFH Y402H*. Further analysis revealed the interaction to be explained by zinc. Interaction was noted in the groups taking zinc when compared to those not taking zinc. However, the authors did not feel their results justified routine screening. No genetic treatment interaction was noted for patients with LOC387715/ARMS2[47].

Awh *et al*[48] studied 989 patients from the AREDS trial and showed that patients with a 1 or 2 CFH at risk alleles benefited from antioxidants and not zinc and that

patients with ARMS2 at risk alleles benefited from zinc only regimens[48]. Patients with at risk ARMS2 and CFH alleles showed no benefit to any of the AREDS supplementation. The authors recommended that patients with moderate AMD would benefit from selective nutritional supplementation based on genetic profile[49].

Both studies derived their cohort from the AREDS trial and yet the results are different. However, the AREDS trial was a prospective study that wasn't designed to look into a genetic treatment interaction. Statistically, these studies were too underpowered to achieve statistical significance. In 2012, a task force from the American academy of ophthalmology advised against genetic testing for AMD and that recommendation is unlikely to change with the current evidence[50].

Photodynamic therapy

Initially, 2 small studies have suggested a possible association between CFH and PDT response, but their results were conflicting. In 2008, Goverdhan *et al*[49] published a study of 27 patients and showed that patients carrying 2 CFH at risk alleles responded poorly to PDT compared to other groups. This study was limited by the small sample size. Brantley *et al*[51] looked at a group of 69 patients and showed that in patients with classic CNV, response to PDT was worse for patients with no risk alleles compared to those with one or two at risk alleles[51].

Additional studies with larger sample sizes did not show any association between CFH variants and response to PDT. The largest study of 273 Australian patients looked into this association and found no significant difference in CFH genotypes and response to PDT[52].

Chowers *et al*[53] looked at the association of response to PDT and CFH in an Israeli population of 131 patients and showed no significant association between the genetic variants and response to PDT and number of PDT sessions needed[53]. The same team evaluated the association of PDT response to ARMS2/HTRA1 and showed no significant association between the different genetic variants and the response to PDT or the number of PDT sessions required[54].

Anti-VEGF

Anti-VEGF agents have also been explored. Initially, several studies showed a potential association CFH genotype and response to anti-VEGF response. One group found that intravitreal bevacizumab was associated with worse visual outcomes in patients with the *CFH Y402H* risk genotype[55]. The same group found in a different study that patients with the high risk genotype may require more injections of ranibizumab, but that there was no impact on visual acuity[56]. Hagstrom *et al*[57] recruited 834 patients participating in the Comparison of AMD Treatment Trials (CATT). Each patient was genotyped for rs1061170 (*CFH*), rs10490924 (*ARMS2*), rs11200638 (*HTRA1*), and rs2230199 (*C3*). The study showed no significant difference in patients with high risk alleles (*CFH*, *ARMS2*, *HTRA1*, *C3*) compared to low risk allele in final vision, change in vision, anatomical outcomes (OCT, FA, thickness, lesion size) or number of injections whether bevacizumab or ranibizumab was used[57].

Association between polymorphisms in VEGFA and VEGFR and the response to bevacizumab and ranibizumab were explored. Several studies showed a treatment benefit to anti-VEGF agents, however these studies were limited by the small sample sizes and the limited standardization of their outcomes[58-60]. Hagstrom *et al*[61] showed a different conclusion in a cohort of patients from the Comparison of AMD Treatment Trials. They recruited 835 patients participating in CATT and the patients were genotyped for 7 SNP's in *VEGFA* gene and 1 SNP for *VEGFR2* gene. Results showed no association between the studies genotypes and vision or number of injections[61].

Despite the limited results with AMD, successful examples of genotype directed interventions do exist in other areas of medicine. For example, the drug Abacavir, a reverse transcriptase inhibitor has been associated with an uncommon but potentially fatal and unpredictable hypersensitivity reaction in Human Immunodeficiency Virus patients. In a study published in the New England journal of Medicine, patients with HLA B5701 allele have a 50% chance of developing hypersensitivity while patients without the allele have no risk of developing the hypersensitivity reaction. It is now the standard of care to test patients for this allele prior to starting Abacavir[62].

GENE THERAPY

An emerging therapeutic option is to deliver anti-angiogenic genes using a viral vector. This could allow a sustained delivery of the desired peptide. The challenges here lie in the engineering of a vector that will both target a specific cell (retinal pigment epithelial cell) and allow effective translation of the desired protein.

Pigment epithelial derived factor (PEDF) is a potent anti-angiogenic compound. Campochiaro and colleagues completed a phase I clinical trial in individuals with advanced neovascular AMD using Adenoviral vectors expressing human PEDF (AD-PEDF-11). Twenty eight patients received a single intravitreal injection of low or high dose AD-PEDF-11. Results at 6 and 12 mo showed that the median size of the lesion increased by ½ and 1 disc area respectively in the low dose group compared to no change in the lesion area for the high dose group at 6 and 12 mo. A phase Ⅱ is planned in the future[63].

Another potential VEGF blocker is soluble fms-like tyrosine kinase (sFLT), an endothelium specific receptor tyrosine Kinase. It binds to VEGF with high affinity. A phase I trial of 6 patients who were treated with intravitreal ranibizumab on day 0 and day 30 and received a subretinal injection of a high or low dose sFLT-1 integrated into adeno-associated virus serotype 2 (AAV-sFLT) on day 7. Patients were followed monthly with strict ranibizumab retreatment criteria. By day 380, the high dose group gained 12.5 letters, low dose 8.7 and the control untreated group lost 3.5 letters. Re-treatment with ranibizumab was also less frequent in the treatment group than control. Patients treated with AAV-sFLT showed no

significant adverse events[21]. AAV2-sFLT01 is another sFLT viral vector designed to block VEGF function and is currently in a phase 1 trial[64].

BRIEF HISTORY OF STEM CELL RESEARCH

The terminology of "stem cells" - regenerative precursor cells - was first postulated in 1909 by Alexander Maksimov, a Russian histologist[65]. Since that time there have been many advances in our understanding of stem cells and our ability to isolate them. There are several different approaches to obtaining these progenitor cells; some are derived from adult tissues and others from embryos (embryonic stem cells). Embryonic stem cells are totipotent, meaning they can differentiate into any cell type from any of the three germ layers. In addition, embryonic stem cells have the capacity of unlimited, undifferentiated proliferation *in vitro*. Embryonic stem cells express a high level of telomerase activity, which yields a prolonged replicative life span. Human embryonic stem (hES) cells were first successfully isolated from human blastocysts in 1998[66]. The hES cells were initially grown on a mouse embryonic fibroblast feeder layer[66,67]. Further progress allowed the hES cells to be grown on human feeder layers, and avoid the risk of exposure to animal retroviruses[68]. Now techniques are available to grow hES cells using a serum free, sterile generated protein cocktail that avoids the use of human or animal serum, or human feeder layers[69]. Recent studies also demonstrate that hES cells can be successfully isolated from human blastocysts produced by *in vitro* fertilization rather than from ex-utero embryos[66,70].

Inevitably, ethical and moral issues exist in the use of embryonic stem cells for research purposes. In an effort to avoid such controversy, much work has been done to develop pluripotent adult stem cells that are also capable of differentiating into virtually any tissue in the body. These cells are referred to as induced pluripotent stem (iPS) cells. Such iPS cells have been derived successfully both in mice and in humans[71]. In addition to avoiding the many of the ethical concerns, these adult stem cells can be derived from the patient for whom they would be used, potentially minimizing complications such as rejection of donor tissue.

METHODS OF DIFFERENTIATION INTO RPE CELLS

The RPE has become a primary target for stem cell therapy of AMD. The RPE functions include phagocytosis photoreceptor outer segments, supply of nutrients to the retina, absorption of stray light that passes through the photoreceptors, and formation of the blood retinal barrier[72-74]. Dysfunction of this vital cellular layer in macular degeneration ultimately leads to photoreceptor loss and decreased visual acuity. Differentiation of hESC to RPE was first described in 2004; these cells were compared to fetal RPE cells and were found to express RPE specific markers[75]. RPE cells have been successfully derived using various methods such as co-culture on inactivated mouse embryonic fibroblasts coupled with stromal cell-derived inducing activity, utilizing embryoid body formation, as well as exposing the cells to several signaling pathways[72,75-78]. One group utilized to NIC and Activin A to differentiate hES cells to RPE and successfully transplanted them into the Royal College of Surgeons (RCS) rat and demonstrated rescue of retinal function[71].

In addition to differentiating hES cells into RPE, human induced pluripotent stem cells (iPSCs) have also been described[79-81]. RPE derived from iPSCs (iPS-RPE) expressed cell markers similar to RPE from hESCs. A retinal outer segment phagocytosis assay demonstrated similar efficacy in iPS-RPE and hESC-RPE to fetal retinal pigment epithelium[79]. Another group was able to grow iPS-RPE as a monolayer without an artificial membrane and successfully implant it into the RCS rat with restoration of ERG responses[80].

Adult human RPE stem cells (hRPESC) are another source of RPE cells. These cells are derived from elderly donor eyes and expanded to differentiate into RPE cells. One study found that a single donor may be able to provide enough cells to cover hundreds of patients using stem cell proliferation techniques[82]. Further study is needed to determine if these cells are suited for intraocular transplantation.

One study evaluated the essential role of RPE in the proper structural formation of photoreceptors, including the outer segments. Therefore, the ability to create polarized RPE cells may aid in the differentiation of functional photoreceptors for possible therapeutic use in ocular diseases causing photoreceptor dysfunction or death[83]. Overall, a key to developing successful stem cell therapies for AMD is establishing a high-yield, accurate, and reproducible method of differentiating stem cells to RPE that can survive *in vivo*, integrate properly into the host retina, and perform the essential RPE functions.

In addition to the above advances in RPE derivation from stem cells, hESC derived photoreceptors can be successfully implanted into $Crx^{-/-}$ mice with improved ERG responses compared to controls[84]. This may allow for not only photoreceptor rescue but potentially replacement of dead/degenerated photoreceptors in the future.

METHODS OF INTRAOCULAR IMPLANTATION

After isolation of retinal pigment epithelial cells from either hRPESC, iPSC or hESC, the next challenge becomes creating an effective method of intraocular implantation to maximize the therapeutic effect. Two primary techniques have been employed: injection of a cell mass into the subretinal space, or implantation of a monolayer prepared on a thin membrane.

Cell suspension injection techniques

In nude rats a 1.2 mm scleral incision was made 1.5 mm posterior to the limbus and then a local retinal detachment was created by injecting 5 microliters of balanced saline solution. Next, *via* a 32 G blunt-end injection cannula, 2 microliters of phosphate-buffered saline solution containing the hESC-RPE was injected into the subretinal space *via* the sclerotomy site[85]. A different group also utilized a trans-scleral technique in rats, however, no subretinal bleb was created prior to cell suspension injection[86,87].

Thin membrane implantation techniques

Given that the RPE is a single layer of polarized cells it is presumed that the best functional outcome of transplantation would yield a monolayer of new RPE. Injecting a cell mass can lead to clumping of RPE cells rather than the formation of a monolayer. In search for a solution, groups have cultured RPE cells on thin membranes as a monolayer followed by implantation of the membrane-RPE complex into the subretinal space[82,85,88-90].

One group, utilizing chinchilla rabbits, performed a two-port core vitrectomy, then created a small bleb retinal detachment with 25-30 mL of balanced saline solution using a 41 G Teflon cannula. Conventional infusion caused the bleb to flatten during the procedure, therefore a custum-made infusion with 2 side ports was utilized to minimize disturbance of the bleb[88]. The retinotomy was enlarged with scissors and then a polyester membrane lined with hESC-RPE was inserted using a custom-made subretinal shooter instrument[82,88]. Electrostatic adhesions between the implant and the delivery device often required additional maneuvering (with subsequent retinal damage) to successfully place the thin membrane into the subretinal space. Utilizing a hydrogel encapsulation of the implant significantly decreased these hydrostatic forces and improved the success of subretinal placement[88]. Other customized injection instruments have been designed, including one that gently delivers a parylene membrane lined with a monolayer of hESC-RPE using an infusion of balanced salt solution through small holes in the device[90]. A previous group had used a similar technique using an injection instrument and mircoforceps. This group also utilized perfluorocarbon to create an intraocular tamponade to prevent reflux of fluid through the retinotomy site[89].

Another group, utilizing nude rats, compared the injected RPE cells cultured on a parylene membrane into the subretinal space *via* a trans-scleral incision. First, a 1.2 mm scleral incision was made 1.5 mm posterior to the limbus and then a local retinal detachment was created by injecting 5 microliters of balanced saline solution. Next, the choroid was cut, taking care to avoid retinal damage, and the hESC-RPE membrane substrate was inserted into the subretinal space utilizing forceps[85].

In addition to hESC-RPE, hRPESC have also been used and proliferated on a polyester membrane and implanted into rabbit eyes and survive with maintenance of cellular polarity up to 4 wk after graft implantation[82].

IMPACT ON VISUAL ACUITY

Comparison of injection hESC *via* a cell suspension vs hESC cultured on a parylene membrane demonstrated increased cell survival in the polarized monolayer group. In this same study, the rats were observed for up to 12 mo with persistent cell survival and there was no evidence of teratoma or ectopic tissue formation[85]. Another group injected the RCS dystrophic rats with different doses of a subretinal hESC mass (either with 50000 or 100000 hESCs) and found that treated rats demonstrated better spacial acuity when compared to sham and untreated rats. Once again, this study demonstrated no evidence of teratoma or tumor formation (up to 220 d)[87]. Also, utilizing the RCS rats and the cell suspension technique, Lund *et al*[91] demonstrated improvement in vision in the RCS rats that achieved spacial acuity up to 70% of the non-dystrophic rats[91]. Transplantation of iPSCs have also been performed in RCS rats and demonstrated slowed visual decline, however, the transplanted cells were lost to immune response despite immunosuppressive therapy[92].

Human trials

The preliminary results of 2 human subjects, one with Stargardt's macular dystrophy and one with dry AMD are now available. The patients were given low dose tacrolimus and mycophenolate mofetil 1 wk prior to the procedure. HESC MA09 cells were used for implantation. The procedure entailed a pars plana vitrectomy with induction of a PVD from the optic disc followed by the injection of approximately 50000 hESC-RPE (150 microliters) into the subretinal space at a predetermined location based on OCT findings consistent with an area of RPE and photoreceptor compromise. The induced bleb had flattened by 4 h after the surgery in both patients. The patient with Stargardt's disease improved from hand motion to 20/800, and the patient with AMD improved from 20/500 to 20/320. However, it is unclear whether the mild improvement was due to the transplanted cells, immunosuppressive medications, or to placebo effect. In the future as more data are collected we will have a better understanding of the effect of implanted hESC-RPE in the human subretinal space[93].

CONCLUSION

AMD affects millions of people worldwide and is the leading cause of blindness in the United States[1]. As our understanding of molecular medicine has expanded so has our approach to disease treatment. The severe vision loss that almost always accompanied exudative macular degeneration in years past is now being widely treated with anti-VEGF injections[4-7]. Current therapies, including viral vector delivery of VEGF binding proteins, may allow for prolonged VEGF blockage allowing for a significantly reduced number of intravitreal injections[63]. Also, understanding the complex array of genes associated with AMD may allow us to make tailored therapeutic decisions and/or lifestyle recommendations depending

on a patient's genetic make-up[47,52,57,62].

Currently there is no treatment to offer patients with advanced non-exudative AMD, however, stem cell therapy may provide a future solution. Techniques to differentiate hESC (or iPSC and hRPESC) into RPE cells allow for a potentially numberless supply of cells to utilize in transplants to treat not only macular degeneration but also other disorders such as Stargardt's macular dystrophy, retinitis pigmentosa, cone-rod/rod-cone dystrophies, *etc*. More data is required to determine if a single origin of RPE is more effective than the others in creating fully functioning RPE cells. Once the RPE cells are successfully derived, there must be safe, reproducible, and effective method(s) to surgically implant the new cells. There are currently different techniques and instruments under investigation, whether it be by subretinal injection of a cell mass or implantation of a pre-RPE cultured thin membrane, and further study is necessary to determine which technique will yield the best visual outcomes with the least degree of surgical complications. In addition to RPE, studies have also been performed demonstrating that hESC derived photoreceptors can be successfully implanted into mice[85]. This may allow for not only photoreceptor rescue but also potential replacement of dead photoreceptors in the future. In light of these exciting advances in both genetic and stem cell therapy, the future of AMD treatment shows substantial promise.

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Improving refractive outcomes in cataract surgery: A global perspective

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Abstract

This review summarises the current evidence base and provides guidelines for obtaining good refractive outcomes following cataract surgery. Important background information is also provided. In summary, the requirements are: (1) standardisation of biometry equipment used for axial length and keratometry measurement and the use of optical or immersion ultrasound biometry; (2) sutureless cataract surgery with "in the bag" intraocular lens (IOL) placement; (3) an appropriate 3rd, 4th or 5th Generation IOL power formula should be used; (4) IOL formula constants must be optimized; (5) under certain conditions, the refractive outcome of the 2nd eye can be improved based on the refractive error of the first eye; and (6) results should be audited for refinement and to ensure that standards are met.

Key words: Biometry; Cataract extraction; Ocular refraction; Intraocular lens; Intraocular lens Power Formula

Core tip: The requirements for good refractive outcomes in cataract surgery are: (1) standardisation of biometry equipment used for axial length and keratometry measurement and the use of optical or immersion ultrasound biometry; (2) sutureless cataract surgery with "in the bag" intraocular lens placement; (3) an appropriate 3rd, 4th or 5th Generation intraocular lens (IOL) power formula should be used; (4) IOL formula constants must be optimized; (5) under certain conditions, the refractive outcome of the 2nd eye can be improved based on the prediction error of the cataract surgery for the first eye; and (6) results should be audited for refinement and to ensure that standards are met.

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INTRODUCTION

Advances in technology and improvements in technique have made cataract surgery safe and effective at restoring vision to millions of patients worldwide. Phacoemulsification with intracapsular intraocular lens (IOL) implantation has been universally adopted in developed countries and manual small incision cataract surgery has revolutionized service delivery elsewhere. Achieving the desired refractive outcome is now a primary aim of surgery and so can be used as a measure of the quality of clinical services. In developed countries, patients expect reduced spectacle dependence and in developing countries residual uncorrected high refractive error remains an important cause of visual disability, which can be caused by

inappropriate selection of IOL power at surgery[1]. This article reviews the evidence base and offer guidelines to achieve optimal refractive outcomes.

THE INFLUENCE OF SURGICAL TECHNIQUE ON REFRACTIVE OUTCOMES

Conventional extracapsular cataract surgery with a large corneal section requiring sutures has declined in popularity. Its main disadvantages were the delay in visual rehabilitation due to the induction of corneal astigmatism as well as the need to remove corneal sutures following surgery[2]. Furthermore, sulcus IOL placement, makes the actual post-operative IOL position, and hence refraction, less predictable[3]. Continuous curvilinear capsulorhexis allows for predictable placement of the IOL in the capsular bag and small self sealing corneal incisions induce less post-operative astigmatism[4-6]. Manual small incision cataract surgery can also result in low amount of induced astigmatism, especially when a temporal approach is used[7].

Optimal refractive outcomes can be achieved both in phacoemulsification and small incision manual cataract extraction when the following conditions are met: (1) reproducible measurement of axial length and keratometry (preferably but not necessarily with optical biometry), (2) good surgical technique with a low rate of posterior capsular rupture; (3) in-the-bag IOL placement and a capsulorhexis size smaller than the optic diameter; (4) appropriate choice of IOL power formula and, most importantly, (5) availability of post operative refraction; and (6) adjustment of the IOL formula constant (optimization) for the specific IOL model and the specific methods of biometry used.

BIOMETRY METHODS

The measurement of the physical dimensions of the eye is necessary to calculate the intraocular lens power. The minimum measurements required are axial length and corneal power. Many suitable devices can take these measurements but all these have systematic differences in measurement. It is therefore very important that the intraocular lens formula is used with the correct formula constant that corrects for these systematic differences in measurement[4]. This not only applies for the axial length measurement method but also for the keratometry method.

Axial length measurement

Axial Length measurement can be performed using ultrasound or optical methods. Optical methods use partial coherence interferometry or low coherence reflectometry[8]. Their advantages over ultrasound methods are that they are non-contact, precise and reproducible and have a low dependence on operator skill. Optical methods are considered to be the standard of care in developed countries. Nevertheless, they are more expensive and less portable than ultrasound methods and cannot provide measurements in the presence of dense axial lens opacities. Contact ultrasound methods give systematic errors in measurement of the axial length due to the inadvertent compression of the cornea[9] and the magnitude of error is influenced by the operator experience[10]. Immersion ultrasound techniques do not cause corneal compression and can deliver refractive outcomes similar to optical methods[11].

Keratometry

Modern optical biometry devices have in-built keratometers, which enable very good refractive outcomes with respect to correcting spherical error. It is outside the scope of this review to discuss the assessment and correction of astigmatism at the same time as performing cataract surgery. Published optical IOL formula constants for each IOL model are derived from axial length and keratometric data obtained from each device. These published IOL constants can be used with confidence by surgeons when they start using a new IOL model, provided they are using the same instrument.

Combining separate axial length and keratometry instruments (when for example ultrasound is used for axial length measurement) can also give very good results but departments must make sure that they optimize their IOL formula constants based on their data for the specific set of instruments used. Manufacturers' IOL constants can not be relied upon for good refractive outcomes.

Other biometric measurements

Newer biometry formulae use one or more of the following biometric measurements: Anterior Chamber Depth, Lens thickness, White to White diameter, age and preoperative refraction. The benefits of using these additional measurements are not proven and excellent results can be obtained using a combination of 3rd generation IOL formulae with optimized IOL constants.

Choice of biometry instruments

For established eye departments where the supply of electricity is reliable, optical biometry has clear advantages over ultrasound biometry as very precise measurements can be obtained quickly and without any contact of any instrument with the eye. In the setting of limited resources, ultrasound axial length measurements can offer good outcomes, especially when an immersion technique is used. The added time required for traditional immersion techniques with a shell have been a limiting factor with respect to their adoption as it would affect the flow of patients in high volume practices. Newer immersion techniques include the use of a clip-on attachment that requires minimal amount of saline or the use of lubricant eye gel as a coupling agent. These immersion techniques are more time efficient than using a traditional immersion shell and offer advantages in precision over contact methods. In cases where electricity supply is not reliable, both ultrasound biometry and keratometry are available as portable battery operated units. Some portable

Table 1 Available intraocular lens power formulae

Name of formula	Variables required	Comments
SRK I and Binkhorst I 1st Generation	Keratometry, Axial Length	Obsolete High levels of error, should not be used
SRK II and Binkhorst II 2nd Generation	Keratometry, Axial Length	Obsolete High levels of error, should not be used
Holladay 1 3rd Generation	Keratometry, Axial Length	Trend toward better outcomes for eyes between 22.00 mm and 26.00 mm, compared to other 3rd generation[14]
SRK/T 3rd Generation	Keratometry, Axial Length	Better outcomes for eyes over 26.00 mm, compared to other 3rd generation formulae[14]
Hoffer Q 3rd Generation	Keratometry, Axial Length	Better outcomes for eyes under 22.00 mm, compared to other 3rd generation[14]
T2 3rd Generation	Keratometry, Axial Length	Very good outcomes for eyes over 22.00 mm[15] It corrects the cusp phenomenon, an error observed using the SRK/T on certain eyes[16]
Holladay 2 4th Generation	Keratometry, Axial Length, Anterior Chamber Depth, Lens Thickness, Horizontal White to White, Age, Pre operative refraction	No data has been reported showing an advantage over an appropriately selected 3rd generation formula
Olsen 4th Generation	Keratometry, Axial Length, Anterior Chamber Depth, Lens Thickness, Horizontal White to White	There is eidence suggestive of improved performance over 3rd generation formulae for eyes with axial length between 20.00 and 26.00 mm[17,18]
Haigis 5th Generation	Keratometry, Axial Length, Anterior Chamber Depth	Very good outcomes for eyes across the axial length range and best reported outcomes for eyes longer than 28.00 mm[19] For best results, three IOL constants need to be optimized requiring data from at least 500 eyes

IOL: Intraocular lens.

keratometers are combined with an autorefractor, which is very valuable as IOL constant optimization depends on the availability of post-operative refraction data. The international agency for the prevention of blindness publishes a standard list of equipment for Vision 2020 eye care service units and this can be used for guidance[12,13].

IOL POWER FORMULAE

The evolution of IOL power calculation formulae has consistently improved the predictability of refractive outcomes, since Fyotorov's first IOL formula. There are now a plethora of IOL formulae but only some of these are still considered fit for purpose. Table 1 summarizes the IOL formulae found in biometry instruments, along with comments for each one.

Outcomes with single power implantation

Implanting a single power IOL without biometry assessment used to be common in developing countries as it was said that certain populations do not have as high variability in axial length as in developed countries[20]. Nevertheless, choosing an appropriate IOL power based on pre-operative biometry promises improved unaided vision[21] and much more predictable refractive outcomes. Many patients in developing countries do not have access to optical correction and therefore high refractive errors are a significant cause of visual disability[22].

Outcomes with formulae using two biometric variables (Axial length and Keratometry)

For the majority of cataract surgery cases worldwide, the biometric measurements that can be practically assessed are axial length and keratometry. These can be performed at a low cost using portable battery operated instruments. Using axial length and keratometry, the refractive outcomes of cataract surgery have the potential to reach a very high level of accuracy and precision provided that a number of conditions are met.

An appropriate 3rd generation IOL power formula should be used: The Hoffer Q should be used for eyes less than 22.00mm, the Holladay 1 should be used for eyes between 22.00 and 26.00 and the SRK/T is more appropriate for eyes over 26.00 mm. These formulae are available in commercial biometry instruments. The T2 formula has addressed a source of error inherent to the SRK/T formula, called the cusp phenomenon and can therefore be used in eyes 22.00 or longer[15]. Although the T2 formula has been published, it is not currently included in commercial biometry products. The formula is available as an Excel spreadsheet at http://www.richardsheard.net/T2Formula.aspx. Previous generation two-variable formulae are obsolete and should not be used. These include the SRK- Ⅰ, SRK Ⅱ, Binkhost Ⅰ and Ⅱ, and the original Hoffer formula.

An optimized IOL constant should be used: The IOL constant value depends on (1) the IOL model; (2) the biometry instruments used; and (3) the position of the IOL implantation (in the bag *vs* sulcus). These factors are far more important than any differences between surgeons, something formerly thought to be important. Indeed for small incision phacoemulsification surgery and optical biometry it has been demonstrated that there are no significant differences between most surgeon's optimized constants, only between methods of measurement.

It is worth noting that using manufacturer's (non-

optimized) constants even with an appropriate 3rd generation IOL formula can give very poor refractive outcomes, which are usually in the hyperopic direction when using optical biometry[4]. The IOL constant that is contained on the IOL packaging is often not appropriate for IOL calculations. When starting to use a new IOL implant, it is suggested that published IOL constants are used[23]. For ultrasound biometry, the manufacturer may have data to help departments until they have enough cases to optimize their own IOL constants.

If an incorrect IOL constant is used, the formula would give results which are systematically skewed towards the hypermetropic or myopic end and result in consistently poor outcomes. The optimization of the IOL constant "resets" the mean error of the formula to 0. This means that on average the refractive aim and the post op refraction are the same. From there on, the method of biometry and the appropriateness of the IOL formula help minimise the distribution of errors.

IOL power formulae using three or more biometric variables

The Holladay 2 was the first published formula that used these variables, but its code has never been available in the public domain. Later on, Thomas Olsen and Wolfgang Haigis separately published their own eponymous IOL formulae and these have been published[17,24]. The evidence so far suggests that the Olsen formula has a statistically significant advantage over the Hoffer Q, the Holladay 1 and the SRK/T in eyes between 20.00 and 26.00 mm[17,18]. The Haigis formula with all three IOL constants optimized has been found to perform very well across the axial length range as well as giving a lower prediction error in very myopic eyes, compared to the SRK/T[19]. We could not find any published evidence showing that the Holladay 2 formula performs better than an appropriately selected 3rd generation IOL formula.

ACHIEVING HIGH ACCURACY AND PRECISION IN REFRACTIVE OUTCOMES

The need to describe and quantify refractive outcomes arises from the fact that in many cases, the predicted postoperative refraction is not the same as the actual (or observed) post operative refraction. Observed refraction minus the Predicted Refraction is the Refraction Error. For example if for a patient the refractive aim with the chosen IOL power is -0.53 D and the actual post operative result was -0.25 D, then the Prediction Error for this eye would be +0.28D.

When describing refractive outcomes for a large sample of eyes, the measures need to quantify: (1) how close to zero the average prediction error of this sample of eyes is (Mean Error); and (2) how widely dispersed are the errors spread around this mean. The approach of choosing an appropriate IOL power could be likened to a rifle competition. The success of using a rifle depends not only on the technology of the aiming device it carries but also on whether the aiming device has been appropriately calibrated. Mean Error is a measure of Accuracy, *i.e.*, an AVERAGE measure of how close most shots hit the target. On the other hand, Precision represents the spread of the shots around the mean, and this can be measured by the Standard Deviation of the Prediction Error. Figure 1 gives examples of targets shot with: (1) High Accuracy and High Precision; (2) High Accuracy and Low Precision; (3) Low Accuracy and High Precision; and (4) Low Accuracy and Low Precision.

In the same way, in order to achieve good refractive outcomes in cataract surgery, it is not enough to use appropriate biometry methods and formulae. The calculations need to be calibrated (or optimized) in order to achieve the target refraction for the majority of eyes. The availability of good biometry methods and modern biometry formulae has improved the precision of achieving the refractive target. Nevertheless, this is not enough and surgeons need to use an appropriately Optimized Formula Constant for the particular IOL model used in order to correct the accuracy of the results. There is a very good example of an eye department in the United Kingdom, which made the transition from ultrasound to optical biometry and subsequently audited their refractive outcomes[25]. Their initial results showed that when the manufacturer's IOL constant was used with optical biometry, patients became on average 0.63D more hypermetropic than expected with only 65% achieving refraction within 1.0 Dioptre from target. Following adjustment of the IOL constant based on audit results, the Mean Error was reduced to -0.14D and 95% of cases achieved refraction within 1.0D of their target. Using the rifle paradigm, the move from ultrasound to optical biometry can be likened to an upgrade of the aiming device of the rifle. The new aiming device was not calibrated and therefore was consistently resulting in shots hitting +0.63D away from target, despite the fact that these shots were tightly grouped. The adjustment of the IOL constant moved the average deviation closer to zero.

Optimizing the IOL constants provides a greater magnitude of improvement in results than choosing the correct IOL formula for a given axial length range[14].

GUIDELINES FOR OPTIMIZING THE IOL CONSTANT

When using a new IOL model, formula constants should be obtained from a reputable source such as the manufacturer or the ULIB website and should be appropriate for the method of measurement used (*i.e.*, for the specific instruments used for axial length and keratometry measurement). The refractive outcomes using this IOL model should be audited and once more than 100 eyes are obtained, the IOL constant may be modified in order to improve future refractive outcomes.

Most IOL constant optimization protocols define a minimum post operative time period from cataract surgery for refractive data collection. This is usually set at 1

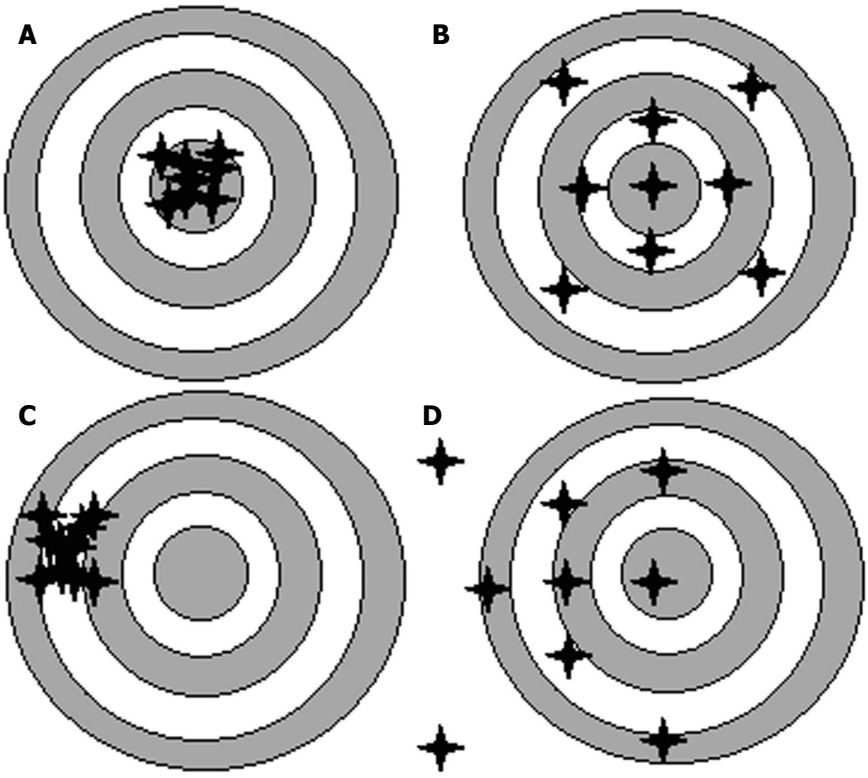

Figure 1 Examples of changing accuracy and precision on a shooting target. A: High accuracy and high precision; B: High accuracy and low precision; C: Low accuracy and high precision; D: Low accuracy and low precision.

month, by which time post operative refraction is considered stable. This should be the standard for most eye units. In situations where patients travel a large distance and they are only available on day 1 post operatively (such as in eye camps), day one autorefraction is a reasonably reliable source of post op refraction, which can be performed by non medical staff and therefore have a small impact on staff resources[21]. In such circumstances cases, day one best corrected visual acuity of 6/18 may be used as the minimum level of VA in order for cases to be included for IOL constant optimization.

DATA REQUIREMENT AND SELECTION OF EYES

For 3rd generation IOL formulae, there should be around 100 such eyes to calculate an optimized IOL constant. The data required are: (1) preoperative Axial length; (2) preoperative keratometry; (3) IOL model and power used; (4) IOL constant used; (5) post operative refraction (spherical equivalent); and (6) post operative visual acuity. Appropriate eyes for inclusion are those that had uncomplicated cataract surgery with in the bag IOL implantation and a final best corrected visual acuity of 6/12 or better (or minimum BCVA 6/18 for day 1 refraction in eye camps). Eyes that had coexistent corneal pathology such as pterygium and keratoconus or concurrent surgery such as trabeculectomy, corneal surgery or vitrectomy should be excluded. It is worth noting that the same sample of eyes containing the full range axial lengths can be used for optimizing the Hoffer Q, the Holladay 1 and the SRK/T even though the Hoffer Q formula is recommended for eyes shorter than 22 mm. If optimization relied only on eyes < 22 mm in length a very large number of cataract operations would be required to include 100 eyes under 22 mm in length.

METHODS OF OPTIMIZING IOL CONSTANTS FOR 3RD GENERATION IOL FORMULAE

With some electronic patient records or with optical biometers such as the Zeiss IOLMaster or the Haag-Streit Lenstar 900, there are inbuilt processes in its software for automatically calculating optimized IOL constants. When these are not available, data can be processed manually. One option is to use a validated iterative method where the IOL constant for each eye is retrospectively calculated so that the post operative prediction error is 0. These IOL constants are then averaged (after excluding 5% outliers on each side of the distribution). This method requires access to specialized software as well as having a high level of programming skills. A third option would be to manually estimate a close approximation of the optimized IOL constant, which does not require specialized IT skills or equipment. Using (1), (2), (3) and (4) from the list above, the predicted refractive error is calculated for each eye. Subtracting the post operative refraction from the predicted refraction in each eye gives the prediction error for each eye. When the average prediction error

is calculated for a sample of 100 suitable eyes, the IOL constant is increased if the average prediction error is hyperopic or reduced if it is myopic. The magnitude of IOL constant alteration can be calculated in the following manner: For each 0.1 Dioptre of hyperopic error, the following adjustments need to be made: 0.06 for the pACD(Hoffer Q), 0.06 for the SF (Holladay 1) and 0.12 for the AC (SRK/T)[4]. For example, if for a specific IOL model the average prediction error for 100 appropriate eyes was +0.53D using a pACD of 4.97, an SF of 1.22 and an AC of 118.0, the following optimization would need to be made. For the pACD the new constant would be increased by 0.318 to 5.288, for the SF the constant would be increased by 0.318 to 1.538 and for the AC it would be increased by 0.636 to 118.636. In practice, the IOL constants for 3rd generation formulae are used to an accuracy of 2 decimal places for the pACD and the SF and one decimal place for the AC.

FURTHER OPTIMIZATION OF REFRACTIVE OUTCOMES: IMPROVEMENTS FOR THE 2ND EYE

If the IOL constants are optimized and appropriate IOL formulae are used, refractive outcomes can be further improved when operating on the 2nd eye of a patient. It has been calculated[26-28] and prospectively validated[29] that the second eye can obtain improved refractive outcomes by modifying its refractive aim by half of the prediction error of the first eye. For example, if the first eye of a patient had a prediction error of +0.64D following surgery, the second eye should be aimed at -0.32D from the intended refraction. The requirements for this method to be applicable are: (1) in the bag IOL placement for both eyes; (2) the same IOL model and formula used in both eyes ;(3) interocular difference in keratometry of less than 0.6D; and (4) prediction error for the first eye +/-1.5D or less[27]. The same IOL formula should be used in both eyes and an optimized IOL constant should be used. This relationship has been demonstrated with the Hoffer Q, the Holladay 1, the SRK/T and the Olsen formulae. All papers were based on data obtained using optical biometry so this should not be used for eyes measured with contact ultrasound. No recommendation can be made for immersion ultrasound.

ADDITIONAL CONSIDERATIONS FOR REFRACTIVE PLANNING IN CATARACT SURGERY

This article is aimed at a worldwide audience and aims to review the evidence on predicting spherical prediction error following cataract surgery, which globally is the most important refractive determinant of visual function following cataract surgery. In any surgical setting, may this be a tertiary centre in an economically fully developed country or an eye camp in a developing country, minimizing spherical refractive error should be one of the primary aims of cataract surgery. The relative importance of other factors that may be considered greatly depend on the resources available. These include the management of corneal astigmatism[30], concurrent correction for presbyopia using a variety of intraocular lens designs[31] and the use of femtosecond lasers[32]. It is not in the scope of this review to assess the evidence on the management in these situations.

STANDARDS FOR REFRACTIVE OUTCOMES

Using an appropriate 3rd generation IOL formula with optimized constants and optical biometry with phacoemulsification and intracapsular IOL placement, around 70% and 95% of eyes can achieve refraction within ± 0.50D and ± 1.00D of the refractive target, respectively[14]. Using immersion ultrasound, similar results to optical biometry can be obtained as long as optimized IOL constants and appropriate 3rd generation IOL power formulae are used[33].

CONCLUSION

Refractive outcomes are a very important aspect of cataract surgery in any clinical setting. Good results primarily depend on the use of optimized IOL constants and appropriate IOL formulae. Clinical audit of post operative refraction is required in order to validate and refine IOL constants. The availability of optical biometry has enabled further improvements by the efficient capture of precise data but in departments where optical biometry is not available, very good outcomes can be obtained using modifications of immersion ultrasound technique and optimizing the IOL constants for the particular department.

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MINIREVIEWS

Current evidence of pathophysiology of diabetic macular edema: A review

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Abstract

Diabetic macular edema (DME) is an important cause of vision loss in patients with diabetes mellitus. The pathophysiology of DME can be described as a process whereby hyperglycaemia leads to overlapping and inter-related pathways that play a role not only in the initial vascular events, but also in the events that cause the edema to become chronic. On a macrocellular level, DME is believed to be in part caused by alterations in hydrostatic and oncotic pressures and shear stress. Angiogenic factor expression, inflammation and oxidative stress constitute the key components of microvascular pathways. The interactions, signalling events and feedback loops between the various molecules are complicated and are not completely understood. These molecular mediators, acting in conjunction with macrocellular factors, which are all stimulated in part by the hyperglycaemia and hypoxia, can have a direct endothelial effect leading to hyperpermeability, disruption of vascular endothelial cell junctions, and leukostasis. Macular edema is thought to be caused as a result of these consequences.

Key words: Diabetes mellitus; Macular edema; Pathophysiology; Vascular endothelial growth factor; Inflammation

Core tip: Diabetic macular edema (DME) is an important cause of vision loss in patients with diabetes mellitus. The pathophysiology of DME can be described as a process whereby hyperglycaemia leads to overlapping and inter-related pathways that play a role not only in the initial vascular events, but also in the events that cause the edema to become chronic. On a macrocellular level, DME is believed to be in part caused by alterations in hydrostatic and oncotic pressures and shear stress. Angiogenic factor expression, inflammation and oxidative stress constitute the key components of microvascular pathways. The interactions, signalling events and feedback loops between the various molecules are complicated and are not completely understood. These molecular mediators, acting in conjunction with macrocellular factors, which are all stimulated in part by the hyperglycaemia and hypoxia, can have a direct endothelial effect leading to hyperpermeability, disruption of vascular endothelial cell junctions, and leukostasis. Macular edema is thought to be caused as a result of these consequences.

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INTRODUCTION

Most common reason of visual loss in diabetes mellitus (DM) is diabetic macular edema (DME)[1,2]. Macular edema can develop in any stage of the disease but the risk increases as the disease progresses[3]. The role of hyper-

glycemia on development of DME has been investigated in a population based study, Wisconsin Epidemiologic Study of Diabetic Retinopathy (DR). In this study, the risk of developing DME in 10 years is reported as 20.1% in type I DM, 13.9% in noninsulin-dependent type Ⅱ DM and 25.4% in insulin-dependent DM patients[4].

The classification of DME has changed over time as new imaging techniques have evolved. DME is classified as clinically significant according to visible retinal thickening and hard exudates in relation to distance from macula in Early Treatment Diabetic Retinopathy Study. In Global Diabetic Retinopathy Project, mild, intermediate or severe DME have been described according to the severity of involvement of macular center in light of ocular coherence tomographic findings[5,6].

Since the macular edema in presence the of DM may lead to permanent visual loss, it is of great importance to understand the pathophysiology of DME in order to prevent this complication and to develop new treatment strategies. The factors leading to development and progression of DME and the macrovascular and microvascular changes induced by DM are summarised in this review.

GENERAL INFORMATION

Why is the macula involved?

Even though there is a generalized micro vascular damage and vascular leakage throughout the retina, there are some predisposing histological and metabolic properties of the macula that render it prone to edema: (1) high cellular concentration; (2) high metabolic activity; (3) the oblique-horizontal course of Henle fibers toward periphery; (4) weak intercellular junctions in the external plexiform layer; and (5) presence of central avascular zone.

Normal retinal circulation and blood-retinal barrier

Among the tissues in the body, retina is one of the tissues with highest oxygen requirement and is supplied by two different circulations. Inner 2/3 of retina is supplied by retinal circulation and outer 1/3 is supplied by choroidal vessels. Endothelial cells on vascular wall and the surrounding pericytes and astrocytes constitute the inner blood retinal barrier. Outer blood retinal barrier is formed by tight junctions between the cells of retinal pigment epithelial (RPE) layer.

In retinal circulation, arteries branch into precapillary arterioles which are surrounded by smooth muscle cells controlled by autonomic nervous system. Beyond this level, in the capillary layer, pericytes take place of smooth muscle cells and the flow rate is determined by autoregulation. Under normal circumstances, capillaries and venules are primary sites of fluid passage and the flow changes according to local metabolic needs, oxygen and carbon dioxide partial pressures. In the early stages of diabetic retinopathy, there is damage to inner blood retinal barrier and the increased filtration of fluid from capillaries and venules result in macular edema.

PATHOPHYSIOLOGY

There are numerous pathophysiologic mechanisms that have been proposed as the role of diabetes on development of DME. But, the exact mechanism of the damage to the blood-retinal barrier caused by hyperglycemia is not known. Several pathways involving angiogenic and inflamatory factors and oxidative stress are considered to take role.

Macrovascular effects of diabetes

In all tissues including retina, the movement of fluid and particles across vascular wall depend on intravascular and extravascular hydrostatic and oncotic pressures. According to Starling's Law, equilibrium is reached when the differences between intra and extravascular the oncotic and hydrostatic pressures are equal. In retina, capillary hydrostatic pressure is related with systemic blood pressure, and the oncotic pressure is related with the albumin level that constitute majority of serum proteins. Tissue hydrostatic pressure is equal to intraocular pressure and tissue oncotic pressure is related with interstitial protein content. This equilibrium is disrupted in case of diabetes by several factors. Increased transluminal hydrostatic pressure due to hypertension and increased tissue oncotic pressure due to blood- retinal barrier damage and leakage of intravascular proteins into the interstitial space result in retinal edema. If a there is coexistent diabetic nephropathy, the decreased serum albumin levels lower intravascular oncotic pressure which contribute to edema[7].

There are animal models which show increased ocular blood flow in case of increase in blood glucose levels. It is also reported that acute increases in plasma glucose levels cause increase in ocular blood flow in human studies. Increased thromboctye aggregation, decreased erythrocyte deformability and increased blood flow cause an increase in shear stress on the vascular endothelial cells. The resulting secretion of vasoactive and inflammatory factors contribute to the pathological process on the molecular level[8,9].

Microvascular effects of diabetes

Pericyte loss is the earliest and most specific sign of diabetic retinopathy. Cogan *et al*[10] have shown the loss of the pericytes as ghost cells surrounding the capillary walls. The mechanism of pericyte loss in diabetes is not clearly known. Pericytes express advanced glycosylation endproducts (AGE) receptors and thus may be susceptible to damaging effects of AGEs. Additionally, it may be indirectly related to the leukocyte adhesion to the vasculature[11].

Pericyte loss is the first sign that can be shown histologically, whereas the first clinical sign of diabetic retinopathy that can be shown by fundus examination and fundus flourescein angiography is microaneurysm formation. Pericytes exert antiproliferative effect on endothelial cells and their loss results in hypercellular microaneurysm formation. Hypocellular aneurysms are thought to be formed by apoptosis of these proliferated endothelial

cells. Pericyte loss also results in loss of support around the vascular wall which leads to focal dilatations at the weak points contributing to microaneurysm formation[10].

Thickening of the capillary basal membrane and accumulation of the extracellular matrix elements are shown in diabetes retinopathy. It is thought that these changes result in abnormal autoregulation of vascular flow and retinal hemodynamic instability.

Endothelial cells have intercellular tight junctions which act as barrier to intravascular components. These junctions are formed by numerous intercellular proteins including occludin, claudin and zonula occludens-1 which are responsible for most of the barrier function. In diabetes, the synthesis and expression of these proteins are affected resulting in weakening of intercellular bonds.

Combined effect of loss of pericytes, microaneurysm formation, basement membrane thickening and loss of intercellular junction proteins result in DME.

Biochemical effects of diabetes

Four pathways have been proposed as the mechanism of microvascular damage as a result of hyperglycemia. These are: (1) polyol pathway (Aldose reductase pathway); (2) advanced glycation end product formation; (3) protein Kinase C activation; and (4) hexosamine pathway.

Until recently, these four pathways were thought to operate separately to form vascular damage. But all these pathways are shown to operate by increasing superoxide formation by the mitochondria and increased superoxide levels play the central role in the combined theory of diabetic retinopathy mechanism[12].

Growth factors and inflamation

Vascular endothelial growth factor (VEGF) is a growth factor that regulates embryologic vasculogenesis and pathologic angiogenesis by stimulating endothelial cell migration and proliferation and increasing survival. Among different members of the VEGF family, VEGF-A plays the key role in ocular angiogenesis and vascular permeability. VEGF-A has 9 isoforms, VEGF-A165 being mostly involved in ocular pathologies[13-15]. VEGF causes DME by the stimulation of the development of neovascularization that are devoid of tight junctions between the endothelial cells[16]. In addition, VEGF has a proinflamatory effect by causing increase in ICAM-1 and VCAM-2 resulting in stimulation of leukocyte chemotaxis and adhesion.

One VEGF family member that has become an important treatment target is Placental Growth Factor (PlGF) which is first isolated from the placental tissue. It causes DME by causing damage to intercellular tight junctions on vascular wall and retinal pigment epithelium. Tissue hypoxia and insulin stimulates PlGF formation which causes subretinal fluid accumulation and increase in retinal edema[17].

There are many evidence that show inflammation plays a role in diabetic retinopathy and DME. The mechanism of intravitreal corticosteroids in decreasing macular edema has not been fully understood but it supports the hypothesis that inflammation is part of the DME process.

The blood retinal barrier does not allow passage of leucocytes under normal conditions. In DM, leucocytes produce toxic superoxide radicals and proteolytic enzymes that weaken the intercellular tight junctions and denature extracellular matrix proteins. This leads to vascular leakage and edema. Leucocytes become rigid and bind strongly to endothelial cells. Combined with rigid erythrocytes and thrombocytes, these leucocytes also cause vascular occlusion. This causes focal retinal ischemia and hypoxia which further leads to increase in inflammatory reaction[18-20].

There are many inflammatory mediators that have been shown to increase in vitreus and systemic circulation in case of diabetes mellitus and diabetic retinopathy. Most studied mediators are tomur necrosis factor-alpha (TNF-α), interleukin-6 (IL-6) and intercellular adhesion molecule-1 (ICAM-1). TNF-α is a proinflammatory cytokine and is thought to serve by increasing leucostasis and is related with VEGF and ICAM-1 levels[21]. ICAM-1 is an intracellular protein that is required for the adhesion of leucocytes to endothelial cells. ICAM levels increase with VEGF stimulation and AGE (Advanced glycation products- ileri glukozilasyon ürünleri) products. This also exerts its effect by aiding leucostasis[22]. IL-6 is shown to increase VEGF expression and causes edema by increasing vascular permeability[23,24].

Other factors

Matrix metalloproteinases are cytokines that increase locally with advanced glycation end products, reactive oxygen and direct effects of hyperglycemia. Under normal conditions, they play role in extracellular matrix formation, repair and angiogenesis. They cause protein degradation and weakening of intercellular tight junctions which lead to increase in vascular permeability[25].

Type 1 carbonic anhydrase enzyme has been shown in choroidal endothelium and retina pigment epithelium[26]. CA causes a more profound increase in vascular permeability when compared to VEGF. CA inhibitors are used to treat macular edema caused by other pathologies in which these are thought to inhibit CA in retinal pigment epithelial cells resulting in increased absorbtion of extracellular fluid. But DME patients do not respond well to CA inhibitors. RPE is presumed to be damaged in DM or the abnormal amount of extracellular fluid exceeds the limits of RPE[26-28].

Hypertension is a known risk factor in development and progression of diabetic retinopathy. Angiotensin 2 (Ag-2) increases VEGF and related vascular permeability. Ag-2 is shown to cause pericyte migration and hypertrophy. Angiotensin converting enzyme receptors are found on endothelium, choroid and pericytes. ACE inhibitors decrease blood pressure as well as decreasing retinal blood flow. ACE inhibitors are shown to decrease development of DR in type 1 DM but does not seem to have effect on progression and DR development in type 2 DM patients[22,29,30].

CONCLUSION

In conclusion, as a major cause of visual loss in diabetic patients the pathogenesis of DME is complex, and a variety of factors and biochemical pathways are involved, which provides an opportunity for the development of a number of therapeutic modalities to treat the condition.

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MINIREVIEWS

Predictors of visual outcome in traumatic cataract

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Abstract

Traumatic cataract resulting from open- or closed-globe ocular trauma is one of the most common causes of blindness. Visual outcome is unpredictable because this is not determined solely by the lens. There is a lack of a standard classification, investigations, and treatment guidelines related to the outcome, with considerable debate regarding predictive models. We review the predictors of visual outcome following surgical treatment of traumatic cataracts, which may act as a guide to clinicians.

Key words: Traumatic cataract; Visual outcome; Birmingham Eye Trauma Terminology System; Ocular trauma score; Morphology of traumatic cataract; Open globe injuries; Classification of ocular trauma; controversy; Pediatric ocular trauma

Core tip: Visual outcome of traumatic cataract is controversial and confusing as it is not only the lens which decides prognosis, but many other factors also responsible. We have tried to address predictors which may forecast visual outcome in case of traumatic cataract.

Shah M, Shah S, Gupta L, Jain A, Mehta R. Predictors of visual outcome in traumatic cataract. *World J Ophthalmol* 2014; 4(4): 152-159 Available from: URL: http://www.wjgnet.com/2218-6239/full/v4/i4/152.htm DOI: http://dx.doi.org/10.5318/wjo.v4.i4.152

INTRODUCTION

Ocular trauma can induce cataract formation[1-6]. The methods used to evaluate the visual outcome in eyes managed for traumatic and senile cataracts are similar; however, the damage to other ocular tissues resulting from trauma may additionally compromise the visual gain following surgery. Therefore, the visual outcome may differ depending upon co morbidities. Ocular trauma remains a controversial topic and the debate over management strategies continues. The international classification of ocular trauma proposed almost 15 years ago requires re-evaluation and should be more robust in terms of predicting the outcome of open-globe injury (OGI)[7].

The introduction of the Birmingham Eye Trauma Terminology System (BETTS) has standardized ocular trauma documentation[8]. Consequently, visual outcomes following traumatic cataract surgery and the determinants predicting the outcome can be investigated with respect to the BETTS category[8,9]. Although visual outcomes of traumatic cataracts have been reported, most studies involved only small populations or were case studies.

The timing of cataract surgery and intraocular lens (IOL) implantation in trauma continues to be debated worldwide. A number of issues regarding the management of traumatic cataract remain unresolved. The high risk of amblyopia and intraocular inflammation as well as strong vitreoretinal adhesions in the pediatric age group require management based on different principles. Prospective, controlled clinical studies of OGI are not possible. This article reviews pertinent data regarding these management issues and controversies, and provides recommendations for treatment based on the available published data and the authors' personal experience. Blindness due to injury is a social and economical burden on society and the individual[6,7,9].

This study was performed with the approval of the

Table 1 Factors effecting visual outcome

Variable	*P* value
Socio-economic status	0.308
Age	0.020
Sex	0.600
Hospital entry	0.010
Habitat	0.431
Previous treatment	0.068
Object causing the injury	0.103
Activity during injury	0.340
Preoperative vision	0.000
Morphology	0.015
Surgical technique	0.000
Primary posterior capsulotomy and vitrectomy	0.001
Time interval between injury and intervention	0.030
Lens implant	0.000
Number of surgeries	0.125
Type of injury (BETTS)	0.000
Type of injury (BETTS subgroup)	0.007
Relative afferent pupillary defect	
Ocular trauma score	0.000
Infection	0.000

BETTS: Birmingham Eye Trauma Terminology System.

Hospital Ethical Committee and complies with the tenets of the Declaration of Helsinki. Written consent in the local language was obtained for the use of the information in this article.

EPIDEMIOLOGY AND INCIDENCE

The incidence, based mainly on retrospective studies and eye injury registries, varies in different regions of world. Incidence variability also arises because of different demographic conditions, including age, sex, environment, and socio-economical conditions[4]. The incidence of traumatic cataract also varies within the pediatric age group[4-6,10,11].

It is imperative that surgeons are aware that traumatic cataract is not a senile cataract. The injury is rarely limited to the lens, but may also be associated with the zonules, posterior capsule, and posterior segment. A patient with traumatic cataract should be informed of the potential visual outcome and the high risk of intraoperative complications[12-19].

It is important to be able to predict visual outcome during the pre-treatment examination as prognosis is to be known to clinician as well as patient. The influence of different variables has been investigated, which we review here with respect to the final visual outcome[20-26].

THE VARIABLES INVESTIGATED AND THEIR SIGNIFICANCE REGARDING THE FINAL VISUAL OUTCOME

Socio-economic factors

Life style, activities, and a lack of protective devices in those of the lower socio-economic group in developing countries make them more vulnerable to ocular injuries; however, visual outcome did not differ with respect to socio-economic factors (Table 1)[1-3].

Age

Younger people are more prone to ocular injuries. The age at intervention has a significant effect, with a better visual outcome achieved in the early age group. It is evident from almost all studies that younger patients respond well to treatment except children under age of 5 who are prone to develop amblyopia.

SPECIAL CONSIDERATION OF TRAUMATIC CATARACT IN THE PEDIATRIC AGE GROUP

Incidence: The incidence varied among studies, most of which were retrospective and involved small databases. Studies on traumatic cataracts in children reported incidences of 25% in southern India, and 12% and 46% in Western India[4-6].

Challenges in children with traumatic cataract include amblyopia, a tendency for inflammation, synechiae and secondary cataract[20]. Children account for approximately one-third of all serious eye injuries[22]. Despite this, the classification and scoring systems in pediatric trauma are based on those developed for adults[22]. The debate over the position of zones Ⅱ and Ⅲ is even more pronounced in pediatric trauma. During the first 5 years the length of the pars plana changes rapidly from approximately 1.8 mm in neonates to 3 mm by 1 year of age, and attains 5 mm at 5 years of age[23,24]. Therefore, pediatric trauma assessment for research purposes is liable to inaccuracy, depending on how the injury is classified.

Children and younger patients exhibit stronger adherence between the posterior capsule and the anterior vitreous centrally; furthermore, the central vitreous is anatomically connected to the peripheral retina at the vitreous base[17]. Any traction on the anterior vitreous face is transmitted to the retina, and the younger the patient, the greater the risk. Additionally, children are at risk of amblyopia. In younger children, a surgeon may resort to a single-step procedure and perform lens extraction, IOL implantation and, if required, anterior vitrectomy for an optimal outcome[25-30]. Primary IOL implantation not only prevents amblyopia but also synechiae formation, which can close the lens capsule by the time secondary IOL implantation is due to be performed[31-33].

Although the management of trauma in children has many similarities to that in adults, striking differences also exist. Foremost is that adults have reached visual maturity, whereas amblyopia is a major contributor to poor outcomes in children, especially in under 5 year olds. The worst outcomes reported were that < 50% of the children with an OGI achieved good vision and amblyopia was a major confounding factor[31-33]. To achieve a clear visual axis following globe repair when treating children with OGI, this must be accompanied by accurate refraction and aggressive patching therapy to improve the visu-

al outcome[34]. A further difference is that a simple examination can prove difficult in a child, especially during the early stages after trauma, resulting in the requirement for general anesthesia or sedation for proper assessment. The involvement of a pediatric ophthalmologist and access to pediatric facilities is therefore essential for ultimate management.

Optical rehabilitation is important because an IOL is not implanted in all cases[21]. Orthoptic treatment following optical correction, including patching and monitoring of visual regain, is vital because amblyopia is an important factor[21].

In conclusion, children with an OGI cannot simply be treated as small adults. Patient age and the effects of amblyopia should be included as additional negative prognostic factors.

Sex

Generally, males are more affected by injuries because of greater participation in outdoor activities; however, no significant difference was found in visual outcome according to sex.

Hospital attendance

Patient hospital attendance has had a significant effect on visual outcome (Table 1)[2,4,34-40]. Patients attend a hospital either by self reporting or *via* outreach activities, including mobile diagnostic camps and school screening. Patients who have attended an outreach program usually present late; thus morphological changes and visual outcome differ.

Habitat

Ocular injuries are more common in rural areas because of the type of related domestic and professional activities[2,4,39,40]. However, the visual outcome did not differ significantly in relation to the habitat.

Previous treatment

The number of patients who received previous treatment depended upon awareness and the availability of services. Past treatment did not have a significant effect on the final visual outcome[39,40].

Object causing the injury

The object responsible for an injury varies according to geographical and socio-economic status, with a marked variation in the United States Eye Injury Register and reports from other sources[2,4,39]. However, there was no significant difference with respect to the visual outcome.

Activity during injury

The type of activity during injury also varies according to geographical and socio-economic status, as indicated by the United States Eye Injury Registry and reports from other sources[2,4], although no significant difference was found regarding visual outcome[39,40].

Preoperative visual acuity of no light perception and poor visual prognosis

Visual acuity can be profoundly impaired, even to the extent of no light perception (NLP), in the presence of significant media opacity (*e.g.*, corneal edema, hyphema, cataract, dense vitreous hemorrhage), retinal detachment, associated subretinal or subhyaloid hemorrhage, hemorrhagic choroids, and even psychological factors (*e.g.*, hysteria). The assessment of light perception is a subjective measurement and not a fool-proof test in the presence of severe media opacity secondary to dense vitreous hemorrhage, traumatic cataract, dense hyphema, or corneal edema. Even with the bright light of an indirect ophthalmoscope, the assessment of light perception can give a false impression of NLP[38]. Ultrasonography is useful in assessing the posterior segment in eyes with media opacity, and to differentiate between retinal detachment and vitreous hemorrhage[38]. However, when using this methodology it is sometimes difficult to differentiate a detached retina from blood clots in the vitreous cavity and membranes[38]. Before deciding on enucleation in NLP patients, reversible causes of vision loss should be excluded, including psychological factors[38]. Even when enucleation appears inevitable, the ophthalmologist should still discuss the possible options with the patient before making a final decision. Primary enucleation of severely traumatized eyes with NLP is controversial due to the risk of sympathetic ophthalmia. Sympathetic ophthalmia with the potential for bilateral blindness is a relative indication for enucleation of an injured eye. Therefore, primary surgical repair should not necessarily be discounted because of the risk of sympathetic ophthalmia in eyes with NLP. Currently, most surgeons recommend a globe-salvaging procedure for eyes with severe trauma with NLP vision at initial presentation.

The age in children at which IOL insertion and rehabilitation of aphakia can be undertaken remains under debate.

Morphology of traumatic cataract

There is no standard morphological classification. Attempts at grading have been made, but these are arbitrary[12]. The morphology of traumatic cataract depends mainly upon the type of injury and the time interval between the injury and intervention.

Based on lenticular opacity, cataracts were classified as: total (Figure 1); white soft with soft material floating in the anterior chamber with broken anterior capsule (Figure 2); membranous, in which both capsules were fused with little or no cortical material (Figure 3); and rosette (Figure 4). A cataract was defined as total when no clear lens matter was observed between the capsule and nucleus. For a membranous cataract the capsule and organized matter were fused and formed a membrane of varying density. A cataract was considered to be white soft when loose cortical material was found in the anterior chamber together with a ruptured lens capsule. A lens with a rosette pattern of opacity was classified as

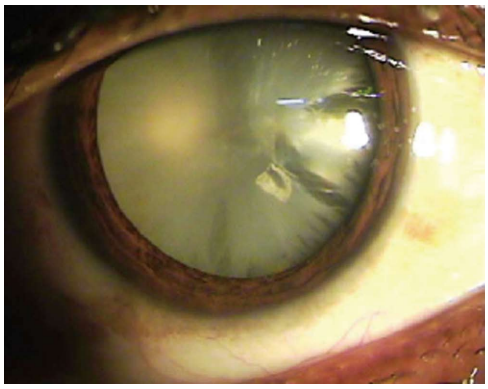

Figure 1 When no clear lens matter was visible between the capsule and the nucleus, the cataract was defined as a total cataract.

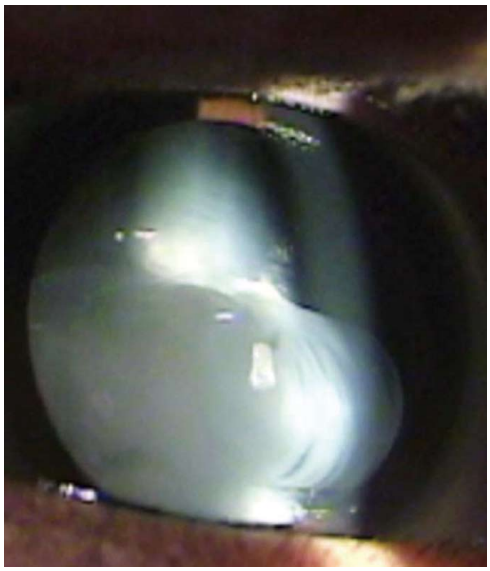

Figure 2 When loose cortical material was found in the anterior chamber together with a ruptured lens capsule, the cataract was defined as a white soft cataract.

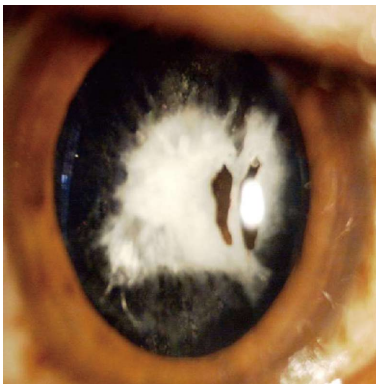

Figure 3 When the capsule and organised matter were fused and formed a membrane of varying density, the cataract was defined as a membranous cataract.

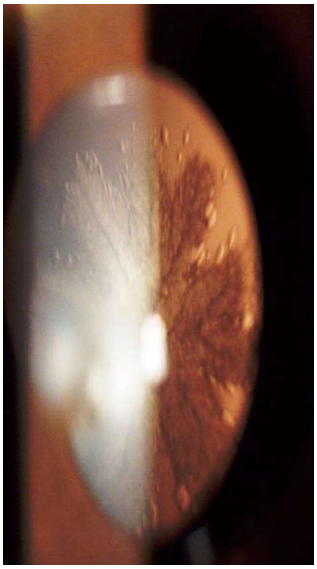

Figure 4 A lens with a rosette pattern of opacity was classified as a rosette type cataract.

a rosette cataract. One study proposed that all cataract cases could be assigned to these groups[13].

Management and surgical approaches to traumatic cataract

The choice of surgery in adults in whom amblyopia is not an issue is governed by the surgeon's own preferences and to a certain extent by the status of the cataractous lens. If the anterior capsule is significantly disrupted and there is free floating lens matter in the anterior chamber, the surgeon may be justified in primary cataract extraction with or without IOL implantation (Figure 3).

Eyes with a lens vitreous admixture should be considered for combined cataract extraction with limited anterior vitrectomy. Judicious use of a vitrector and not an aspirator should be made while removing vitreous admixture in the ruptured lens matter (Figure 4). Any traction on the vitreous may result in inadvertent retinal breaks[14]. When there is additional injury to the posterior segment, early pars plana lensectomy and vitrectomy by a posterior segment specialist is warranted[14]. In eyes with an intact anterior capsule and total traumatic cataract, a second-sitting cataract extraction with IOL implantation should be the best and safest approach for optimal visual outcome[17,18].

Wherever possible, a multistep procedure after control of inflammation, with adequate corneal clarity and an appropriate IOL power calculation, should be adopted[18,19]. It remains debated whether an anterior or posterior surgical approach via the pars plana route should be performed.

The following forms of surgical approach may be used, according to morphology: (1) unimanual or bimanual aspiration; (2) lensectomy/membranectomy using the limbal or pars plana approach and insertion of the lens in the sulcus; and (3) phacoemulcification or small-incision cataract surgery when the nucleus is harder[13].

Primary posterior capsulotomy

Determination of the correct IOL power prior to surgery

may be difficult, if not impossible, for a variety of reasons. Often the other eye serves as a guide, and inflammatory debris can settle on the IOL surface, cleansing of which may require postoperative yttrium-aluminum-garnet laser treatment or even surgery. In addition, the edge of the IOL will interfere with the surgeon's visualization of the peripheral retina should subsequent development of proliferative vitreoretinopathy necessitate vitrectomy[35]. There has been considerable debate over the use of primary posterior capsulotomy[39-41].

Primary posterior capsulotomy and vitrectomy in traumatic cataract have proved to be positive outcome predictors[39,40]. It was found that condensation of the anterior vitreous in severe inflammation was a positive outcome predictor in nonrandomized studies, while a randomized controlled trial suggested that this was a positive predictor.

Timing of intervention

The timing of cataract extraction and IOL implantation has been discussed extensively. Because evidence supports both primary and secondary cataract extractions, a number of crucial factors should be considered before making a decision. Cataract extraction together with primary wound repair may have distinct advantages, including controlling inflammation, however, this may raise intraocular pressure because of soft lens matter in the anterior chamber[13]. Secondary advantages include the direct visualization of the posterior segment and optic nerve[14]. Similarly, in pediatric patients the removal of a media opacity may be crucial to prevent vision-deprivation amblyopia. In patients with a lens vitreous admixture, this is a potent stimulator for further proliferative vitreoretinopathy and may also result in traction on the retina; hence primary extraction of the lens and vitreous is imperative in such patients [35,36]. Minor advantages of primary lens removal are the patient's convenience and possibly cost effectiveness[14].

Proponents of second-sitting cataract extraction recommend effective control of intraocular inflammation, good media clarity, and a stable wound before considering traumatic cataract extraction[14,39]. On adequate control of inflammation, IOL implantation at second-stage cataract extraction may be associated with a better outcome[14,39]. An IOL power calculation is appropriate when IOL implantation is planned for a second sitting[18,35].

Current data suggest that improved visual outcome results from intervention at 2-30 d[36]. Awareness of several details is necessary before embarking on primary or delayed cataract extraction with IOL implantation. These include the age of the patient, the expertise of the surgeon and assisting staff, the infrastructure available, and the status of the cataractous lens and the lens vitreous admixture, which will act as a guide to the surgeon in planning the surgery.

The ophthalmologist must not subject a patient to half-completed or compromised surgery because of a lack of expertise or proper infrastructure. If the facility is not equipped to provide the surgeon after hours with the full range of equipment, instruments, and material together with a full and knowledgeable staff, it is preferable not to contemplate primary lens removal. In most hospitals globally when an OGI is seen after hours, the state-of-the-art facilities necessary to attempt cataract extraction and IOL implantation are not normally available.

Lens implant

Lens implantation is an important stage in traumatic cataract surgery. A primary implant at the time of cataract extraction or a secondary implant during a second sitting is important for optical rehabilitation[39,40]. The lens implant may be placed in the capsule or sulcus, be iris supported, or involve scleral fixation depending upon the extent of the damage. Lens implants help in optical rehabilitation and the prevention of amblyopia in children. Lens insertion makes a significant difference to visual outcome.

Number of surgeries

Ocular injuries may cause damage to multiple ocular structures. It may therefore be impossible to treat all of the tissues in one session; thus a number of surgeries may be required to complete surgical management. Corneal/scleral wound repair, cataract extraction, lens implant, membranectomy, or vitrectomy may be performed at different stages[39,40]. Various studies reported that the number of surgeries did not have a significant effect on the final visual outcome.

Type of injury

The type of injury may influence visual outcome. Reports have suggested that OGI has a better outcome, whereas the opposite was true for penetrative injury[38-40]. Influences open globe of BETTS as a predictive factor (Table 1)[39,40]. When compared to the open-globe subgroups, cataract caused by penetrating injury had a better outcome whereas globe rupture had a poorer outcome[39-41].

CLINICAL CONDITIONS THAT MAY PREDICT PROGNOSIS

Relative afferent pupillary defect

There is sufficient evidence to suggest that relative afferent pupillary defect (RAPD) may produce false positives with regard to damage to the optic nerve or retina in the presence of severe hyphema or subretinal vitreous hemorrhage, which may resolve after resorption or removal of the hemorrhage[41-44]. Therefore, RAPD alone is a poor prognostic factor, it may be inappropriate, and there is the possibility of reversal[37]. Therefore, RAPD should be weighted equally with other preoperative variables following ocular trauma.

Predictive methods

The ocular trauma score (OTS) was developed to provide more accurate information regarding the visual prognosis. However, it is unclear whether children were included

in the databases of the over 2500 serious ocular injuries from which the method was formulated[45-47]. Two reports from India validated OTS using 787 cases of traumatic cataract[48,49].

Two important factors in calculating the OTS, initial visual acuity and RAPD, are difficult to obtain for children after trauma, especially those in the younger age group, rendering the OTS inaccurate or even unusable. Two groups recently assessed the value of the OTS in pediatric patients aged from 2 years, coming to opposite conclusions, thus adding to the controversy[50,51]. A new pediatric OTS that aimed to refine prognostic accuracy in children in whom the initial vision is not accurate was published recently[52]. As in many other studies on pediatric trauma, it lacks the statistical power of the OTS because of its relatively small population size, and its predictive power remains untested. The OTS appeared be a valid predictor of visual outcome in children following surgery in a study of 354 pediatric traumatic cataracts[49]. Regression tree analysis has also been used, but has not been validated[53,54].

Infection following OGI

Many studies have reported infection and endophthalmitis following OGIs[56-70]. Intraocular infection is also common with a retained intraocular foreign body[70-72]. The absence of infection following injuries caused by a wooden stick when using plants with antimicrobial and antifungal properties has been reported[73-79].

CONCLUSION

Despite the advances in state-of-the-art surgery and understanding ocular trauma, a range of unresolved, controversial issues remain in the management and treatment of OGIs. During the last two decades all of these issues have been addressed and real progress has been made in many aspects of the definitive management of traumatic cataracts.

The timing of the intervention in traumatic cataract appears to be a never-ending debate. "Sooner the better" was the traditional view; however, an alternative view is that a better outcome results from intervention between 3-30 d. Although a controlled, prospective clinical trial would be the ideal, no two ocular trauma cases are alike, and confounding factors can affect the final outcome.

A morphological assessment may be used to guide management. The age at intervention and laterality play important roles as predictors of visual outcome[21,40,49]. The accuracy of predictive models varies between adult and pediatric traumatic-cataract cases.

Controlling for the significant differences that occur among individual injuries is difficult. This makes the independent assessment of potential risk factors and treatment variances for visual and anatomical outcome difficult. Current management is based on the surgeon's experience, and will continue to be based on a retrospective review of accumulated data and the personal preferences of the treating ophthalmologist in OGI. These types of management problems are dealt with on a case-by-case basis, and even the most experienced ophthalmologists will at some time find themselves in a dilemma regarding the strategic planning of ocular trauma management of OGI. This review has attempted to provide a comprehensive overview of most of the controversies related to the management of OGI, and has presented our preferred guidelines. This should aid ophthalmologists in patient counseling and the process of making decisions regarding the management of OGIs involving the anterior or posterior segment.

In summary, the vast majority of ophthalmologists who encounter a traumatic cataract have sufficient experience in lens extraction and IOL implantation in the non-traumatic setting. What every ophthalmologist must accept is that an injured lens requires many individualized, conscious decisions regarding what to do, when to do it, and how to achieve the best possible outcome.

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MINIREVIEWS

Donor cornea quality used for penetrating keratoplasty *vs* deep anterior lamellar keratoplasty

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Abstract

Deep anterior lamellar keratoplasty (DALK) has recently been introduced as an alternative procedure to penetrating keratoplasty (PK) for corneal pathologies not affecting the corneal endothelium. DALK does not rely on donor endothelium and requires less rigid criteria for donor corneal tissue quality. Therefore, DALK makes it possible to use donor corneas deemed unsuitable for PK. Furthermore, lamellar keratoplasty allows acellular corneal tissue to be transplanted. As a result, long-term preservation techniques are being revisited to increase the availability of donor corneas and subsequently alleviate constraints of availability, cost, storage, and transportation in many countries. The recent alterations in corneal transplantation techniques and hence the type of donor cornea tissues used for each technique, may require corneal surgeons and eye banks to reevaluate their selection criteria. The purpose of this systematic review is to present an updated analysis on the type and quality of donor corneas used for PK and DALK, assess the influence of donor and eye bank factors on the quality of donor corneas, and determine whether any of these donor factors affect clinical outcomes, complications, and graft survivals.

Key words: Corneal transplantation; Penetrating keratoplasty; Full-thickness keratoplasty; Deep anterior lamellar keratoplasty; Deep lamellar keratoplasty; Maximum depth anterior lamellar keratoplasty; Donor corneal quality; Graft quality

Core tip: Deep anterior lamellar keratoplasty (DALK) is recently used for treating corneal diseases not affecting the corneal endothelium. This makes it possible to use donor tissue with poor endothelium. Furthermore, DALK allows acellular corneal tissue to be used and long-term preservation techniques are being considered as a method for donor storage. The recent alterations may require eye banks and corneal surgeons to reassess their selection criteria to ensure donor grafts which are inappropriate for penetrating keratoplasty because of low endothelial cell count can be safely used for DALK.

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INTRODUCTION

Penetrating keratoplasty (PK) is a surgical technique in which the full thickness of the recipient cornea is replaced by donor tissue. Deep anterior lamellar keratoplasty (DALK) is intended to selectively replace the abnormal stroma while preserving the recipient's endothelium in place[1]. Therefore, DALK can eliminate the risk of

endothelial graft rejection and has minimal detrimental effect on endothelial cell density[2]. Some investigators report that visual acuity and refractive error following DALK can be similar to those following PK[3-6].

The recent alterations in corneal transplantation techniques and consequently the type of donor cornea tissues employed for each technique may require corneal surgeons and eye banks to reevaluate their donor selection criteria.

Controversy exists regarding the donor corneal tissue quality used for each transplantation technique. Donor factors such as age, local and systemic diseases, cause of death, and traumatic damages or surgical procedures as well as the storage factors (mainly method of storing, time between death and preservation, and duration of tissue preservation) can influence the final quality of the corneas. When indicated for optical purposes, PK surgeons prefer transplanting donor cornea tissues with quality ranging from good to very good to excellent to provide adequate endothelial cells for a lifelong period. Since the introduction of DALK, many surgeons have been accepting donor corneas with lower quality compared with PK. DALK does not rely on quality of the donor endothelium and requires less strict criteria for donor selection[7]. This feature is imperative in increasing the availability of corneal grafts in regions where there is shortage of donor corneas[7].

The purpose of this systematic review is to present an updated analysis on the type and quality of donor corneas used for PK and DALK, to assess the influence of donor and eye bank factors on the quality of donor corneas, and furthermore to determine whether any of these donor factors affect clinical outcomes, complications, and graft survival.

RESEARCH

Questions for assessment

The objective of this assessment is to address the following questions: (1) what type and quality of donors are used for PK and DALK? (2) What is the influence of donor and eye bank factors on the appropriateness of corneal grafts for transplantation [endothelial cell density (ECD)] and graft quality)? (3) Do donor and eye bank variables affect clinical outcomes, complications, and graft survivals following PK and DALK?

Description of evidence

A search of the peer reviewed English literature was performed using the PubMed database between January 14, 2014 and April 15, 2014. Article reference lists were also reviewed to identify relevant articles. Keywords used in the search included the MeSH heading "corneal transplantation" combined with text words "deep anterior lamellar keratoplasty" or "DALK" or "deep lamellar keratoplasty" or "maximum depth anterior lamellar keratoplasty" and "penetrating keratoplasty" or "PK" (MeSH and text) or "full-thickness keratoplasty" accompanied with "donor quality" or "graft quality".

Then, a group of methodologists assigned a level of evidence rating to each article. A level Ⅰ rating was assigned to well-designed randomized clinical trials; a level Ⅱ rating was assigned to poor-quality randomized clinical trials or well-designed case-control and cohort studies; and finally a level Ⅲ rating was assigned to case reports and poor-quality case-control or cohort studies.

In order to evaluate the minimal endothelial cell count limits, the upper and lower limits of donor age, maximal time intervals from death, enucleation or excision to preservation, and maximal storage time deemed suitable for corneal transplantation, studies on the characteristics of donor corneas used for transplantation were reviewed.

The author assessed the 61 citations and selected 48 articles that potentially or definitely met the inclusion criteria. The full text of these 48 articles was obtained for further evaluation.

Nine studies were prospective, double-masked clinical trials (level Ⅰ) reported by the Cornea Donor Study[8-16]. Four studies were prospective non-randomized trials (level Ⅱ)[17-20]. The remaining 35 articles were comparative or non-comparative case series and were rated as level Ⅲ evidence[21-47].

Type and quality of donors used for PK and DALK

Assigned corneas for PK with quality ranging from good to excellent had the following characteristics: donor age varied from 1 to 96 years[9,10,19-23,46]; endothelial cell density varied from 2000 to ⩾ 3000 cells/mm^2[9,10,18,24]; death-to-preservation time was between 45 min and 22.3 h[19,22,23,25]; maximum storage time was 14 d in cool-storage media and 4 wk in organ culture[19-21].

In contrast to penetrating keratoplasty, donors with quality ranging from fair to excellent were employed for DALK[26,27]. Furthermore, long-term preserved donor tissues completely devoid of cells were also transplanted[28-31]. One DALK study used donor cornea tissues with age between 12 and 72 years, graft rating from fair to excellent, ECD between 1128 and 4255 cells/mm^2, death-to-preservation time up to 56 h, and storage time up to 13 d in Optisol medium (-4 ℃)[26]. Another DALK study used donors with the following features: age between 28 and 88 years, ECD between 100 and 3300 cells/mm^2, and storage time up to 35 d in organ culture medium (31 ℃)[27].

Long-term preserved corneas with mean storage time between 2.7 and 9.6 mo were also used for DALK by some surgeons[28-31]. The majority of studies used lyophilization or chemical agents to dehydrate corneas before cryopreservation[28-30]. One study, however, employed cryopreservation without dehydration before freezing[31].

Effect of donor and eye bank variables on endothelial cell density and graft quality

Most studies that evaluated effects of donor characteristics and eye bank variables on graft quality and ECD concluded that the age of donor and time interval in organ culture were the main variables influencing the quality of endothelium. Gavrilov *et al*[32] reported that the rate

of organ-cultured corneas which were inappropriate for PK as a result of inadequate endothelium increased from 13% in donors < 40 years to 32% in donors > 80 years. The Cornea Donor Study revealed a negative correlation between donor age and ECD[16].

Armitage *et al*[24] revealed that the age of donor and preservation time in organ culture were the main variables which could affect endothelial suitability for PK. The odd of ECD less than 2500 cells/mm^2 was increased with longer preservation time and increasing donor age. Increasing time interval from enucleation to corneoscleral disc excision also increased the likelihood of ECD less than 2500 cells/mm^2 but the overall impact was small and significant only for a time interval greater than 18 h[24].

Grabska-Liberek *et al*[33] found that the rating of the morphological state of corneas suitable for PK depended mostly on the time between death and preservation, donor's age, cause of death and duration of preservation. The overall rating of tissues obtained in a very short time after death (to 5 h) was higher (excellent and very good) compared with corneas removed 8-12 h after the donor's death. An increasing percentage of endothelial cell loss was observed after 7 d of preservation independent of other factors[33].

One study found that initial ECD was lower and elimination for low ECD was more frequent in donors aged 85 years and over, compared to younger donors[17]. However, after storage in organ culture, very old corneas lost fewer endothelial cells than younger ones resulting in ECD which did not differ at the end of storage[17].

One study measured endothelial cell loss during preservation in organ culture[25]. The donor's gender, age, cause of death, and postmortem interval had no significant correlation with the percentage of endothelial cell loss. However, the preservation time demonstrated a significant correlation with a loss of 0.07% for each day of preservation[25].

Additionally, the combined effects of cause of death and donor age on ECD were evaluated. It was identified that chronic and long-lasting, severe diseases like cancer reduced ECD to a greater extent as compared to diseases causing a more rapid death. This negative impact of chronic diseases was aggravated by the general reduction in ECD observed with increasing age[34].

Effect of donor and eye bank variables on clinical outcomes, complications, and graft survivals following PK

Five studies investigated the effect of donor and eye-bank variables on epithelium-related problems following PK[19,23,35-37]. Death-to-preservation time and total storage time were significantly associated with an increased prevalence of epithelial defects on day 1 or hurricane and filamentary keratopathy[19,23]. Kim *et al*[35] outlined that the degree of epithelial defect had a statistically significant association with the time interval from preservation to surgery. Borderie *et al*[36] reported that death-to-storage time, storage time, and deswelling time significantly influenced the graft reepithelialization time in univariate analysis. In multiple regression however, none of the donor variables significantly influenced the graft reepithelialization time. As for the surface keratopathy 1 wk following PK, Mannis *et al*[37] observed no correlation between this complication and donor age, death-to-preservation time, preservation-to-surgery time, and the donor epithelial status.

Another widely investigated correlation was the effect of donor and eye-bank variables on postoperative ECD which yielded contradicting results. Langenbucher *et al*[21] reported no significant association between the annual endothelial cell loss and the donor age as well as postmortem interval. However, the storage time had a statistically significant correlation with the annual endothelial cell loss. Parekh *et al*[25] reported postmortem interval ≥ 10 h tends to have a higher percentage of endothelial cell loss than < 10 h of interval at both 1 year and 3 years postoperatively.

Postoperative higher ECD values were significantly associated with higher baseline ECD and younger donor age in one study[9]. When the follow-up period was extended to 10 years, the study group observed that the donor age influenced ECD, although this finding was primarily influenced by a small group of the youngest donors (12 to < 34 years of age) that had the least cell loss and the best graft survival[9]. Lass *et al*[11] observed the younger age and female gender of the donor had a significant correlation with higher ECD over time. However, cause of death and time interval from death to preservation or to surgery failed to demonstrate any significant association with changes in ECD during follow-up[11]. One study found a statistically significant negative influence of postmortem time and donor age on chronic loss of endothelial cell density after PK for keratoconus[38].

Two studies reported the effect of donor age on visual outcomes. Gain *et al*[17] found no significant difference between the two groups (donors younger than 85 years and donors aged 85 years and older), in terms of visual acuity and astigmatism. Halliday *et al*[39] found no significant correlation between the time taken to reach a postoperative acuity of 6/12 and the age of donor.

One study reported that donor age, ABO compatibility, and other donor factors were not associated with graft rejection[8]. Younger donor age, however, was found a risk factor for graft rejection (but not for graft failure) by three other studies[17,40,47].

Despite contradictory results of studies evaluating the effect of donor and eye-bank variables on ECD and morphology, the majority of studies showed that donor preservation method and time, donor age, cause of death, and preoperative donor ECD and/or morphometric measures (coefficient of variation and hexagonality) had no influence on overall graft failure[12,13,17,20,22,40,41]. However, one study reported that preoperative risk factors for developing late endothelial failure included low ECD and older donor age[46]. Authors from the Cornea Donor Study observed that grafts from donors aged between 66 and 75 years old that met the eligibility criteria of their study had a 5-year graft survival rate, comparable to grafts from younger donors[10]. However, higher donor

age was significantly associated with lower graft success during a longer follow up period[15].

Effect of donor and eye bank variables on clinical outcomes, complications, and graft survivals following DALK

Borderie *et al*[27] evaluated the effect of donor variables on the result of different anterior lamellar keratoplasty techniques in a heterogeneous group of corneal disorders with normal endothelium. The age of donor was the only factor which influenced visual rehabilitation postoperatively; visual acuity was significantly lower in recipients who received corneas from donors > 80 years[27]. Heindl *et al*[42] did not observe any significant association between donor storage time intervals and visual results one year following DALK. Feizi *et al*[26] observed that graft rating and preservation-to-surgery time had a significant correlation with the presence of graft stromal edema and epithelial defects on postoperative day 1 following DALK. Suture-related complications, graft rejection episodes, graft clarity, visual acuity and refractive outcomes at the final follow-up examination were found to have no correlations with any donor or eye-bank factors[26].

Five studies concluded that long-term cryopreserved donors can provide similar visual results comparable to fresh corneal tissues following DALK[28,29,31,43,44]. Another advantage of long-term preservation of the cornea by lyophilization and chemical glycerin-dehydration is to eliminate cells such as epithelium, keratocytes, and antigen-presenting cells and create the acellular biological materials[28,45]. As such, acellular corneal tissues may significantly reduce or even eliminate the incidence of graft rejection after lamellar keratoplasty[28,29,31]. Complications such as persistent epithelial defects, filamentary keratitis, and suture-related complications were more likely to occur when such a low quality graft was transplanted[31].

There is currently a paucity of evidence for setting an acceptable minimum donor conditions for corneal transplantation, especially for lamellar keratoplasty. According to Eye Bank Association of America standards for human corneal transplantation, minimal endothelial cell count limits, the upper and lower limit of donor age, time intervals from death, enucleation or excision to preservation are left to the discretion of the eye banks[48]. An understanding of the effect of donor variables including age, time interval from death to enucleation and to preservation, storage time, and endothelial cell density both on the quality of donor corneas and on post-transplantation outcomes help to set eye banking standards. To establish the criteria, it is vital to find out the correlation between these donor parameters and the appropriateness of corneas for transplantation as well as between donor parameters and post-transplantation outcomes. The aim of this review, therefore, was to assess the influence of donor and eye bank factors on the graft quality as well as clinical outcomes.

Based on to the results of this review, the minimum ECD for PK is 2000 cells/mm^2 and there is no age limit for donors. Death-to-preservation time up to 24 h is accepted and maximal storage time is 14 d in cool-storage media and 4 wk in organ culture.

Because endothelial cell graft attrition takes place at an accelerated rate[49], a higher initial endothelial cell density of the donor tissue can improve long-term graft survival[9]. Older donor age and longer storage time are more likely to be associated with lower ECD but, as long as the ECD is greater than a given minimum at the time of corneal transplantation, these parameters will have insignificant influence on long-term graft survival. The Cornea Donor Study results indicate that donor age is not an important factor in most penetrating keratoplasties performed for endothelial disease[15]. Therefore, functional and cellular results of PKs are not dramatically influenced by very old donor age and the very elderly should not be deemed off limits for corneal procurement.

The results of this review showed that epithelium-related complications such as filamentary keratitis and persistent epithelial defects correlate with longer death-to-harvest time and longer storage time[19,23,35]. In addition to donor endothelial status, graft corneal surface is a determinant for the success of corneal transplantation in the postoperative period. Although the donor cornea is ultimately resurfaced by the recipient's epithelium, an intact donor epithelium on postoperative day 1 implies a smoother course after corneal transplantation. An instable graft surface can lead to poor visual acuity due to an irregular tear film interface, discomfort, permanent damage to Bowman's layer, sub-epithelial scarring, and even infectious keratitis[19].

DALK has recently been introduced to replace abnormal corneal stroma while preserving the host's healthy endothelium. DALK does not rely on donor endothelial cells and less strict criteria can be used for donor graft quality. Therefore, it increases the availability of donor tissues that do not require high-quality endothelium to be appropriate for PK. However, the use of low quality donors for DALK could cause epithelium-related complications more frequently, besides more edematous alterations of the graft necessitating a closer follow-up immediately after surgery. Apart from that, low quality donors can provide good visual acuity and refractive outcomes with complication rates comparable to those achieved after the use of good quality donors following DALK.

The two main techniques for storing corneas are organ culture and hypothermia[50,51]. Since lamellar corneal transplantation makes it possible to use acellular corneal tissue, long-term preservation methods have emerged as a means to provide a greater availability of corneal tissue to alleviate constraints of availability, cost, storage, and transportation in many countries. The results of several studies indicate that cryopreserved corneal tissues can successfully substitute for fresh grafts in DALK using the big-bubble technique. One advantage of long-term preservation of the cornea is to significantly reduce or even eliminate the incidence of graft rejection. However, complications such as persistent epithelial defects, filamentary keratitis, and suture-related complications are more likely to develop with such low quality grafts making closer

follow-up visits essential immediately after DALK.

CONCLUSION

Although both donor and eye bank variables have effects on the quality of donor corneas, and post-PK outcomes and complications, these effects would be little provided that the minimum selection criteria set by eye banks are respected. DALK makes it possible to transplant corneas with low quality and allows using the long-term methods of storage. Because, epithelial defects and stromal edema are more frequently encountered, closer follow-up visits are required when a low-quality graft is transplanted.

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15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

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