Cataract surgery and age-related macular degeneration. An evidence-based update

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ABSTRACT.
Purpose: Age-related macular degeneration (AMD) and cataract often coexist in patients and concerns that cataract surgery is associated with an increased risk of incidence or progression of existing AMD has been raised. This systematic review and meta-analysis is focused on presenting the evidence concerning progression of AMD in patients undergoing cataract surgery.

Methods: We performed a systematic literature search in the PubMed, Medline, Cochrane Library and CINAHL databases. Two randomized trials and two case–control trials were identified. Quality of the studies was assessed using the Cochrane risk of bias tool, data were extracted, and meta-analyses were performed. Quality of the available evidence was evaluated using the GRADE system.

Results: We found that visual acuity at 6–12 months follow-up was significantly better (6.5–7.5 letters) in eyes that had undergone cataract surgery than in unoperated eyes, but the included number of subjects was small, and hence, the quality of evidence was downgraded to moderate. We did not find an increased risk of progression to exudative AMD 6–12 months after cataract surgery [RR 3.21 (0.14–75.68)], but the included number of subjects was small, and thus, the quality of the evidence was moderate.

Conclusion: Cataract surgery increases visual acuity without an increased risk of progression to exudative AMD, but further research with longer follow-up is encouraged.

Key words: age-related macular degeneration – cataract surgery – exudative age-related macular degeneration – outcome – visual acuity

Introduction
Cataract and age-related macular degeneration (AMD) are both common causes of impaired visual acuity and blindness in the elderly population in westernized countries. Globally, cataract is the most common cause of blindness (Resnikoff et al. 2004). In westernized countries where there is relative easy access to cataract surgery, blindness from cataract is very rare, but it remains the leading cause of impaired visual acuity in the elderly population with AMD ranking second (Klaver et al. 1998). In Denmark, cataract and AMD together account for 74% of the number of visually impaired in the age group >65 years and 57% of the number of blinded individuals >65 years (Buch et al. 2004). Cataract can be treated effectively by removing the opaque lens, and exudative AMD can be treated by intravitreal injection of anti-VEGF, but we still do not have a treatment for the dry form of AMD.

Concern has been raised that cataract surgery may increase the risk of incident AMD or progression of pre-existing AMD. Early histological examinations (van der Schaft et al. 1994) and case studies reported an occurrence of wet AMD after cataract surgery (Blair & Ferguson 1979; Pollack et al. 1997, 1998). In theory, two likely mechanisms could lead to a progression in AMD after cataract surgery. One theory is based on blue light toxicity (Algvere et al. 2006; Glazer-Hockstein & Dunaief 2006). Intense, acute exposures to short-wavelength irradiation are toxic to the retina (Ham Jr. et al. 1976). The aged human lens effectively absorbs short wavelengths (Kessel et al. 2010).
thereby providing protection against short-wavelength irradiation. During cataract surgery, the natural lens is removed and replaced with an artificial intraocular lens (IOL) that provides less protection against short wavelengths (Mainster 2006). The relationship between short wavelengths and AMD has, however, so far not been proven. The second theoretical link between AMD progression and cataract surgery is related to the immune system and inflammatory response induced by cataract surgery. Increasing evidence points towards imbalance in inflammatory regulation as a hallmark in the pathogenesis of AMD (Buschini et al. 2011) as well as in the progression to neovascular AMD (Singh et al. 2012). Manipulation of the immune system could form the basis of a potential future therapy for the dry form of AMD (Chen & Smith 2012). At least in theory, cataract surgery could upset the immunological balance and thereby increase the risk of progression of AMD although no evidence supports this theory yet.

Cataract and AMD often coexist in patients. The presence of AMD may adversely affect the visual outcome after cataract surgery. However, deferring surgery for visually significant cataract in patients with AMD will also negatively influence the visual function of patients. At the same time, case reports and cohort studies have raised concern that cataract surgery may increase the risk of progression of AMD. So, how do we advise the patient with visually significant cataract and AMD?

The effect of cataract surgery on progression of AMD was previously evaluated by a Cochrane review (Caspisar et al. 2012). That review only included data from published randomized controlled trials, resulting in a recommendation based on one included study. Thus, the authors of this study found it reasonable to review the literature to include data from prospective, non-randomized trials in addition to randomized, clinical trials. Furthermore, the evidence from epidemiologic studies will be summarized. The present work was undertaken after an initiative by the Danish National Health and Medicines Authorities to formulate evidence-based national guidelines on surgery for age-related cataract.

**Methods**

The aim of the present meta-analysis was to examine whether cataract surgery increases the risk of progression of dry AMD using an evidence-based approach. The systematic review and subsequent meta-analysis were performed based on the principles described in the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach (Guyatt et al. 2011f). The first step in the working process was to define the topic of the systematic review using the PICO approach (Guyatt et al. 2011a). In short, PICO stands for: Patient, Intervention, Comparison and Outcome.

For this specific meta-analysis, we chose to examine the risk of progression of AMD in patients with AMD and age-related cataract (P) after cataract surgery by comparing eyes with AMD and cataract that underwent cataract surgery (I) to eyes with AMD and cataract where cataract surgery was not performed or where surgery was postponed for 6–12 months to allow for a sufficient long observational period (C). As specific outcome measures, we chose best corrected distance visual acuity (BCDVA) as well as fundoscopic (photographs, fluorescein angiograms, fundus autofluorescence or OCT) signs of AMD progression as defined by the studies at least three months after surgery (O).

A systematic literature search was conducted in August 2014 in the Embase, Medline, Cochrane Library and CINAHL databases using a combination of the search terms (((disease progression) OR age-related macular degeneration) OR macular degeneration) AND ((cataract extraction) OR cataract surgery). The search was limited to references published from 1996 and onwards in the English or Scandinavian languages. The search yielded a total of 1765 hits. Of those hits, 52 references were of potential interest, and full-text papers were obtained. Whenever there could be any doubt as to the relevance of a reference, the abstract was read, and if there was still any doubt, the reference was read in full-text. In addition, four papers that were not identified by the systematic literature search were identified by other means, for example the literature list of search-hit references.

The quality of each included study was assessed using the Cochrane risk of bias tool (Higgins & Green 2011). In short, the Cochrane risk of bias tool assesses risk of bias associated with the selection of patients (randomization or patient allocation and concealment of allocation), study performance (blinding of patients and personnel), detection of outcomes (blinding of outcome assessment), attrition of data (such as missing patients or dropouts), reporting of study findings (selective outcome reporting) or other types of bias. This part of the systematic review was carried out using the Review Manager Software (Review Manager (RevMan) 2014).

The quality of the evidence for each prespecified outcome was evaluated across the included studies using the GRADE system. Each outcome was analysed for study limitations that could affect the outcome (risk of bias, e.g. lack of allocation concealment or lack of blinding of patients or outcome assessors, incomplete accounting of patients and outcome, selective outcome reporting or other limitations) (Guyatt et al. 2011g), inconsistency (different results between studies) (Guyatt et al. 2011d), indirectness (e.g. use of surrogate measures) (Guyatt et al. 2011c), imprecision (large confidence intervals or the lack of statistical strength by included studies to answer the posed question) (Guyatt et al. 2011b) and risk of publication bias (e.g. lack of reporting of negative findings) (Guyatt et al. 2011e). The quality of the evidence for each of the prespecified outcomes could be up- or downgraded based on the assessment of each of the limitations mentioned above. This part of the review including preparation of summary of finding tables was prepared using the GRADE Profiler Software (GRADE profiler 2011).

For each prespecified outcome, data were extracted from the included studies independently by two reviewers (LK and DE). Cases of disagreement in data extraction were solved by consensus.

Dichotomous outcome data were analysed by calculating risk ratios. Continuous outcome data were analysed using the mean differences approach. The Review Manager 5 Software (Review Manager (RevMan) 2014) was used for estimation of overall treatment effects. Random-effects
models were used to calculate pooled estimates of effects.

Results

After a systematic literature search, we identified two randomized, controlled trials that evaluated the progression of AMD after cataract surgery (Lamoureux et al. 2007; Hooper et al. 2009; Brunner et al. 2013). One of the studies was published in two separate publications (Lamoureux et al. 2007; Hooper et al. 2009). Only the most recent publication was included in the analyses below (Hooper et al. 2009). Furthermore, we identified three case–control studies evaluating the outcome in patients with AMD after cataract surgery (Armbrecht et al. 2000, 2003; Baatz et al. 2008; Wang et al. 2012). Again, one of the studies was published in two separate publications (Armbrecht et al. 2000, 2003), and only the most recent publication was included in the analyses below (Armbrecht et al. 2003). One of the non-randomized studies was excluded because the control group included patients that could have had cataract surgery within the last 12 months of the 36 months follow-up period, but the number of eyes that did have cataract surgery in the control group was not reported (Wang et al. 2012). The last case–control study reported visual function and progression to wet AMD in a group of patients with AMD who underwent cataract surgery and compared with a group of patients who were diagnosed with dry AMD in the same time period (Baatz et al. 2008). Thus, two randomized, controlled trials and two case–control studies were available for the analyses below. Randomized and non-randomized studies were analysed separately. The characteristics of included and excluded studies are provided in Table S1 and Table S2, respectively.

Visual acuity 6–12 months after cataract surgery

Visual acuity after cataract surgery was reported in all four included studies. One of the randomized studies used a design where surgery was performed immediately in one group and deferred 6 months in another group, but visual acuity was not reported before 12 months after the first surgery, that is at a time-point when both groups had had surgery (Brunner et al. 2013). Hence, the study result could not be included in the analysis below. The two case–control studies reported visual acuity after 1 year of follow-up (Armbrecht et al. 2003; Baatz et al. 2008). Visual acuity was significantly better in patients with AMD who underwent cataract surgery, and the mean difference (95% CI) was −0.15 (−0.28 to −0.02) logMAR for the RCT and −0.13 (−0.17 to −0.09) for the case–control studies corresponding to 7.5 and 6.5 letters on the 20 feet ETDRS chart for the RCT and case–control studies, respectively. The differences were highly statistically significant (see Fig. 1).

The quality of evidence concerning visual outcome after cataract surgery was graded as moderate for the randomized trials and very low for the case–control studies. According to the GRADE guidelines, non-RCTs start as low-quality evidence (Balshem et al. 2011). The quality of evidence was downgraded because of the low number of patients included (RCTs) and the imbalance in AMD characteristics between the surgery and non-surgery groups (case–control studies). The quality of the evidence and summary of findings are presented in Table 1.

Progression to exudative AMD

All four included studies reported the number of eyes progressing to wet AMD within the observational period. One of the RCTs used a study design where only patients with a high risk of progression were included (Hooper et al. 2009) whereas this was not part of the study design in the other RCT (Brunner et al. 2013). One of the case–control studies had an unequal distribution of wet AMD at baseline with 5% of eyes in the surgery group and the 25.6% of eyes the control group. Furthermore, control subjects were younger (75 years versus 80 years), potentially suggesting a more aggressive course in the control group than in the surgery group. The second case–control study did not report the duration of AMD in patients in the surgery group at baseline (Baatz et al. 2008). By comparison, early AMD had been diagnosed 1 year before follow-up in the control group. In other words, there is a risk that AMD severity was not balanced in the surgery and control groups in the case–control studies. In total, 30 eyes of 1242...

![Fig. 1. Forest plot comparing visual acuity (logMAR) at 6 months (Hooper et al. 2009) or 12 months (Armbrecht et al. 2003 and Baatz et al. 2008) after cataract surgery or observation. SD = standard deviation, IV = inverse variance, CI = confidence interval.](image-url)
in the surgery group (2.4%) and 8 of the 437 control eyes (1.8%) progressed to exudative AMD. The difference was not statistically significant. Risk ratios (95% CI) were 3.21 (0.14–75.68) for the RCTs and 1.25 (0.55–2.85) for the case–control studies, see Fig. 2. The quality of evidence concerning progression of AMD to wet AMD after cataract surgery was graded as moderate for the randomized trials and very low for the case–control studies. The quality of evidence was down-graded due to low number of included subjects (RCTs) and due to the imbalance in AMD characteristics between the operated and non-operated eyes in the case–control studies. The quality of evidence and summary of findings are presented in Table 1.

Overview of findings on cataract, cataract surgery and AMD risk from epidemiologic studies

A number of large cross-sectional or prospective epidemiologic studies have reported on the association between cataract, cataract surgery and AMD risk. These findings are tabulated in Table 2. The odds ratio (95% CI) for any AMD was significantly increased in participants who had cataract at baseline examination [1.7 (1.5–2.0)] and for participants who had cataract surgery before baseline examination [1.5 (1.1–2.1)] but not for incident AMD <5 years after cataract surgery [1.1 (0.8–1.7)]. The odds ratio for early AMD was non-significant except for an increased OR for early AMD in participants with cataract at baseline examination [1.9 (1.0–3.6), p = 0.05]. The odds ratio (95% CI) of late AMD was 1.1 (0.7–1.7) for participants with cataract at baseline examination, 1.7 (1.3–2.3) for participants who had had cataract surgery at baseline, 1.4 (1.0–2.1) for incident late AMD <5 years after cataract surgery, 2.2 (1.4–3.5) for incident late AMD >5 years after cataract surgery and 1.6 (0.7–3.9) for incident late AMD >10 years after cataract surgery. The odds ratios for neovascular or geographic AMD were not significant.

**Discussion**

Cataract and AMD often coexist, especially in elderly patients. Concerns have been raised that cataract surgery may increase the risk of progression of AMD. The many large epidemiologic studies do not provide a clear indication of whether cataract surgery is associated with an increased risk of AMD progression or not. The general picture, based on the overview of findings in Table 2, is that the risk of AMD is not greater in patients undergoing cataract surgery than in patients with unoperated cataracts. The presence of cataract may preclude the diagnosis of AMD or correct staging of AMD (Dong et al. 2009). Late stage AMD can be assessed reliably before cataract surgery, whereas retinal pigment epithelium abnormalities may be harder to diagnose correctly prior to cataract surgery (Pham et al. 2005). This may be an important confounder in studies evaluating the association between cataract surgery and AMD progression. Much of the data from the epidemiologic studies dates back to the mid- or late 1990s and the type of cataract surgery (phacoemulsification versus extracapsular or intracapsular cataract extraction), and hence, the degree of surgical trauma was not reported in any of the epidemiologic studies and is likely to have changed over the years. For these reasons, we chose to restrict our analyses to studies using phacoemulsification. Considering the high relevance of the topic and the high prevalence of coexisting cataract and AMD, it is surprising that only two randomized (Lamoureux et al. 2007; Hooper et al. 2009; Brunner et al. 2013) and two case–control studies (Armbricht et al.

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**Table 1.** Quality of evidence and summary of findings.

| Outcomes                     | No. of participants (studies) | Quality of the evidence (GRADE) | Relative effect (95% CI) | Risk without surgery | Risk difference with cataract surgery (95% CI) |
|------------------------------|-------------------------------|---------------------------------|--------------------------|----------------------|-----------------------------------------------|
| Visual acuity (RCT)          | 56 (1 study)                  | ⬤ bpm                         | RR 75.68 (0.14–75.68)    | 0 per 1000           | Could not be estimated due to low event rate |
| Visual acuity (case control) | 1574 (2 studies)              | ⬤ bpm                         | RR 3.21 (0.14–75.68)     | 0 per 1000           |                                               |
| Progression to exudative AMD (RCT) | 105 (2 studies)                  | ⬤ bpm                         | RR 1.25 (0.55–2.85)      | 21 per 1000          |                                               |
| Progression to exudative AMD (case control) | 1574 (2 studies)              | ⬤ bpm                         |                         |                      |                                               |

**CI = confidence interval, RR = risk ratio, RCT = randomized controlled trial.**

**GRADE Working Group grades of evidence.** High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate.

* Very few subjects were included.

† AMD characteristics were not balanced between surgery and control groups in the case–control studies.
2003; Baatz et al. 2008) were identified and could be included in the meta-analysis. A great number of other studies were identified by the literature search but could not be included as these studies did not compare the clinical course in patients with AMD undergoing versus not undergoing cataract surgery.

The aim of our review was to provide evidence-based recommendation on the care of patients with coexisting AMD and cataract. Evidence-based medicine has been criticized for not being suited for patients with complex disease patterns as most patients in the primary studies are patients with a single disease and also because some guidelines have focused more on statistical significant p-values than clinical considerations. For the case-control studies, surgery patients and controls were not matched for AMD characteristics, and hence, the quality of the evidence was graded as low in the randomized trials, and although the number of included patients was low in the randomized trials, and the quality of the evidence was graded as moderate. For the case-control studies, surgery patients and controls were not matched for AMD characteristics, and hence, the quality of the evidence was graded as very low. We found that cataract surgery increased the visual acuity corresponding to 6.5–7.5 letters on the ETDRS 20 feet chart. This is less than the 10 letter improvement found in ANCHOR and MARINA participants undergoing cataract surgery (Rosenfeld et al. 2011), but it is still a visual improvement that is noticeable to patients.

Cataract surgery most often results in favourable visual outcome even in patients with AMD (Shuttleworth et al. 1998). As expected, the degree of visual gain is directly related to the severity of AMD at the time of surgery (Farooghian et al. 2009; Huynh et al. 2014). Visual acuity may decline in the years following cataract surgery, and the rate of decline is faster in patients with AMD than in eyes without comorbidity (Monestam & Lundqvist 2012). Although the self-assessed visual outcome of cataract surgery is poorer for patients with AMD with 24.5% of patients with AMD reporting questionable or no benefit from surgery versus 11.1% in non-AMD patients, the great majority of AMD patients (75.6%) still report that they had very good, good or moderate benefit of cataract surgery (Lundstrom et al. 2002). Cataract surgery increases the quality of life in AMD patients (Armbricht et al. 2000). The benefit (in terms of visual gain and subjective visual function) of cataract surgery in patients with AMD is sustained at least for 2–3 years postoperatively (Pham et al. 2007). Furthermore, cataract surgery offers the opportunity of implanting special optics IOLs to increase magnification or displace the image to healthy retina (Orzalesi et al. 2007; Potgieter & Claoué 2014) although these techniques are still experimental. Although the long-term results of cataract surgery in AMD patients, both visually and with respect to potential worsening of AMD, are still unknown, it does seem reasonable to offer the patient the visual benefit of cataract surgery and not limit access to surgery based on long-term theoretical risks, especially when the age group of AMD and cataract patients is taken into consideration.

With the introduction of anti-VEGF treatment, a large number of patients with exudative AMD retain fair visual function for many years (Bloch et al. 2012). However, patients with exudative AMD are older patients, and they often have or develop cataract to an extent that is considered to interfere with visual function. We did not find...
any prospective studies evaluating the course of exudative AMD in patients receiving or not receiving cataract surgery. Case series have shown favourable outcome at one month postoperatively in patients with wet AMD receiving combined cataract surgery and intravitreal bevacizumab (Furino et al. 2009). Combined intravitreal bevacizumab and cataract surgery was found to prevent reactivation of choroidal neovascularizations (CNV) in patients previously treated for CNV (Ruiz-Moreno et al. 2010). Two case series did not find that the need for anti-VEGF injections was increased after cataract surgery (Muzyka-Wozniak 2011; Gricht et al. 2014). A small, retrospective study found that cataract surgery should be performed after a sufficiently long exudative-free period to prevent recurrence of exudation (Lee et al. 2014).

**Conclusions and Recommendations**

In conclusion, we found that cataract surgery increases visual function in patients with AMD and that the 6- to 12-month risk of exudative AMD was not increased after cataract surgery. However, further studies with longer follow-up are encouraged. We recommend that patients with AMD and cataract are offered cataract surgery if the cataract is thought that affect vision significantly. We cannot provide evidence-based recommendations concerning cataract surgery in patients with exudative AMD receiving anti-VEGF treatment, but we suggest that cataract surgery can be performed when the exudative AMD is in a quiet phase, and combination of cataract surgery with intravitreal anti-VEGF injection seems to be advisable.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1 Characteristics of included studies
Table S2 Characteristics of excluded studies