Cataract surgery in diabetes mellitus: A systematic review

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India is considered the diabetes capital of the world, and a significant proportion of patients undergoing cataract surgery are diabetic. Considering this, we reviewed the principles and guidelines of managing cataract in patients with diabetes. The preoperative, intraoperative, and postoperative factors are of paramount importance in the management of diabetic cataract patients. Particularly, the early recognition and treatment of diabetic retinopathy or maculopathy before cataract surgery influence the final visual outcome and play a major role in perioperative decision-making. Better understanding of various factors responsible for favorable outcome of cataract surgery in diabetic patients may guide us in better overall management of these patients and optimizing the results.

Key words: Cataract, diabetes mellitus, diabetic retinopathy, treatment outcome, vitrectomy

Worldwide, more than 285 million people are affected by diabetes mellitus. This number is expected to increase almost twofold to 439 million by 2030 according to the International Diabetes Federation. In India, approximately 69 million people are affected by diabetes mellitus as of 2015. Diabetic patients are 2–5 times more likely to develop cataract and it tends to happen more so at an earlier age. On the other hand, diabetes-induced microangiopathy leads to diabetic retinopathy (DR), nephropathy, and neuropathy. Recently, retinal neurodegeneration has been described in diabetes and has been suggested to precede or occur concurrently and aggravate retinal vasculopathy. Diabetic retinal neurodegeneration clinically manifests as reduction in the retinal nerve fiber layer, ganglion cell layer, as well as Muller cells, color vision loss, and spatial frequency changes on electrophysiology. In addition to the retinal changes, diabetes leads to structural and morphological alterations in other parts of the eye including the cornea, tear film, and crystalline lens, which lead to changes in the optical quality of the diabetic eye.

Globally, cataract remains the leading cause of blindness, affecting approximately 18 million people. Cataract is considered a major cause of visual impairment in diabetic patients as the incidence and progression of cataract are higher in patients with diabetes mellitus. Several clinical studies have shown that cataracts occur more frequently and at an earlier age in diabetics. Overall, it is estimated that up to 20% of all cataract surgeries are performed in diabetic patients.

Some studies have reported that cataract surgery when performed in diabetic patients may lead to relatively rapid progression of DR, precipitate vitreous hemorrhage, induce iris neovascularization, and ultimately lead to decrease or loss of vision. Uneventful cataract surgery results in increased inflammatory cytokines in the eye. Patel et al. reported that 1 day after uneventful phacoemulsification and intraocular lens (IOL) implantation, there were significant increases in vascular endothelial growth factor (VEGF), hepatocyte growth factor, interleukin-1 (IL-1), and pigment epithelium derived factor concentrations and that these increases took up to 1 month to decline to preoperative levels. These cytokines may induce clinical or subclinical worsening of DR and maculopathy. Although there have been a number of studies on the progression of DR status and factors influencing such progression after cataract surgery, further studies are still required, especially in the longer term.

Previously, monitoring changes in DR, especially maculopathy, were based on clinical examination including biomicroscopy and fundus fluorescein angiography. The recent introduction of optical coherence tomography (OCT), especially spectral-domain models, into clinical practice has improved the noninvasive monitoring of retinal thickness changes in DR including postcataract surgery.

This article reviews the development and progression of cataract, as well as cataract surgery and its outcomes in diabetic
patients with emphasis on the relationship between cataract surgery and DR progression.

**Methods**

To ensure the accuracy of this review, this literature review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement. A comprehensive search of the literature was conducted for papers using the online biomedical search engines PubMed, EMBASE, and the Cochrane library. The following terms were used for the searches: diabetes AND (cataract) AND (timing OR pathophysiology OR phacoemulsification OR complications OR visual outcome OR visual prognosis OR retinopathy progression OR diabetic macular edema). Two authors identified the articles, and all relevant articles were included in this review. Limits for our literature search filters included papers published in English between 1987 and June 2017, including human studies published as randomized controlled trials and nonrandomized comparative studies (systematic reviews, cohort or retrospective studies, or case–control series).

**Results**

Of 105 studies included in this review article, 14 studies reported the visual outcome as an endpoint after the cataract surgery. The meta-analysis[21] was carried out using poor visual outcome as an outcome variable. Table 1 shows the flowchart for the literature search and study selection.

**Meta-analysis**

The results are presented in Table 2. It is clear that there is a significant heterogeneity being reported in the literature in terms of poor visual outcome, following the cataract surgery (Q-Statistic - 386.2768, P < 0.001). Fig. 1 shows the forest plot that includes the proportions with 95% confidence interval found in the studies included in the meta-analysis. Fig. 2 shows the funnel plot[22] as a graphical tool for detecting bias in the meta-analysis. Since the funnel plot is asymmetric, there is a clear evidence of publication bias. Meta-analysis was carried out using MedCalc Statistical Software version 18.2.1 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2018).

**Discussion**

**Pathogenesis of diabetic cataract**

Various types of lens changes occur in diabetic patients. Snowflake cataract is a type of cataract seen very commonly in Type 1 diabetics. However, the most frequent type of cataract seen in diabetics is senile type.[23] Various studies have been carried out to study the type of cataract associated with diabetes. Posterior subcapsular cataract has been shown to be significantly associated with diabetes.[24] In fact, increased levels of glycated hemoglobin was shown by some authors to be associated with increased risk of nuclear and cortical cataract.[25] In further analysis, it had shown that diabetic patients were prone to develop cortical cataract and it was associated with duration of diabetes.[26]

Various mechanisms have been proposed for the pathogenesis of cataract in diabetes mellitus. In the lens, sorbitol is produced faster than it is converted to fructose by the enzyme sorbitol dehydrogenase, a process that is increased in diabetics compared to nondiabetics.[27] The increased accumulation of sorbitol creates a hyperosmotic effect that results in an infusion of fluid to counteract the osmotic gradient. Hyperglycemia per se may also contribute significantly to the osmotic retention of fluid in the lens fibers with resultant osmotic stress and is aggravated by increased intracellular production of cytokines/growth factors and oxidative stress.[28-30] The role of osmotic stress is particularly important for the rapid cataract formation in young patients with Type 1 diabetes mellitus[31,32] due to the extensive swelling of cortical lens fibers.[33]

Accumulation of sorbitol and advanced glycation endproducts lead to the generation of superoxide radicals and hydrogen peroxide (H\textsubscript{2}O\textsubscript{2}). Normally, antioxidant enzymes help in degradation of superoxide radicals into H\textsubscript{2}O and oxygen. However, lens antioxidant enzymes such as superoxide dismutase and catalase are compromised in diabetes, thus leading to oxidative stress which contributes to cataract formation.[35-38]

**Pathophysiological changes in crystalline lens with fluctuations in blood glucose levels**

Hyperglycemia causes a myopic shift and is the major cause of transient refractive changes in diabetic patients. With intensive
medical therapy, a considerable number of patients tend to become more hyperopic as compared to hyperglycemic state. The refractive changes observed during periods of unstable blood sugar are thought to be related to both morphologic and functional changes in the crystalline lens.\textsuperscript{[36]} In addition, changes in corneal topographic parameters during glycemic fluctuations are a potential source of error in keratorefractive and cataract surgery assessments.\textsuperscript{[37]} The basement membrane of the lens (or lens capsule) is known to be thicker in people with diabetes, leading to refractive changes. Saxena \textit{et al}.\textsuperscript{[38]} found a twofold higher incidence of cortical cataracts in patients with diabetes mellitus over 5 years and postulated the same mechanism.

**Timing of cataract surgery**

The growing tendency toward earlier cataract surgery in patients with diabetes has contributed to improved visual outcomes.\textsuperscript{[39]} Visual outcomes are likely to be worse in patients in whom surgery is deferred until late when it is not possible to identify or adequately treat DME before cataract surgery. Where cataract surgery is undertaken before lens opacities obscure adequate macular assessment preventing the recognition of retinal thickening, the risk of DME is decreased and the visual outcome may be improved considerably.\textsuperscript{[40]}

**Preoperative considerations**

Preoperative counseling is crucial. Before surgery, patients should have good glycemic control and no evidence of ocular or periocular infection. Some organisms in the conjunctiva are more prevalent in diabetic patients such as \textit{Staphylococcus aureus}, Enterococci, certain Streptococci, and \textit{Klebsiella} species compared to nondiabetics.\textsuperscript{[41]} Hence, the need for thorough asepsis cannot be overemphasized in these

| Study                                                                 | Sample size | Proportion (%) | 95% CI          | Weight (%) | Fixed | Random |
|-----------------------------------------------------------------------|-------------|----------------|-----------------|------------|-------|-------|
| Study 1 (Jaffe \textit{et al}. 1992)                                   | 21          | 38.095         | 18.107 to 61.565 | 0.50       | 6.70  |       |
| Study 2 (Jaffe GJ \textit{et al}. 1992)                               | 21          | 9.524          | 1.175 to 30.377  | 0.50       | 6.70  |       |
| Study 3 (Harbour JW \textit{et al}. 1996)                             | 10          | 30.000         | 6.674 to 65.245  | 0.25       | 5.90  |       |
| Study 4 (Henricsson M \textit{et al}. 1996)                           | 70          | 11.429         | 5.065 to 21.283  | 1.61       | 7.40  |       |
| Study 5 (Dowler JG \textit{et al}. 1999)                              | 32          | 15.625         | 5.275 to 32.788  | 0.75       | 7.02  |       |
| Study 6 (Chew EY \textit{et al}. 1999)                                | 3711        | 54.999         | 53.381 to 56.608 | 83.94      | 7.75  |       |
| Study 7 (Zaczek A \textit{et al}. 1999)                               | 74          | 12.162         | 5.715 to 21.836  | 1.70       | 7.42  |       |
| Study 8 (Mitra RA \textit{et al}. 2000)                               | 150         | 22.000         | 15.654 to 29.485 | 3.41       | 7.59  |       |
| Study 9 (Pendergast SD \textit{et al}. 2000)                           | 55          | 50.909         | 37.071 to 64.646 | 1.27       | 7.31  |       |
| Study 10 (Squirrel D \textit{et al}. 2002)                            | 50          | 22.000         | 11.527 to 35.961 | 1.15       | 7.27  |       |
| Study 11 (Krepler K \textit{et al}. 2002)                             | 50          | 16.000         | 7.170 to 29.113  | 1.15       | 7.27  |       |
| Study 12 (Liao SB \textit{et al}. 2003)                               | 51          | 35.294         | 22.431 to 49.932 | 1.18       | 7.28  |       |
| Study 13 (Wilson ME Jr \textit{et al}. 2007)                           | 28          | 14.286         | 4.034 to 32.665  | 0.66       | 6.93  |       |
| Study 14 (Canan H \textit{et al}. 2013)                               | 85          | 7.059          | 2.634 to 14.733  | 1.94       | 7.46  |       |
| Total (fixed effects)                                                | 4408        | 49.036         | 47.552 to 50.521 | 100.00     | 100.00|       |
| Total (random effects)                                               | 4408        | 23.633         | 12.476 to 37.042 | 100.00     | 100.00|       |

**Test for heterogeneity**

\[ Q = 386.2768 \]
\[ DF = 13 \]
\[ P = 0.0001 \]
\[ I^2 = 96.63\% \]
\[ 95\% CI for I^2 = 95.49 to 97.49 \]
Patients with neovascularization of the iris (NVI) need prompt treatment to induce regression before cataract surgery. Conventionally, this was done with PRP. When neovascular glaucoma (NVG) develops, medical therapy alone is usually not effective. Topical beta-adrenergic antagonists, alpha-2-adrenergic agonists, carbonic anhydrase inhibitors, cycloplegics, and corticosteroids may be useful in reducing IOP and decreasing inflammation. Eyes with NVG have demonstrated dramatic short-term regression of neovascularization and IOP reduction with intravitreal injection of anti-VEGF agents. Once NVI regresses, phacoemulsification should be considered with or without vitrectomy at the earliest to enable treatment of the posterior-segment pathology. Alternatively, combining phacoemulsification with endoscopic diode laser cyclophotocoagulation is an option for eyes where the anterior-chamber angles are closed with mature (fibrosed) new vessels. Combining trabeculectomy with phacoemulsification may also be planned in eyes with coexistent NVG and cataract when NVI has regressed. However, the visual outcomes following phacoemulsification in eyes with NVG are usually poor.

Cataract surgery (intraoperative considerations)

Phacoemulsification with IOL implantation yields better visual results and less inflammation as compared to extracapsular cataract surgery. Anterior capsular phimosis is more common in diabetic eyes. The capsulorhexis size should, therefore, be larger than normal but smaller than IOL optic diameter to prevent anterior IOL displacement and posterior capsular opacification (PCO). A large diameter optic (i.e., 6.0 mm or larger) also facilitates diagnosis and treatment of peripheral retinal pathology postoperatively. Longer duration and complicated cataract surgery are associated with a greater risk of progression of retinopathy and subsequent visual compromise. In diabetic patients, there is high likelihood of poor pupillary dilatation due to damage to pupillary parasympathetic supply. Thus, iris hooks, malyugin ring, or other iris expanders should be considered for intraoperative use in these patients. In addition, complications such as intraoperative hyphema due to the presence of rubeosis iridis need to be kept in mind. Some studies have shown that preoperative intravitreal anti-VEGF agents may decrease the chances of bleeding from iris neovascularization. Cetinkaya et al. showed that photic retinopathy during cataract surgery was more prevalent in diabetic patients than nondiabetics. The mere presence of diabetes does not increase the risk of intraoperative complications such as posterior capsular rupture, zonal dehiscence, and vitreous loss. However, the diabetic eye is more prone to keratop epitheliopathy, including corneal epithelial defects/abrasions, which may heal slowly. The impaired corneal wound healing has multiple etiologies including neurogenic (subbasal nerve abnormalities) and impaired corneal stem cell and epithelial cell division. Studies have also shown greater predisposition to corneal endothelial cell loss in people with diabetes compared to nondiabetics. Hence, routine specular microscopy is recommended for all people with diabetes, and greater care should be taken with regard to endothelial protection when operating on diabetic patients.

Intraocular lens choice

Large diameter IOLs are preferred to facilitate visualization and treatment of the peripheral retina in DR. Diabetic patients
seem to develop more severe PCO than nondiabetics. The level of phosphorus in the serum and aqueous humor of diabetic patients, particularly those with PDR, is significantly higher than normal individuals and may lead to opacification of hydrophilic acrylic IOLs. Hydrophobic acrylic IOLs are associated with slightly more anterior-chamber flare in the early postoperative period. However, PCO develops less frequently, and hydrophobic acrylic lenses have the lowest propensity for silicone oil adhesion and should be the IOL of choice in diabetic patients when anticipating vitrectorial surgery.

Rodriguez-Galietro et al. evaluated blue-light-filtering IOLs and reported that such lenses did not cause chromatic discrimination defects and even improved color vision in the blue-yellow chromatic axis. The use of multifocal and accommodative IOLs in people with diabetes remains controversial. Multifocal IOLs, especially, may alter postoperative laser treatment (focal/grid) and fundus visualization during vitrectomy surgery, making the optics of multifocal IOLs difficult. In addition, altered contrast sensitivity due to multifocal IOLs can aggravate and be a cause of visual dissatisfaction in patients with preexisting maculopathy. Iris claw lenses, both anterior and posterior claw, should be avoided in patients with diabetes who are at an increased risk for iris neovascularization. In addition, ovalization of the pupil and poor mydriasis after iris–claw IOL make posterior-segment evaluation difficult. In addition, the theoretical risk of cystoid ME is higher when iris–claw IOLs are used, especially in diabetics.

Visual prognosis following cataract surgery
Recent studies on cataract surgery in diabetics tend to report a lower incidence of complications and better visual outcomes due to better preoperative management of retinopathy, evolutions in operative techniques, better glycemic and hypertensive control, and better surgical technique of phacoemulsification. Diabetic patients with little or no retinopathy enjoy good visual prognosis similar to that in individuals without diabetes. The presence of DME and poor preoperative VA (reflecting diabetic maculopathy, ischemia, and traction) has been recognized as risk factors for poor postoperative VA following cataract surgery.

Mozaffarir et al. evaluated patients with more advanced DR and showed no functional improvement in VA. Pollack et al. reported VA better than 20/40 in 31% of patients, noted CME as the main cause of poor visual outcome following cataract extraction in patients with diabetes, and proposed that “cataract extraction should not be recommended for eyes with DR until VA has deteriorated to 20/100–20/200.” This view was later endorsed by Schatz et al., who reported in their study that only 9% of eyes achieved postoperative VA better than 20/40. Overall, visual recovery after uncomplicated phacoemulsification and IOL implantation is governed by the macular perfusion status, presence of ME, and stage of DR.

Indicators of poor visual outcomes following cataract surgery
According to the Early Treatment of Diabetic Retinopathy Study (ETDRS), the presence of CSM/E at the time of cataract surgery is significantly associated with poor VA and a predictor of final VA worse than 20/200 following uncomplicated phacoemulsification. The severity of DR at the time of cataract surgery is also a significant determinant of postoperative VA; more severe retinopathy seems to be associated with an increased prevalence of macular ischemia (edema) and a reduced tendency for spontaneous resolution of postoperative ME with associated poor postoperative VA. Treatment-naive PDR before cataract surgery may progress to vitreous hemorrhage and TRD following phacoemulsification, thus threatening good visual outcome.

Cataract surgery and intravitreal injection
Intravitreal steroids may be considered during cataract surgery in the eyes with DME without epiretinal membrane or tractional component, particularly if the patient has not been treated previously. Intravitreal injections of bevacizumab (Avastin, Roche) have been employed for the treatment of neovascular and exudative ocular diseases since 2005. Since then, several small studies have evaluated the effect of intravitreal bevacizumab on neovascular complications of diabetes.

Coexistent center-involving DME at the time of cataract surgery warrants combined phacoemulsification and anti-VEGF injections as treatment for the DME simultaneously. Repeat intravitreal anti-VEGF injections can be planned based on the DRCR.net retreatment criteria.

Combined cataract surgery and vitrectomy
Diabetic patients undergoing vitrectomy often have coexisting cataracts. Furthermore, lens opacities often progress following vitrectomy. Phacoemulsification may be combined with pars plana vitrectomy in the presence of coexistent cataract and nonclearing vitreous hemorrhage, macular TRD, combined mechanism retinal detachment, and persistent DME not responding to intravitreal anti-VEGF agents and/or steroids. Several studies have suggested that the vitreoretinal interface is a contributing factor in the development of persistent DME following laser photocoagulation and have demonstrated significant anatomic and visual improvement with combined surgery when indicated. Internal limiting membrane (ILM) peeling in the eyes with persistent DME has been shown to be beneficial. However, it is also known that the ILM in diabetics is more difficult to peel due to increased adhesions.

Careful patient selection and combining the two procedures can offer more rapid visual rehabilitation, avoid a second operation, and simplify surgical interventions in patients who are likely to require multiple procedures. Patients with severe traction and ischemia and those with active rubecosis are less suitable candidates. Younger patients with little preoperative lens opacity may be better managed without lens extraction.

Effect of cataract surgery on retinopathy
Some studies have demonstrated DR progression after phacoemulsification surgery, while others reported no significant change. Squirrell et al. have shown an increased risk of DR progression following cataract surgery in patients with elevated hemoglobin A1C. In a retrospective study, Krepler et al. found that DR was associated with male sex, disease duration, and poor glycemic control.

To differentiate the effect of cataract surgery from the natural course of the disease, Dowler et al. designed
Effect of cataract surgery on macular edema

Altered concentrations of angiogenic factors after cataract surgery may aggravate maculopathy. Following uneventful cataract surgery, OCT imaging showed increased retinal thickness in diabetic eyes without retinopathy in comparison to eyes from non-diabetics. Recently, report 2 from the UK DR electronic medical record users group published real-world data for the impact of cataract surgery on DME. They studied 4850 eyes without any DME before cataract surgery and followed them up for 2 years using the electronic records. VA and “treatment requiring DME” were available on this large cohort. The authors found that the risk of “treatment-requiring DME” increased sharply after surgery and peaked in the 3–6 months' period (with annualized rates of 5.2%, 6.8%, 5.6%, and 4.0% for the 0–3, 3–6, 6–9, and 9–12 months' postoperative time periods, respectively). The risk of ME was associated with preoperative grade of retinopathy; the risk of DME in the 1st year postoperatively was 1.0% (no DR preoperatively), 5.4% (mild non-PDR [NPDR]), 10.0% (moderate NPDR), 13.1% (severe NPDR), and 4.9% (PDR). This large real-world study proves that the risk of treatment requiring DME increases sharply in the 1st year after cataract surgery and that those with moderate and severe NPDR are most at risk of such progression.

Postoperative laser photocoagulation for DME is now less performed than previously. In the current era of anti-VEGF therapy, the role of focal and grid laser photocoagulation has diminished generally as the treatment of DME and especially for DME following cataract surgery. Pollack et al. evaluated the natural course of DME after cataract surgery and found that only a minority of patients who developed ME required focal laser photocoagulation. Dowler et al. suggested that early laser treatment of all cases of postoperative DME was unnecessary because many cases of edema resolve spontaneously if it arose after surgery but not when present before surgery.

Differentiating diabetic macular edema from pseudophakic macular edema in diabetic patients

It is important to differentiate DME from pseudophakic cystoid ME (PCME), especially because people with diabetes are more prone to develop PCME. The pathogenesis, treatment, natural course, and outcomes are very different in these two entities: (1) presence of underlying DR, exudates, and ME point toward DME (2) no or minimal DR and absence of exudates in the posterior pole hint toward PCME. In doubt, fundus fluorescein angiography should be performed which reveals optic disc staining (“hot disc”) and typical petalloid pooling of dye in PCME, whereas the disc is usually normal and leaking micro-aneurysms and/or capillary plexus are identified as the causes of ME in DME.
PCME is managed predominantly with topical steroids and nonsteroidal anti-inflammatory drugs including bromfenac (Yellow, Bausch, and Lomb) and nepafenac (Nevanac, Alcon) and rarely requires steroids in the form of posterior subtenon’s or intravitreal injections, whereas DME is managed mainly with intravitreal injections of anti-VEGF agents or steroids with or without laser photocoagulation.

Postoperative consideration

All patients diagnosed with NPDR should undergo detailed retinal examination within 3 months before cataract extraction. Patients with diabetes, especially those with proliferative retinopathy or those with inadequate view of the retina before cataract extraction, should be evaluated closely after surgery for monitoring retinal status.[17]

Diabetic patients are prone to corneal epithelial defects and persistent erosions due to impaired corneal innervation; these occur more frequently with increasing patient age and duration of diabetes.[108] Eyes of diabetic patients showed more severe corneal endothelial cell damage following cataract surgery and delayed recovery of corneal edema as described previously.[70,109] Other anterior-segment complications such as severe iritis, posterior synechiae, pupillary block, and pigmentated precipitates on the IOL are more frequently observed in diabetic patients.[110] The incidence of NVI which is the most dreaded anterior segment complication in diabetic patients following cataract surgery has been reduced with modern cataract surgery which is less traumatic than previous techniques. In addition, PRP and intravitreal injections of anti-VEGF agents have been reported to control NVI albeit for short periods.[57,90‑92] Diabetic patients may have increased risk of postoperative endophthalmitis which may be associated with a poor visual prognosis.[111]

Conclusion

The number of people with diabetes mellitus is increasing exponentially. People with diabetes have not always shared the favorable outcomes after cataract surgery as their nondiabetic counterparts. Diabetic patients with visually significant cataracts pose unique challenges during surgery and postoperative recovery, which vary according to the severity of the DR. However, with careful pretreatment of the DR and minimally invasive surgical techniques, these patients do very well and recover excellent vision just like other cataract patients without diabetes. Special attention to systemic and ocular conditions is needed.

Modern surgical and pharmacologic therapies may allow for safer and more effective surgery in diabetic individuals. This emphasizes the importance of patient education before surgery.

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Conflicts of interest

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