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Cataract surgery and diabetic retinopathy

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Abstract

Diabetes is a risk factor for the development of cataracts. Studies have shown an increased risk of ocular complications in diabetics after cataract surgery, but modern surgical techniques have minimized them, leading to an overall good visual outcome. Macular edema before surgery is the most common condition that limits post-operative visual recovery. Thus, pre-operative laser treatment is needed. Photocoagulation of preproliferative or early proliferative diabetic retinopathy is also advisable, due to the increased risk of iris neovascularization or retinopathy progression after surgery.

Introduction

Diabetes mellitus and cataract are two highly prevalent conditions. The global prevalence of diabetes is increasing worldwide, with prevalence estimates reaching 221 million people by 2010 and approximately 300 million by the year 2025.[1,2] According to the World Health Organization (1997c) cataracts are the leading cause of blindness both in the world, accounting for 16 million cases, and in the US.[3,4] Diabetic retinopathy is the first cause of legal blindness among people of working age in North Western countries. People suffering from diabetes are at higher risk of developing any type of cataract: this risk is 2 to 4 times higher than in non-diabetic people and it can increase 15–25 times in diabetics under the age of 40.[5] In addition they have an increased risk of post-operative complications. In 1993 Bron reported that the occurrence of cataract is a predictor for increased mortality in diabetics.[6] Seven years later the UKPDS, in a study concerning the relationship between exposure to glycaemia over time and the risk of macrovascular or microvascular complications in patients with type 2 diabetes, found that the incidence of clinical complications was significantly associated with hyperglycaemia. Each 1% reduction in updated mean HbA1c was associated with a risk reduction of 21% for any end point related to diabetes, 21% for deaths related to diabetes, 14% for myocardial infarction, and 37% for microvascular complications. Any reduction in HbA1c is likely to lower the risk of complications: the hazard ratio for cataract extraction decreased by 19% per 1% decrement in HbA1c.[7] Nowadays no medical therapy for cataract is available, so the standard treatment is surgery. In diabetic populations the indications for cataract surgery are the same as for non-diabetic patients, but they also include the need of visualisation of the fundus to perform laser therapy. Unfortunately, diabetic cataract extraction has been associated with higher post-operative complication rates than non-diabetic surgery.[8] The main problems related to cataract surgery in diabetes that we have to consider are the following: development or worsening of macular edema; progression of diabetic retinopathy; anterior segment neovascularization; posterior capsular thickening; fibrinous uveitis.[9–11] These issues result in poor and unsatisfactory post-operative visual acuity.

Cataract surgery and macular edema

Pseudophakik cystoid macular edema (CME) is still a common problem even after an uncomplicated cataract surgery. The incidence of CME varies widely, but is likely to be in the range of 1–2% when using modern cataract extraction techniques. Leak from perifoveal vessels is induced by inflammatory mediators and results in intraretinal fluid accumulation and corresponding decrease in retinal function. Diabetes is one of the risk factors most frequently associated with CME.[12] Macular edema is the most frequent cause of poor visual acuity after cataract surgery in patients with diabetes mellitus.[13,14] Post-operatively, macular edema tends to become worse if it is caused by underlying diabetes, while it tends to resolve if it is caused by the Irvine-Gass syndrome.[15–17]

Macular edema may in part be caused by breakdown of the blood–retina barrier or inflammation after cataract extraction.[18,19] It has been suggested that inflammatory mediators

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released in response to surgical trauma play a role in the onset of post-operative inflammatory symptoms and macular edema.[20] During the last few years several studies have been published concerning the possible value of the aqueous humor levels of samples of various cytokines, aspirated during cataract surgery, such as vascular endothelial growth factor (VEGF), interleukin-6 (IL-6) and many others, in predicting the postoperative exacerbation of macular edema or retinopathy progression in patients with diabetic retinopathy after uneventful extracapsular cataract extraction (ECCE) and/or phacoemulsification surgery. In a prospective study Funatsu *et al.* evaluated 104 patients with non-proliferative diabetic retinopathy (NPDR) who had undergone phacoemulsification.[21] The exacerbation of macular edema was seen in 30 eyes (29%) after 6 months and was significantly correlated with the aqueous level of VEGF at the time of surgery; their results showed that VEGF was an independent predictor of the post-operative exacerbation of macular edema. For each 100 pg increase in the aqueous level of VEGF, the risk of exacerbation of macular edema was increased 1.53-fold.[21]

Concerning the effect of cataract surgery on diabetic macular edema, although there are several studies and case series reporting a significant prevalence of post-operative macular edema, the ETDRS Report N.25 found a 56% incidence of new clinically detectable macular edema in the first year after surgery, with a trend in spontaneous resolution without treatment in 50% of affected eyes by six months and in 75% one year after surgery.[13,14,22,23] On the contrary eyes with clinically significant macular edema, either refractory to laser therapy or untreatable because of the lens opacity at the time of surgery (29%), showed clinical and angiographic evidence of worsening during one year follow-up.[24] These results pointed out the importance of the pre-operative presence, level and treatment of retinopathy.

Cataract surgery and retinopathy progression

During the past years many studies on the influence of cataract surgery on diabetic retinopathy have been published with controversial findings. Kato *et al.* reported that the progression of retinopathy is not affected by factors such as age, diabetes duration, diabetic treatment method, and hemoglobin A_{1c} level.[25] They also showed that the pre-operative status of retinopathy may influence the susceptibility to surgical invasion. Few studies have examined the post-operative course of diabetic retinopathy using the nonoperated fellow eye as a control. Two that have found that worsening of diabetic retinopathy reflects the natural course of the disease, systemic factors, or both, rather than the influence of cataract surgery.[25,26] In a Japanese study diabetic patients who did not show pre-operative retinopathy were more susceptible to post-operative retinopathy progression after surgical intervention.[25] Diabetic retinopathy, in eyes affected pre-operatively, progressed after cataract surgery. The presence of pre-operative macular edema and poor renal function increased the progression of retinopathy post-operatively.[27]

Diabetic patients having ECCE and phacoemulsification (25,28–31) may have progression of diabetic retinopathy post-operatively.[28,29] Those having ECCE also have an increased rate of anterior segment complications including elevated levels of fibrin and the development of posterior synechias.[32] Similarly, post-operative aqueous flare is greater in diabetic patients having phacoemulsification and occurs with increased intensity with advancing retinopathy.[33] This may be partly explained by higher levels of inflammation post-operatively and a tendency toward anterior segment complications. Patients with more advanced diabetes mellitus may have less optimal post-operative visual acuity after ECCE and phacoemulsification.[28,29,31,34] Diabetic macular edema may persist post-operatively, especially if present at the time of cataract surgery.[17] Progression to proliferative diabetic retinopathy (PDR) may compromise vision. Nonetheless, the prognosis for vision after cataract extraction in diabetic patients is overall favorable, especially in those with no diabetic retinopathy. Modern small-incision phacoemulsification techniques may reduce post-operative inflammation and complications in diabetic patients.

In ETDRS Report N.25 lens surgery was associated with a borderline statistically significant increased risk of progression of diabetic retinopathy in the adjusted analyses ($P = 0.03$).[24] Although patients with severe non-proliferative retinopathy or worse before lens surgery had poorer visual results, visual improvement was seen in 55% of these patients at 1-year follow-up.

Cataract surgery and iris neovascularization

In 1983 Aiello *et al.* reported that in diabetic patients (154 eyes with the other eye serving as the unoperated control, retinopathy level graded) standard intracapsular cataract extraction was associated with a statistically significant incidence of post-operative rubeosis iridis/neovascular glaucoma (7.8% vs 0%).[35] In patients with pre-operative active proliferative diabetic retinopathy, the risk of developing post-operative rubeosis iridis/neovascular glaucoma was even higher (40% vs 0%). This complication was considered related to cataract surgery if it occurred within six weeks of the surgery. In patients with active proliferative diabetic retinopathy, there was an increased incidence of vitreous hemorrhage after surgery (20% vs 6.5%), but this was not statistically significant due to the small number of patients studied.[35] Rice *et al.* in a consecutive series of 596 eyes that underwent combined lensectomy and vitrectomy, or vitrectomy alone, for complications of diabetic retinopathy, found a statistically significant increased risk of post-operative iris neovascularization by a factor of more than three, and the risk of neovascular glaucoma by a factor of more than four, compared to eyes in which the lens was not removed.[36] Other

factors associated with a significantly increased incidence of post-operative iris neovascularization were severe pre-operative retinal neovascularization and the absence of pre-operative scatter retinal photocoagulation.[36]

Diabetic iridopathy (DI), as one of the manifestations of diabetes in the anterior part of the eye, exists even in the early stages of this disease and progresses in parallel with retinopathy. Aqueous flare intensity is dependent on blood-aqueous-barrier breakdown and increased with the grade of retinopathy.[37] Cataract surgery determines an early blood-aqueous-barrier breakdown by mechanical and biochemical stimuli. Iris fluorescein angiography is not commonly employed in clinical practice, but it is the most sensitive technique for the evaluation of iris vessel abnormalities, and is a helpful basis for avoiding complications when scheduling eyes with dioptric media opacities for surgery. Based on iris fluorescein angiography, diabetic iridopathy has been classified as: absence of DI; non-proliferative DI; proliferative DI; neovascular glaucoma.[38,39] In an experimental study on 15 rabbits treated with lensectomy and vitrectomy, fluorescein iris angiography allowed true neovascularization to be distinguished from breakdown of the blood-ocular barrier by the time and extent of the fluorescein leakage. Moreover preservation of an intact anterior lens capsule reduced the incidence of rubeosis from 73% to 33% ($p = 0.05$).[40] In another study, fluorescein iris angiography in 42 eyes of 31 patients with PDR revealed abnormal dye leakage in all eyes.[41] Laser flare intensity significantly correlated with the degree of dye leakage. Eyes with dye leakage from the pupillary border only, had no biomicroscopic rubeosis. High laser flare intensity had a close relationship with advanced blood-ocular barrier disruption. The authors suggested that it may be a helpful indicator in detecting incipient rubeosis or advanced diabetic iridopathy.[41]

It is widely accepted that neovascular glaucoma in patients with diabetic retinopathy is the result of vascular occlusion in the retina.[42] In an unselected diabetic population, the prevalence of iris neovascularization ranged from 1% to 17%, whereas in eyes with proliferative diabetic retinopathy it increased to 65%.[44–45] There was a close relationship between iris neovascularization and the extent of retinal ischemia. In light-pigmented irides, it is easy to detect iris neovascularization with a slit lamp. On the other hand, it is very hard to predict angle neovascularization by observing pupils in diabetic patients with dark-pigmented irides. Ohnishi and associates recently described the importance of fluorescein gonioangiography, first introduced by Kimura for the diagnosis of early-stage neovascular glaucoma.[46,47] Panoramic fundus fluorescein angiography and 360-degree fluorescein gonioangiography to detect angle neovascularization were performed on 70 eyes of 46 patients with proliferative diabetic retinopathy.[46] In a small randomized clinical trial of 42 nondiabetic patients Laurell *et al.* suggest that cataract surgery performed with a small, self-sealing incision, continued curvilinear capsulorexis and phacoemulsification, induces a reduced surgical trauma with less blood-barrier breakdown compared to ECCE using a large sutured incision, linear capsulotomy and nucleus expression.[48] Jonas *et al.* published a case-report in which an old patient, with marked iris neovascularization in proliferative diabetic retinopathy and dense cataract that prevented retinal laser coagulation, underwent standard cataract surgery with implantation of a foldable posterior chamber lens in combination with an intravitreal injection of 25 mg triamcinolone acetonide to prevent the progression of iris neovascularization; the iris neovascularization markedly regressed within the first 5 post-operative weeks, after which a peripheral retinal laser treatment was performed, resolving the iris neovascularization.[49] West *et al.* reported the results of cataract extraction combined with pre-operative indirect laser PRP in a group of 9 eyes of 9 diabetic patients with active retinal or iris neovascularisation in which lens opacities prevented adequate pre-operative laser treatment.[50] Indirect laser PRP was performed after cortex aspiration and before intraocular lens (IOL) implantation. They obtained regression of neovascularisation and suggested pre-operative indirect laser PRP alone (5 eyes), or in associated with further post-operative PRP (3 eyes), could improve the outcome of cataract surgery in eyes with active proliferative diabetic eye disease.

The ETDRS Report N°25 reported a rate of 9% of iris neovascularization in eyes that underwent lens surgery, whereas for the study as a whole the rate was 1.9% ($P = 0.001$). Iris neovascularization was associated with a poor visual outcome: 70% had visual acuity of less than 5/200 at one year after surgery.[24]

Kuchle *et al.* presented a retrospective analysis of 39 eyes of 33 patients, with manifest iris neovascularization and partially treated PDR because of dense cataracts preventing additional photocoagulation, who underwent cataract extraction and posterior chamber lens implantation.[51] They found intra-operative iris hemorrhage in 10 eyes; the complication being significantly more frequent in eyes that underwent nuclear expression (50%) than in those receiving phacoemulsification (12%; $P = 0.019$). Visual acuity improved in 33 (85%) of the eyes. Their conclusion was that cataract extraction with posterior chamber lens implantation does not appear to be associated with unacceptable intra-operative or early post-operative complications.[51]

Surgical technique

Basically there is general agreement on the fact that for non-diabetic people phacoemulsification induces less post operative breakdown of the blood-aqueous barrier than ECCE.[52,53] In diabetic patients with cataracts, such as in non-diabetics, phacoemulsification results in better post-operative visual activity, less post-operative inflammation, and less need for capsulotomy than conventional ECCE.[23] At present the gold standard treatment for surgery remains ultrasound cataract removal with a foldable in-the-bag IOL with a truncated edge.[54]

Posterior capsular opacification

A frequent complication of ECCE with or without posterior chamber IOL implantation is posterior capsule opacification (PCO). This condition is the leading cause of visual loss after cataract surgery and it can be seen in three different forms: fibrosis, Elschnig's Pearls and capsular wrinkling. These complications are secondary to a proliferation and migration of residual lens epithelial cells.[55] Although the proximate cause of PCO is unknown, it has been related to optic material, including surface chemistry, edge design, and surgical technique. Opacification may be reduced by atraumatic surgery and thorough cortical clean-up. Clinical, pathological and experimental studies have shown that use of hydrodissection, the continuous curvilinear capsulorhexis and specific IOL designs, such as square-edge, may help reduce the incidence of this complication.[55] Moreover, anterior capsular phimosis is greater in diabetic than in nondiabetic patients and may have clinical significance if retinal laser treatment is required.

Surface properties of various materials are believed to be an important determinant of cell proliferation and migration. Stoy *et al.* suggested that the development of PCO could be further elucidated by studies using tissue cell cultures.[56] Importantly, if a new polymer material satisfies optical and design criteria, surface chemistry can be customized to assure biocompatibility.[56] In a recent article, Trivedi *et al.* discussed some issues that could be related to PCO, such as proliferation of various anterior capsule cells, silicone oil adherence to IOLs, piggyback IOLs, and opacification occurring on and within IOL optics, both on some modern foldable IOLs as well as degradation of optic occurring with some PMMA models a decade or more after implantation.[57] In the last few years several articles have reported intraoperative and post-operative opacification of foldable silicone and acrylic IOLs, sometimes requiring the explantation of the implanted material and their removal from the market.[58–66]

Conclusions

Developments in cataract surgery techniques and IOL technology have enabled patients to recover rapidly and have reduced the incidence of many post-operative complications. This is true even for diabetic patients, thanks to better management before surgery and surgical techniques, and also to a lower rate of retinal complications due to earlier recognition of diabetic retinopathy and its lower progression with better glycemic and hypertensive control (according to DCCT and UKPDS reports).[67–69] Retinopathy severity and macular edema are the principal determinants of post-operative visual acuity. Dowler *et al.* proposed a shift from conservative management toward earlier surgical intervention before development of retinopathy.[70] So far some items still represent troublesome complications for ophthalmic surgeons, retinologists and, above all, patients. To overcome them we are looking forward to research about increased performances and biocompatibility of IOLs and new pharmacological possibilities in preventing and treating diabetic retinopathy.

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