Review

Systematic review of potential causes of intraocular lens opacification

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Abstract

Intraocular lens (IOL) opacification is an infrequent complication of cataract surgery. Surface analysis has demonstrated that the opacification of IOLs is related to calcium or phosphate precipitation on or within the lenses, but the associated mechanisms are unknown, and the scientific literature is heterogeneous and limited to case series and retrospective studies. The purpose of this systematic review was to analyse the most frequent conditions associated with opacification of IOLs reported by studies. A search was carried out using the PubMed MEDLINE, Web of Science (WOS) and Scopus databases. The quality of the studies selected was evaluated using the Pierson tool. The search provided a total of 811 articles, of which 39 were selected following the inclusion and exclusion criteria. The most common opacified lenses were hydrophilic IOLs according to our analysis. The mean time of appearance of lens opacification was 14.93 ± 17.82 months. The most frequent conditions associated with opacification of the IOLs were Descemet Stripping with Automated Endothelial Keratoplasty (DSAEK/DSEK) and diabetes mellitus (DM), followed by pars plana vitrectomy (PPV), blood hypertension (HT), and glaucoma. Concerning the quality analysis, the mean score was 7.00 ± 1.43 (scoring range from 0 to 10), indicating an acceptable quality of the case reports and retrospective studies. In conclusion, DSAEK / DSEK, DM, PPV, glaucoma and hypertension are conditions with potential risk of IOL opacification after cataract surgery, especially when implanting hydrophilic acrylic IOLs.

Keywords: intraocular lens, IOL opacification, IOL explantation, cataract surgery, acrylic IOL

1. INTRODUCTION

Intraocular lens (IOL) explantation after cataract surgery is a rare condition but is sometimes necessary. The incidence of explantation IOL is 7.7% according to a population-based retrospective data analysis.[1] In 2012, an observational multicentre retrospective study was conducted to retrieve all data from cases in which IOL explantation was performed in 15 different ophthalmological centers.[2] A total of 257 explanted pseudophakic IOLs were reported, with the main causes of IOL explantation being dislocation/decentration (56.3%), incorrect lens power (12.8%), neuroadaptation failure (6.2%), pseudophakic bullous keratopathy (2.3%) and endophthalmitis (1.9%). These authors concluded that IOL opacification was the third most frequent reason for IOL explantation (11.3%).[2]

The causes of opacification have been explored, and factors that might be associated with it include conditions associated with the patient, IOL manufacturer, IOL storage, surgical techniques and adjuvants.[3] Histopathological, histochemical, electron microscopic, elemental and molecular surface analytical techniques have demonstrated that the opacification of IOLs is related to calcium and phosphate precipitation on or within the lenses in PMMA, silicon and hydrophilic acrylic IOLs. In relation to the opacification of hydrophobic lenses, only two cases have been reported in which the opacification of lenses spontaneously occurred in a reversible way.[4]

Some causes and mechanisms associated with the accumulation of deposits on IOLs have been investigated in in-vitro studies. Drimtzias et al[5] suggested that IOL calcification is caused by nucleation and crystal growth of calcium phosphates on the IOL surface, with this process starting in the lens interior. However, there are no studies that explain how this process occurs in vivo. In addition, the scientific literature is heterogeneous with regard the conditions associated with IOL opacification, with most of it being based on case series and retrospective studies, providing low levels of scientific evidence. Furthermore, there are no reviews summarizing the types of conditions associated with IOL opacification. For this reason, a systematic review was performed aimed at analysing the quality of studies on IOL opacification according to the level of scientific evidence found to define the most frequent conditions associated with IOL opacification.

2. METHODS

A systematic review was carried out with a bibliographic search focused on answering the question, “What are the causes of opacification of intraocular lenses?” The search was made using the following databases: PubMed MEDLINE, Web of Science (WOS) and Scopus (all databases).

The search was limited to studies published from 2010 to 2019. The inclusion criterion was that articles must be original articles reporting cases of IOL opacification, including cases of IOL calcification. They could be descriptive studies, with sample populations including all ages, from children to adults. Studies whose main objective was not to describe the lens opacification were excluded. Likewise, studies about expert guidelines or opinions, non-original articles and studies in a language other than English were excluded. The search equation used in this review was as follows:

(opacification OR “loss of transparenc*” OR transparenc*) AND (“intraocular lens” OR IOL OR pseudophakic) NOT/AND NOT (“posterior capsul* opacification”)

Case series and retrospective studies are uncontrolled study designs with an increased risk of bias. However, these studies must present an internal validity that must be evaluated. For such a purpose, the Pierson tool was used. This tool is an approach for evaluating the validity of case reports based on five components:

documentation, uniqueness, objectivity, interpretation and educational value.[6] It provides a score ranging from 0 to 10. A score between 9 and 10 means that the report is likely to be a worthwhile contribution to the literature. A score between 6 and 8 means that the reader should be cautious about the validity and clinical value of the report. A score of less than 5 means that the report is of insufficient quality for publication. In the current systematic review, the mean, standard deviation (SD), maximum and minimum values of the Pierson scores were calculated.

The search was carried out on February 4, 2019. For the elaboration of the flow chart and the data collection process, the guidelines of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) declaration were followed.[7] Figure 1 shows the flow chart followed during the search. Using the search equation, a total of 811 articles was found. After removing duplicates, 294 studies were found. Following the inclusion and exclusion criteria, 45 articles were initially selected for a more comprehensive study and to confirm inclusion. Of the 45 articles, 5 did not fulfil the inclusion criteria and were excluded from further analysis. The remaining included articles numbered 40 and were analysed using the Pierson tool.[8-48]

3. RESULTS

Table 1 contains the main characteristics of each of the studies reviewed. The sample size, the type of IOL implanted and the time of occurrence and causes of lens opacification are displayed. The most common opacified lenses were hydrophilic IOLs according to our analysis. Specifically, lens opacification was reported in 82 cases implanted with different Oculentis IOL models, 7 cases implanted with the Akreos Adapt IOL (Bausch & Lomb), 6 cases implanted with the C-Flex 570C IOL (Rayner Intraocular Lenses Ltd.) and 5 with the Akreos MI60 (Bausch & Lomb). In 2 of the 39 reviewed studies, a hydrophobic lens was implanted. In one of these two studies, the authors stated that opacification of the lens was spontaneously reversed at 5 weeks after its detection.

Concerning the time of appearance of lens opacification with respect to the last intervention administered to the patient, the mean value was 14.93 ± 17.82 months, ranging from a maximum time of 72 months to a minimum time of 10 minutes. There was great heterogeneity in the time of appearance of opacification, regardless of the intervention.

Figure 2 shows the frequency of the conditions associated with the opacification of the IOLs, considering that the total number of eyes showing IOL opacification in the reviewed articles was 245. The most frequent condition associated with opacification of the IOLs was Descemet Stripping with Automated Endothelial Keratoplasty (DSAEK/DSEK), which was reported in 70/245 eyes. This was followed by diabetes mellitus (DM) and pars plana vitrectomy (PPV), which were reported in 37/245 and 30/245 eyes, respectively. Arterial hypertension (HT) and glaucoma were reported in 26/245 and 15/245 eyes, respectively. Likewise, combined conditions were reported in 24/245 eyes, including combinations of DM, HT, glaucoma and different surgical procedures, as has been detailed in Table 1.

The results of the quality analysis of each study included in the review are summarized in Table 2. The mean score was 7.00 ± 1.43, with a maximum score of 9 and a minimum of 5. Seven of the thirty-nine studies got the minimum score, and eight studies got the maximum. The best evaluated item was interpretation, which refers to how the results were interpreted and how the conclusions of the study were reached. On the other hand, the item with the worst score was uniqueness, which evaluates whether the case presented was unique or a case with the same characteristics was previously presented.

One of the main reasons leading to a poor evaluation was lack of information about the implanted lens or how phacoemulsification was performed. In 9 of the 39 studies, the name and characteristics of the opacified lens were not described by the authors.

4. DISCUSSION

In this systematic review, posterior lamellar keratoplasty (DSAEK/DSEK) and diabetes mellitus (DM) were the most frequently reported conditions associated with opacification of IOLs according to the included studies. Other causes, such as pars plana vitrectomy (PPV), glaucoma and arterial hypertension (HT), also had high reporting rates. The exact mechanism leading to IOL opacification in all cases was not clear, but in DSAEK / DSEK, it is believed to be due to repeated exposure to intracameral injections of air or gas and elevated intraocular pressure (IOP).[23,44] The aetiology in the case of DM may be the disruption of the blood-aqueous barrier and the proinflammatory condition. It should be noted that protein deposits have also been detected on the surface of explanted polymethyl methacrylate and hydrophilic acrylic lenses and are more intense in the presence of blood–aqueous barrier (BAB) disruption.[28] Patients with diabetic retinopathy typically have high aqueous humour calcium concentrations, which may contribute to the opacification.[31]

In relation to PPV, either combined with phacoemulsification or alone, it is postulated that intracameral gas could contribute to the calcification of the surface of the IOL.[29,36] Although the exact mechanism of calcification is under investigation, one hypothesis is that local damage to the hydrophilic IOL surface due to direct contact with air/gas at the exposed area may lead to Ca/P deposition from the aqueous humour.[44,46] In glaucoma, the hypothesis is that the presence of calcium deposits in aqueous humour is related to changes in aqueous humour pH after glaucoma surgery, since opacification was described mainly in conjunction with surgical procedures for glaucoma, such as iridotomies, trabeculectomies or Ex-PRESS shunt implantation.[32,40,41] On the other hand, a combination of the previously mentioned techniques (DSAEK/DSEK and PPV) can increase the possibilities of IOL opacification, as is the case of combining an intervention of DSAEK in a patient with diabetes or glaucoma, or PPV in patients with arterial hypertension.[4,13,31,39,42]

Another factor that may increase the risk of IOL surface opacification is the type of material. Most of the included studies employed hydrophilic acrylic lenses, and, in their conclusions, they discouraged the use of this type of lens when carrying out the aforementioned interventions.[37,45,47] In this review, we evaluated whether the different characteristics of the lenses used could be a factor that could influence lens opacification. However, detailed information about the chemical composition of the polymer of each hydrophilic opacified IOL was not provided in the revised studies, with only a report of the percentage of water content, which was in the range of 25-26% in all cases. Regarding hydrophobic lenses, they were used in only 2 studies, in one of which the opacification turned out to be reversible without the need of explantation of the lens.[4,34] The mechanisms by which the opacification was resolved are unknown. However, this fact should be considered when implanting hydrophobic lenses along with another advantage, which is the lower incidence of posterior capsule opacification compared to hydrophilic lenses.[49,50]

Quality analysis of the included studies showed that most of the studies had good methodology and internal validity, although no study reached the maximum score, mainly because they were not original works. This finding shows that opacification of lenses was reported on numerous occasions, although the maximum level of evidence was found in retrospective studies and case series. There were no studies with several cohorts or control groups. It should be considered that these types of studies would be ethically controversial, since the experimental group would receive an implant with a greater possibility of explantation due to potential IOL opacification.

Another reason why the evaluated studies did not achieve a high score with the Pierson tool was the lack of data in their methodology or results, such as the type of lens implanted or how the cataract surgery was carried out.[9,10,20,21,25,29,35] These pieces of information are very relevant and should be considered, as differences in the polymers with which they are made may be crucial for a better understanding of the exact mechanisms of opacification. Likewise, several studies did not specify how the phacoemulsification was carried out, even though the surgical procedure of cataract extraction may be one factor contributing to the process of IOL opacification. This is especially true in those case reports on IOL opacification after DSAEK / DSEK, which were focused on the description of the corneal surgical procedure, but minimal information was provided on the cataract surgery.

One of the strengths of this study is that it is the first systematic review to analyse the main causes of opacification of reported IOLs. However, the main limitation is that this review was carried out on studies with a low level of evidence.[51] Another limitation was the temporal limitations of this systematic review. Arbitrarily, 2010 was defined as the cutoff year for the search, considering that the most recent articles would include more complete information about the conditions associated with IOL opacification due to the enhanced clinical protocols and the advanced technology that clinical researchers have adopted in the last few years.

In conclusion, the main conditions associated with IOL opacification according to published studies are DSAEK / DSEK, DM, PPV, glaucoma and hypertension. These conditions should be given importance in order to avoid the explantation of intraocular lenses by deposits on its surface, especially if they are hydrophilic acrylic lenses. Studies with a greater degree of evidence on this topic are needed in order to better understand the mechanisms of deposition accumulation on or within intraocular lenses and thus how to avoid them.

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FIGURE LEGENDS

Figure 1: Flow chart of the selection process of relevant articles that were included in the systematic review for further quality analysis.

Figure 2: Bar diagram of the conditions associated with lens opacification reported in each study. DSAEK, Descemet Stripping with Automated Endothelial Keratoplasty; DSEK, Descemet's Stripping Endothelial Keratoplasty; DMEK, Descemet Membrane

Endothelial Keratoplasty; PPV, Pars plana vitrectomy; DM, Diabetes Mellitus; HT, hypertension

TABLES

Table 1: Main characteristics of the 40 included studies

Author (year)	*N*	*Type of IOL*	*Time of occurrence of Lens Opacification*	*Conditions associated with Lens Opacification*
Lee SJ (2010)	2	Hydrophilic C-Flex 570C	6 months	PPV, DM 1 case, PPV 1 case
Khan M (2011)	1	Hydrophilic Centerflex 570H	9 months	DSAEK
Park DI (2011)	1	Hydrophilic Akreos MI-60	6 months	DM, PPV, glaucoma
Pehere N (2011)	4	Hydrophilic Akreos MI-60 and SQRYCF	4 months-1 year	PPV
Lim AK (2011)	14	Hydrophilic AcriFlex 50CSE	1 year	DM
Park CY (2012)	1	Hydrophilic Akreos MI-60	1 month	DM, anti-VEGF intravitreal injection
Dhital A (2012)	3	Hydrophilic C-Flex 570C and Akreos Adapt	6 weeks-1 year	PPV, DM, intravitreal injection, DSAEK, HT
Patryn E (2012)	3	Hydrophilic acrylic	18 weks-1 year	DSEK + DM + HT 1 case, DSEK 2 cases
Fellman MA (2013)	1	Hydrophilic acrylic	2 years	DSEK
Forlini M (2013)	1	Hydrophilic Akreos Adapt	1 year	DM, HT, transscleral drainage
Ahad MA (2014)	15	Hydrophilic Akreos Adapt, C-Flex 570C	17 months	DSAEK
Fung SS (2015)	7	Hydrophilic C-Flex 570C and Rayner Superflex 620H	6 months	N/A 3 cases, glaucoma 1 case, DM + PPV 2 cases, DM 1

				case
Verdaguer P (2015)	1	Hydrophilic Akreos Adapt	1 year	DSAEK
Werner L (2015)	7	Hydrophilic acrylic	6 months	DSAEK, DSEK
Ní Mhéalóid Á (2015)	4	Hydrophilic Akreos Adapt and hydrophilic with hydrophobic surface CT Asphina	7 months-2 years	DSAEK
Park JC (2015)	5	Hydrophilic Stabibag, Lenstec LH 3000, MI60	4 mont-1 year	DSAEK
Nieuwendaal C (2015)	8	Hydrophilic 3 Stabibag Zeiss, 3 Rayner 620H, 2 Akreos 160	1-2 years	DSAEK
Morgan-Warren PJ (2015)	6	Hydrophilic acrylic	32 months	DSAEK
Mojzis P (2016a)	1	Hydrophilic CT47S	8 months	DSAEK
Bompastor-Ramos P (2016)	19	Hydrophilic with hydrophobic surface Lentis LS-502-1	1-2 years	DM, glaucoma, epiretinal membrane
Norouzpour A (2016)	1	Hydrophilic Akreos Adapt	10 months	Glaucoma, DSAEK
Mojzis P (2016b)	2	Hydrophilic Ioflex	5 years	DM + AMD + HT 1 case, HT 1 case
Kalevar A (2017)	2	Hydrophilic Akreos AO60	5-6 months	PPV
Giers BC (2017)	13	Hydrophilic acrylic	6 months-2 years	DSAEK, DSEK
Schrittenlocher S (2017)	14	Hydrophilic (11), hydrophobic (2), Hydrophilic with hydrophobic surface (1)	6 months	Triple DMEK
Liu Q (2017)	1	Hydrophilic with hydrophobic surface AT LISA tri 839mp	10 minutes	Fluctuation of temperature
Kim DJ (2017)	2	Hydrophobic Tecnis ZCB00	7 weeks (it was resolved	DM + Glaucoma 1 case, N/A 1

			at 5 weeks)	case
Agresta A (2017)	1	Hydrophilic Akreos Adapt	10 months	Glaucoma, iridotomy and Ex-PRESS shunt
Abdul-Rahman A (2018)	1	Hydrophilic Akreos M160L	4 months	DM, glaucoma, trabeculectomy
Yildirim TM (2018)	10	Hydrophilic CT Asphina 409M, Basis Z B1AW00, C-flex Aspheric 970C	1 year	PPV
Cavallini GM (2018)	1	Hydrophilic Lentis L-313	2 years	N/A
Marcovich AL (2018)	11	Hydrophilic Hanita B lens, Xcellence Idea, Biotech vision care Eyecryl, Rayner Superflex Aspheric 920, M-flex 630F, CT Asphina 409M, C-flex Aspheric 570C	1 month-6 years	PPV
Daigle P (2018)	1	Hydrophilic C-Flex 570C	5 years	DM, breakdown of the blood-aqueous barrier
Graffi S (2018)	4	Hydrophilic acrylic	6 months	DSAEK, DMEK
Choudhry S et al. (2018)	1	Hydrophilic AcrySof	During surgery	DM
Quigley C (2018)	1	Hydrophilic acrylic	N/A	DSAEK, glaucoma
Khurana RN (2018)	1	Hydrophilic NaturaLens	8 months	PPV, DM
Ma ST (2018)	2	Hydrophilic AcrySof SA60AT	9 months	DSAEK 1 case, DM + PPV + Silicone oil tamponade + Intravitreal air injection 1 case
Rahimi M (2018)	2	Hydrophilic acrylic	1-4 years	DM + PPV 1 case, PPV 1 case
Gurabardhi M (2018)	71	Hydrophilic LS-412-1Y, LS-502-1, LS-402-1Y, LS-313-1Y, L-402, L-	50 months	HT 25 cases, HT + DM 2 cases, DM 10

312		cases, HT + Renal failure 2 cases, Renal failure 4 cases, HT + DM + AMD + Glaucoma 2 cases, HT + DM + Glaucoma 2 cases, PPV + Gas tamponade 1 cases, DSAEK 1 case, AMD 11 cases, Glaucoma 9 cases, Anterior uveítis 2 cases

PPV, Pars plana vitrectomy; DSAEK, Descemet Stripping with Automated Endothelial Keratoplasty; DSEK, Descemet's Stripping Endothelial Keratoplasty; DM, Diabetes Mellitus; HT, hypertension; anti-VEGF, anti-vascular endothelial growth factor; DMEK, Descemet Membrane Endothelial Keratoplasty; N/A, Not Available

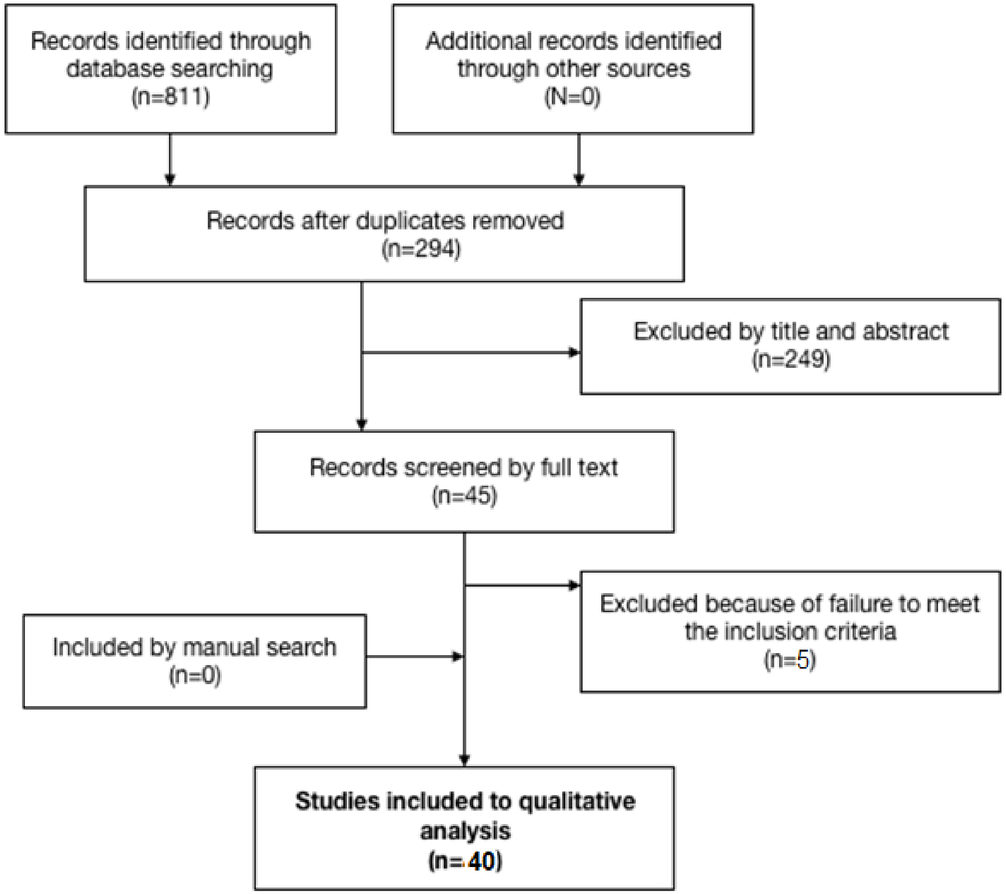
Table 2: Outcomes of the quality analysis with the Pierson tool of the articles included in the review

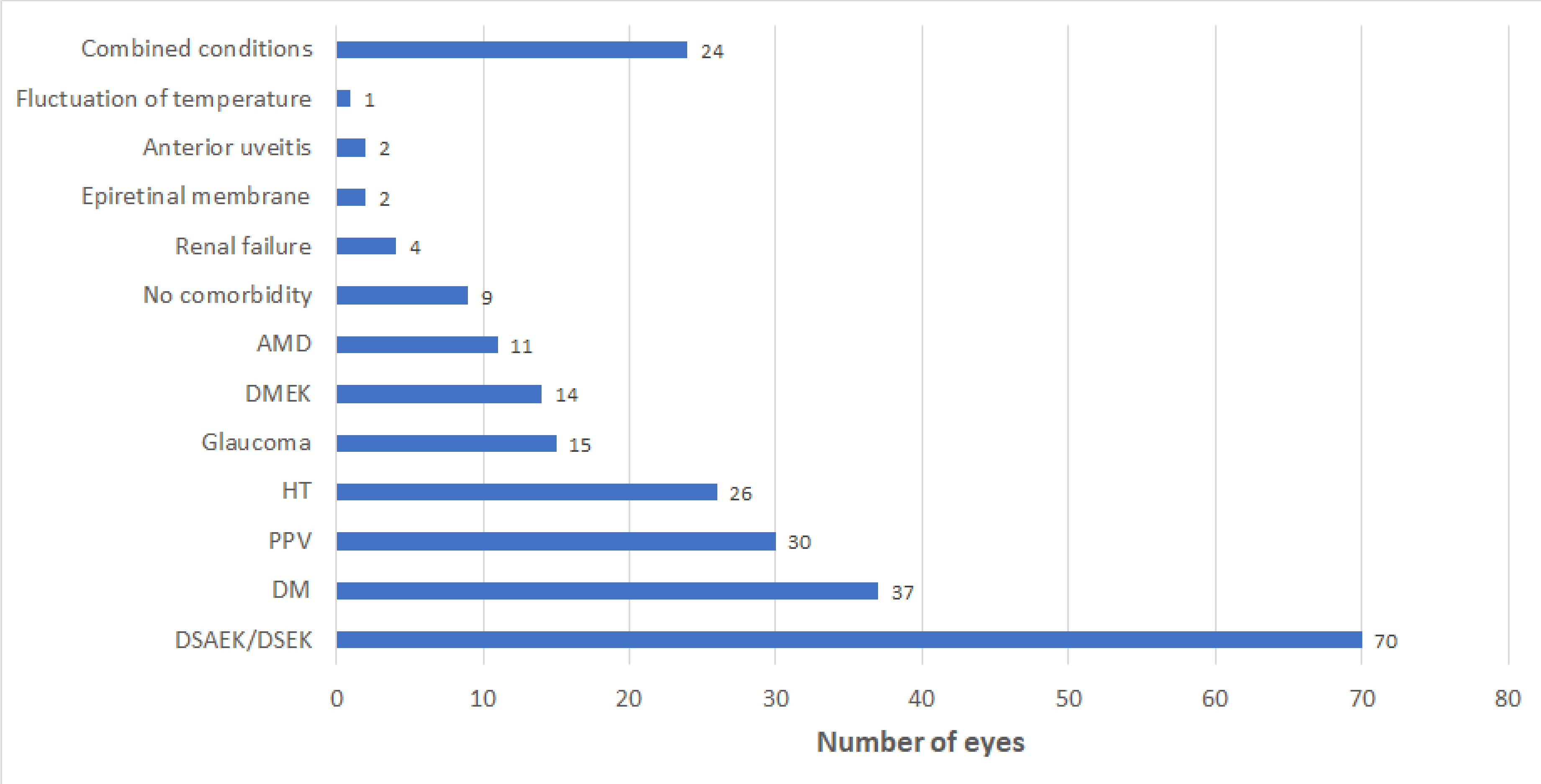
Author (year)	Documentation	Uniqueness	Educational Value	Objectivity	Interpretation	OUTCOME (X/ 10)
Lee SJ (2010)	2	2	1	1	2	**8**
Khan M (2011)	2	1	2	1	2	**8**
Park DI (2011)	2	1	1	1	2	**7**
Pehere N (2011)	2	1	2	1	2	**8**
Lim AK (2011)	2	1	2	2	2	**9**
Park CY (2012)	2	2	2	2	1	**9**
Dhital A (2012)	2	1	1	2	2	**8**
Patryn E (2012)	1	1	1	1	2	**6**
Fellman MA (2013)	2	0	1	1	1	**5**
Forlini M (2013)	2	1	1	2	2	**8**
Ahad MA (2014)	1	0	1	2	2	**6**
Fung SS (2015)	2	2	1	2	2	**9**

Verdaguer P (2015)	2	1	1	2	1	**7**
Werner L (2015)	1	0	1	2	2	**6**
Ní Mhéalóid Á (2015)	2	1	2	2	2	**9**
Park JC (2015)	2	0	1	2	2	**7**
Nieuwendaal C (2015)	2	0	1	2	2	**7**
Morgan-Warren PJ (2015)	1	0	1	2	2	**6**
Mojzis P (2016a)	2	0	1	2	2	**7**
Bompastor-Ramos P (2016)	2	1	2	2	2	**9**
Norouzpour A (2016)	2	1	1	2	2	**8**
Mojzis P (2016b)	2	0	1	1	2	**6**
Kalevar A (2017)	2	1	1	1	1	**6**
Giers BC (2017)	1	0	1	1	2	**5**

Schrittenlocher S (2017)	2	1	1	2	2	**8**
Liu Q (2017)	2	2	1	2	2	**9**
Kim DJ (2017)	1	2	2	2	2	**9**
Agresta A (2017)	2	1	1	2	1	**7**
Abdul-Rahman A (2018)	2	2	1	2	2	**9**
Yildirim TM (2018)	1	1	1	2	2	**7**
Cavallini GM (2018)	1	1	1	1	2	**6**
Marcovich AL (2018)	1	0	1	1	2	**5**
Daigle P (2018)	2	1	2	1	2	**8**
Graffi S (2018)	1	1	1	1	2	**6**
Choudhry S et al. (2018)	1	1	1	1	1	**5**
Quigley C (2018)	1	0	1	1	2	**5**
Khurana RN (2018)	1	0	1	1	2	**5**
Ma ST (2018)	1	0	1	1	2	**5**
Rahimi M	1	1	1	1	2	**6**

(2018)


Records identified through database searching (n=811)
Additional records identified through other sources (N=0)
Records after duplicates removed (n=294)
Excluded by title and abstract (n=249)
Records screened by full text (n=45)
Excluded because of failure to meet the inclusion criteria (n=5)
Included by manual search (n=0)
Studies included to qualitative analysis (n=40)


Combined conditions
Fluctuation of temperature
Anterior uveitis
Epiretinal membrane
Renal failure
No comorbidity
AMD
DMEK
Glaucoma
HT
PPV
DM
DSAEK/DSEK
24
1
2
2
4
9
11
14
15
26
30
37
70
0
10
20
30
40
50
60
70
80
Number of eyes