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Risk Factors for the Development of Ocular Hypertension After Keratoplasty: A Systematic Review

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Purpose: To identify risk factors for the development of ocular hypertension after keratoplasty.

Methods: A systematic search in PubMed and Embase identified 67 relevant articles published between January 1990 and 2019. We preferentially searched for data on an intraocular pressure increase above 21 mmHg at 6 months or a threshold or time point close to that and reported whether the preoperative or intraoperative status of risk factors was defined. The results were presented in evidence tables, visualizing the direction of the association, whether univariate and/or multivariate analysis was performed, and the significance level ($P < 0.05$). Four researchers, blinded for the risk factors, independently assigned a level of evidence (definitely, probably, possibly, not associated). Consensus was met during group meetings.

Results: From the 110 studied risk factors, pre-existing glaucoma, high preoperative IOP and combined keratoplasty with removal or exchange of an intraocular lens (IOL) were definitely associated with an increased risk. In addition, if the pre-or postoperative lens status was undefined, aphakia and pseudophakia with the IOL in the anterior or posterior chamber were also definitely associated with an increased risk when compared to phakia. Glaucoma in the contralateral eye, indication of bullous keratopathy, African American descent, preoperative treatment with cyclosporine or olopatadine 0.1%, postoperative treatment with prednisolone acetate 1%, and combined surgery in general (ie, the type of surgeries undefined in primary studies) were probably associated. Multiple other identified risk factors lack sufficient evidence and need additional investigation.

Conclusions: Risk factors with a definite association can help clinicians select patients at risk and adjust their follow-up and treatment. The other factors need further investigation.

Key Words: keratoplasty, lamellar keratoplasty, penetrating keratoplasty, risk factors, ocular hypertension

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Many corneal conditions such as corneal dystrophies, corneal infections, trauma, and iatrogenic corneal diseases may cause sight-threatening corneal opacities or scarring of the cornea for which keratoplasty is often the only cure. Corneal transplantation is therefore one of the most frequently performed transplantation, and the number of keratoplasties performed each year increases worldwide.[1,2] Ocular hypertension (OHT) is one of the most common complications. It may cause irreversible vision loss after keratoplasty because of graft failure resulting from the impact of OHT on endothelial cell loss.[3–5] A sustained elevation of intraocular pressure (IOP) may also cause glaucomatous damage to the optic nerve, leading to progressive visual field loss and eventually blindness.

The reported prevalence of the development of OHT after keratoplasty varies widely, ranging from 5.5%[6] up to 68%.[7] This is mainly because of the lack of a standardized definition for OHT. Throughout the literature, OHT has been defined as a postsurgical IOP >21 mmHg after surgery or an increase of >10 mmHg over the baseline IOP with or without the need for antiglaucoma medication or surgery.[8]

A corticosteroid-induced elevation of the IOP is known to be the most common cause of OHT after corneal surgery.[9–11] However, various other preoperative, intraoperative, and postoperative risk factors that increase the risk of developing OHT after keratoplasty have been studied. To our knowledge, only 1 meta-analysis, investigating 8 risk factors for OHT after penetrating keratoplasty (PKP), has been performed.[8] Other reviews discussed multiple risk factors[3,12–14]; however, they did not evaluate them systematically, and a meta-analysis reporting and evaluating the available evidence of all suspected risk factors in penetrating and lamellar keratoplasty is currently missing.

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We used a systematic approach to identify to what extent various risk factors have been investigated and a semiquantitative approach to investigate which factors are associated with the development of OHT after keratoplasty. Identification of these risk factors is of clinical importance because they can help determine the prognosis of each individual patient and facilitate preventative measures to reduce the risk of developing glaucomatous damage and/or graft failure.

METHODS

Eligibility Criteria for Considering Studies for This Review

To provide a complete overview of the available evidence, all studies investigating at least 1 risk factor for the development of OHT in any type of keratoplasty were included in this review. Case series, comparative case series, cohort studies, case–control studies, and randomized controlled trials were all included in this review because all of these designs were suitable to investigate risk factors. The search was restricted to articles published after January 1990. There were no restrictions on language or publication status. Only articles reporting a *P* value, odds ratio (OR), or hazard ratio with or without confidence intervals were included. Articles were excluded if the full text could not be retrieved; the article was not available in Dutch, English, French, or German; the study did not investigate risk factors; the study was performed ex vivo; the data were not interpretable; the study included patients < 18 years old; the study included patients before 1990; the sample size was < 25 eyes; and the follow-up was ≤ 1 month or starting > 1 year after keratoplasty. Articles were also excluded if they investigated a specific subpopulation with an a priori higher risk of developing OHT or glaucoma.

Search Methods for Identifying Studies

A systematic search in PubMed and Embase was performed in June 2018, and an update was conducted at the beginning of February 2019. The following key words were used: corneal transplantation surgery, penetrating keratoplasty, lamellar keratoplasty, Descemet membrane endothelial keratoplasty, Descemet stripping (automated) endothelial keratoplasty, deep anterior lamellar keratoplasty, glaucoma, intraocular pressure, ocular hypertension, and steroid-induced ocular hypertension. The complete search for both databases and all used synonyms for each of the abovementioned terms can be found in Supplemental Digital Content 1 (see Supplemental File 1, http://links.lww.com/ICO/A938). To verify whether we did not miss any eligible articles, we searched the reference lists of all included studies and previously published reviews.

Study Selection

All the references resulting from the search in PubMed and Embase were imported in EndNote X8. After the importation of 4424 references, 1140 duplicates were removed automatically and manually. All titles and abstracts of the 3284 unique references were studied by 1 author (I.L.) to detect all references that investigated any risk factor for the development of postkeratoplasty OHT. The titles and abstracts of references that were not selected during this first selection round were double checked by the same author to not miss any relevant articles; however, no additional references were selected. Each of the selection processes entailed 3 days. References not investigating any risk factors were excluded (n excluded = 2765); following which the full-text articles of all relevant abstracts (n = 519) were searched. If the full text could not be obtained through the university portal, we contacted the authors. Four hundred forty-three articles of the 519 retrieved full text did not fulfill the abovementioned selection criteria and were excluded. The remaining 76 articles were used for analysis. A flowchart visualizing the selection procedure can be found in Figure 1. No additional articles could be identified after searching the reference lists of all included studies and previously published reviews.

Data Collection and Risk of Bias Assessment

As indicated above, case series, comparative case series, cohort studies, case–control studies, and randomized controlled trials were all included in this review. We followed the Ophthalmology study design scheme to allocate the included studies properly.[15] We clustered studies with study populations that were likely to overlap into functionally related clusters. The likelihood of overlap was determined on author names, site of recruitment, trial names, period of recruitment, and references to other studies.

To assess the quality of the 76 included studies, we used the checklist developed for quality assessment of prognosis studies which is recommended by the National Institute for Health and Clinical Excellence.[16] This checklist contains 6 criteria which are related to the representation of the study population, risk of bias, loss to follow-up, measurement of the risk factors, outcome measurement, correction for confounders, and reproducibility of the statistical analysis.

Data Synthesis and Analysis

Because the risk factors have been investigated in studies using various study methods, maintaining different definitions of OHT and investigating both penetrating and lamellar keratoplasty within different study populations, we could not perform a formal meta-analysis. Therefore, as performed by Ernest et al,[17] we used a semiquantitative method to investigate to what extent various risk factors are most likely associated with the development of OHT after keratoplasty.

We summarized the evidence for each studied risk factor in separate tables. An example of an evidence table is shown in Table 1. Each outcome regarding the risk factors was classified according to the direction of the association of the risk factors with OHT (higher risk, lower

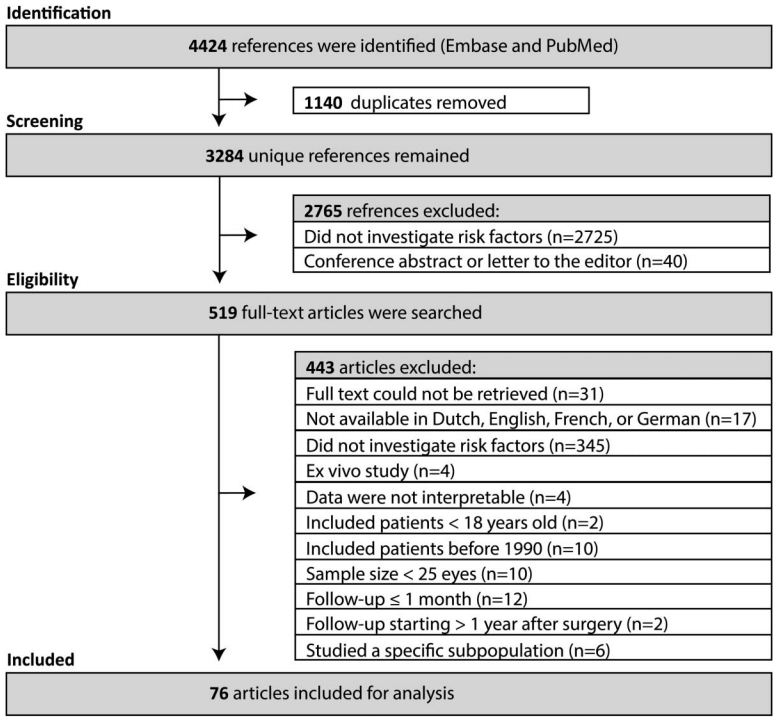

FIGURE 1. Flowchart of the selection procedure of the included articles.

risk) and the reported statistical significance (P value < 0.05). We also differentiated between univariate and multivariate results. We tried to extract 1 conclusion per studied risk factor within 1 study. If a study did not describe the direction of the risk factor, we reported the study in the middle column (relation unknown). Furthermore, we indicated which studies belonged to the same study cluster (Table 1).

Throughout the included studies, various definitions and outcome measures have been used to define the development of OHT after keratoplasty. To report the results as uniformly as possible, we tried to use similar outcome measures. Preferably, we reported the results investigating an increase in absolute IOP. If multiple cutoffs were mentioned, we reported the results of an IOP increase above 21 mmHg or the provided cutoff which was most adjacent to 21 mmHg. If the absolute IOP increase was not reported, we had to use other outcome measures for which we maintained the following sequence: mean IOP (preferably compared with baseline), the need to start or change glaucoma medication, and last, the need for surgical interventions. Furthermore, if the outcome measure was mentioned for multiple time points,

TABLE 1. Example of an Evidence Table Summarizing All Study Results of a Risk Factor

	Increased Risk for OHT		Direction of the Relation Is Unknown		Decreased Risk for OHT	
Factor x	**Significant**	**Nonsignificant**	**Significant**	**Nonsignificant**	**Nonsignificant**	**Significant**
Univariate analysis (n=)	1, 2†, 8*	2††, 4		7		
No. clusters	3	2	0	1	0	0
No. studies	3	2	0	1	0	0
No. patients	236	324	0	48	0	0
Multivariate analysis (n=)	3, 5	6				
No. clusters	1	1	0	0	0	0
No. studies	2	1	0	0	0	0
No. patients	496	116	0	0	0	0

All the risk factors are presented in evidence tables. These tables were used to determine to which extent a risk factor had been investigated and whether it is not, possibly, probably or definitely associated with the development of OHT after keratoplasty. The abovementioned table summarizes all the evidence of the risk factor "X." Each number in the table represents a study. The studies are numbered according to the reference list of Supplemental Digital Content 2 (http://links.lww.com/ICO/A939). The studies are classified based on the direction (increased or decreased glaucoma risk or unknown direction), the significance of the association ($P < 0.05$), and whether univariate or multivariate analysis has been performed. The number of study clusters, studies, and patients is summarized below the study numbers. Numbers between parentheses represent the total number of univariate and multivariate conclusions in the analysis. Tables marked as "general" contain multiple risk factors that have been investigated together (lacking detailed information). † and †† indicate and specify subgroups that have been made within 1 study. Studies 3 and 5 are underlined because they belong to the same study cluster (as defined in Supplemental Digital Content 2 [http://links.lww.com/ICO/A939]).

*Study population of solely steroid responders.

we reported the results after 6 months or the time point which was the closest to 6 months.

To make some of the results of the investigated risk factors throughout the included studies comparable with each other, we changed the reference to which a risk factor was compared and recalculated the OR using a χ^2 or Fisher exact test as appropriate. A P value < 0.05 was defined as statistically significant. We did this for the indication of surgery, lens status, and regrafting. Within multiple studies, different indications had been investigated and compared with each other. To obtain meaningful results, we used keratoconus as a reference. For the lens status, we studied the following comparisons: aphakic versus phakic, pseudophakic versus phakic, and aphakic versus pseudophakic. Furthermore, most studies compared graft failure as an indication for keratoplasty with a single primary indication such as keratoconus, not taking into account that graft failure indicates regrafting instead of performing a primary keratoplasty. Therefore, we recalculated the OR comparing graft failure with the sum of all other studied primary indications within a respective study.

While creating the evidence tables for each risk factor, we tried to maintain the detailed information that had been provided for each risk factor as much as possible, for example, keratoplasty combined with cataract extraction, vitrectomy, or the removal or exchange of an intraocular lens (IOL) implant. However, if a study did not provide this detailed information and only compared combined surgery with no combined surgery in general, we reported those results as well and marked the evidence table as "general." These tables might provide an overview of the available evidence of a risk factor but lack further details.

In addition, if studies specifically defined the lens status to be preoperative or postoperative, we maintained this differentiation because a postoperative lens status might indicate that the patients underwent a combined surgery, for example, keratoplasty and cataract extraction with or without implantation of an IOL. In case initial studies did not define whether the investigated lens status was preoperative or intraoperative, it was studied as a separate category.

Interpretation of the Evidence Tables

The obtained evidence tables were used to determine if and to what extent a risk factor was associated with the development of OHT after keratoplasty. Four different investigators (J.S.A.G.S., C.A.B.W., H.J.M.B., and I.L.) independently investigated the evidence tables and judged whether the risk factor was "not associated," "possibly associated," "probably associated," or "definitely associated" with OHT. Each of the investigators was blinded for the risk factor and the articles that studied the risk factor. The following elements were taken into account during the assessment: the number of study results concerning the risk factor, the total number of participants within these studies, whether studies belonged to the same study cluster, and whether univariate or multivariate results were reported. The same guidelines as applied by Ernest et al[17] were used for the classification. Shortly, risk factors with a consistent pattern of no relation were assigned to "no association." This category also comprised risk factors showing a great heterogeneity in their evidence table and risk factors that had been studied to a limited extent, for which an association was not (yet) found. Risk factors with a weak tendency toward a higher or lower risk were assigned to "possible association." Risk factors with an obvious tendency toward more or less progression in a moderate number of studies with several studies having significant results were assigned to "probable association." "Definite association" was assigned to risk factors with a very consistent pattern of numerous studies with multiple statistically significant results. If an identified risk factor had only been investigated in 1 study, we used the following criteria to assess the level of evidence: a risk factor was graded as "possible association" if it was significantly associated in a univariate analysis, and it was graded as "probable association" if it was significantly associated in a multivariate analysis. A large cohort study showing a significant association in both univariate and multivariate analyses was graded as "definite association." In all other cases, the risk factor was classified as "no association." During group meetings, differences in ratings between the investigators were discussed and consensus was reached.

During the judgment procedure of the evidence tables, we checked the reported results of each risk factor for heterogeneity. Risk factors for which evidence was found in both directions of the association (increased risk and decreased risk) were marked to be heterogeneous.

RESULTS

We identified 76 relevant articles published between 1993 and 2019: 31 case series, 32 comparative case series, 6 cohort studies, 1 case–control study, and 6 randomized controlled trials. The studies are shown in Supplemental Digital Content 2 (see Supplemental File 2, http://links.lww.com/ICO/A939) and were clustered into 49 clusters. The characteristics of the included studies are shown in Supplemental Digital Content 3 (see Supplemental File 3, http://links.lww.com/ICO/A940). Most of these studies consisted of case series (76%) and were performed retrospectively (83%). A univariate analysis was executed in 87% of the studies, and a multivariate analysis was executed in 4%. In 9% of the studies, both univariate and multivariate analyses were performed. The type of surgery which was most often investigated within the included articles was PKP (57%), followed by descemet stripping automated endothelial keratoplasty (27%), DALK (15%), descemet membrane endothelial keratoplasty (10%), deep lamellar endothelial keratoplasty (4%) and EK, ALK and femtosecond laser-enabled keratoplasty (together 5%).

We identified 110 risk factors for the development of OHT after keratoplasty. The judgment procedure of these risk factors identified 6 definite associations, 8 probable associations, 24 possible associations, and 72 no associations. The judgments were overall consistent. In case of different judgments between the investigators, consensus could easily be reached. All the evidence tables are presented in Supplemental Digital Content 4 (see Supplemental File 4, http://links.lww.com/ICO/A941).

Quality Checklist

Supplemental Digital Content 5 (see Supplemental File 5, http://links.lww.com/ICO/A942) provides an overall overview of the scores of the 76 included studies on 6 quality items. In total, we found 1 study with "yes" to all 6 criteria (1.3%), 11 studies with "yes" to 5 criteria (14.5%), 34 studies with "yes" to 4 criteria (44.7%), and 30 studies with "yes" to 3 criteria (42%). Three studies scored "no" to 3 criteria (3.9%), 49 studies "no" to 2 criteria (64.5%), and 23 studies "no" to 1 criterion (30.3%). A total of 39 studies (51.3%) scored "unclear" on the same criterion of the quality checklist (outcome measurement) because these studies did not specify the IOP measurement method. Although it was not specifically mentioned, it is highly likely that the used method is the same as before and after keratoplasty and/or between the subgroups. Therefore, we scored the quality item for these studies as "unclear" instead of "not."

Baseline characteristics (criterion one) were clearly described for 74 of the 76 studies, the 2 other studies provided a very concise description. However, it must be noted that 23 studies did not describe IOP values or the presence of glaucoma in the baseline characteristics. Criterion 2 (loss to follow up) contained per definition 64 times "no" because we included 63 case series and 1 case–control study. The other studies provided sufficient information concerning the follow-up. Criteria 3 and 6, describing the measurement of the risk factors and the reproducibility of the statistical analysis, were scored as "yes" for all included studies.

Preoperative, Intraoperative, and Postoperative Risk Factors

Supplemental Digital Content 6 (see Supplemental File 6, http://links.lww.com/ICO/A943) shows a clinically relevant overview of all the risk factors. We classified the risk factors into 50 preoperative, 41 intraoperative, and 13 postoperative risk factors. For 5 risk factors, all describing the lens status, it was unclear whether the investigated lens status was already present before surgery or was obtained during surgery. Therefore, we classified these risk factors as "preoperative or intraoperative status not defined." One risk factor was described as "preoperatively and/or postoperatively" and therefore clustered separately from the abovementioned categories.

Definite Risk Factors

Six risk factors have been determined to be definitely associated with OHT after keratoplasty: preexisting glaucoma, a higher preoperative IOP, combining keratoplasty with the removal or exchange of an IOL implant, and, in case the operative lens status was unknown, aphakic lens status and pseudophakic lens status with the IOL in the anterior or posterior chamber in comparison with phakic lens status. Preexisting glaucoma had been investigated in 19 different studies, which led to 24 study results of both univariate and multivariate analyses, showing a clear tendency toward an increased risk for OHT. The classification of a higher preoperative IOP and keratoplasty combined with lens removal or exchange were both based on 7 conclusions. Both univariate and multivariate results of these risk factors show a clear tendency toward an increased risk for OHT, and therefore, both risk factors were judged to be definitely associated. The risk factors aphakic compared with phakic lens status and pseudophakic lens status with the IOL in the anterior or posterior chamber compared with phakic eyes (preoperative or intraoperative lens status unknown) were judged to be definitely associated because 1 large cohort study comprising 1657 participants reported a significantly higher risk in both univariate and multivariate analyses.

Probable Risk Factors and Possible Factors

Eight risk factors have been determined to be probably associated with OHT after keratoplasty.

Bullous keratopathy compared with keratoconus and combined surgery in general has been investigated in 11 and 10 conclusions, respectively. Five other risk factors were probably associated with the development of OHT as well, although their judgment was based on a lower number of studies and conclusions. These risk factors were indication of bullous keratoplasty (yes vs. no), African American descent, cyclosporine and olopatadine 0.1% use before keratoplasty, postoperative use of prednisolone acetate 1% versus dexamethasone 0.1%, and glaucoma in the contralateral eye (without glaucoma in the investigated eye).

Possible Associated Risk Factors

Twenty-four risk factors were judged to have a possible association. For most of these risk factors, this was based on a limited number of studies, therefore lacking sufficient evidence to make a more certain conclusion.

Five risk factors were judged to be possibly associated based on at least 8 studies: a younger age of the patient, regrafting, male gender, PKP when compared with DS(A)EK, and a larger graft diameter in PKP. Despite the fact that these risk factors had been investigated in multiple studies, we were not able to find a more robust association with IOP elevation because of the heterogeneity within the evidence. Additional investigation of the possibly associated risk factors is therefore necessary.

An overview of the definite, probable, and possible risk factors can be found in Supplemental Digital Content 7 (see Supplemental File 7, http://links.lww.com/ICO/A944).

Nonassociated Risk Factors

Seventy-two risk factors were judged to be not associated. Note that 56.6% (43) of these risk factors have only been based on 1 conclusion, 14.5% (11) on 2 conclusions, and 14.5% (11) on 3 to 5 conclusions. In addition, these conclusions were mostly derived from studies with a low sample size. These risk factors therefore lack sufficient evidence to know whether they are associated with the development of OHT and need further investigation.

Seven risk factors however were judged not to be associated based on at least 6 conclusions. Remarkably, for 5 of these risk factors, there was a considerable amount of

heterogeneity, indicating contradictive study results. Therefore, we could not conclude any association for the following risk factors: corneal dystrophy as an indication for surgery, preoperative pseudophakic or phakic lens status, PKP compared with DALK, and performing a triple procedure. These risk factors need further investigation as well.

The evidence tables of the other 2 risk factors, infectious keratitis or scar compared with keratoconus, showed no heterogeneity. Their evidence is sufficient and robust, which allows us to conclude that they are not associated with the development of OHT. An overview of all not associated risk factors can be found in Supplemental Digital Content 8 (see Supplemental File 8, http://links.lww.com/ICO/A945).

Heterogeneity

For 20 risk factors, we noted a considerable amount of heterogeneity during the judgment procedure (marked with "H" in table 4 and the Supplemental Digital Contents 3 and 4 (see Supplemental Files 3 and 4, http://links.lww.com/ICO/A940 and http://links.lww.com/ICO/A941). For 4 risk factors, the heterogeneity consisted of significant results in the opposite direction as most of the results. For the other 16 risk factors, the heterogeneity only comprised nonsignificant results.

Despite its heterogeneity, the risk factor history of glaucoma was judged to be definitively associated. It was found to significantly increase the risk for OHT in 17 studies in both univariate and multivariate analyses (12 univariate and 4 multivariate significant; 4 univariate and 2 multivariate nonsignificant). One study with a small sample size found a nonsignificant result but did not specify the direction of the association. Therefore, the heterogeneity consisted of only 2 studies reporting a nonsignificant decreased risk, which is rather trivial compared with the 17 studies showing an increased risk.

We also noticed heterogeneity for 5 and 15 other risk factors that were respectively judged to be possibly and not associated. Multiple of these risk factors had been investigated in a relatively large number of studies. For the possibly associated risk factors, we could, despite the heterogeneity, distinguish a small association toward an increased or decreased risk. A stronger association however could not be concluded. For the not associated risk factors, the heterogeneity was too large to identify a possible direction of the association with OHT.

DISCUSSION

This systematic review provides an overview of all investigated risk factors for the development of OHT after keratoplasty and the level of evidence that is available for each risk factor. By performing a semiquantitative approach, we were able to identify 110 risk factors and classify them into 6 definite, 8 probable, 24 possible, and 72 no associations, as shown in Supplemental Digital Content 6 (see Supplemental File 6, http://links.lww.com/ICO/A943).

Other reviews provide a nonsystematic literature overview of the most extensively studied risk factors for the development of OHT after keratoplasty[3,12–14]; however, a systematic overview of the available evidence is currently missing. Because there is a large diversity in methods and approaches used by the different studies, it was not possible to perform a traditional meta-analysis. Therefore, we used a semiquantitative approach as performed earlier by Ernest et al,[17] allowing us to summarize the evidence of the risk factors systematically and, because the assessors of the risk factors were blinded for both risk factors and included studies, objectively. This method allowed the inclusion of more studies and to summarize the evidence on more risk factors compared with a traditional meta-analysis because we reported every risk factor that had been investigated in the included studies.

For this review, articles were selected through a systematic search and strict selection criteria were applied. One criterion was the exclusion of studies investigating specific subpopulations who are known to have a higher risk for the development of OHT. We excluded studies investigating keratoplasty in patients with iridocorneal endothelial syndrome because approximately 50% to 73% develop glaucoma[18,19] and patients with endotheliitis who are prone to developing an elevated IOP during an active inflammation.[20,21] Furthermore, patients with previous toxic anterior segment syndrome, congenital glaucoma, and eyes with anterior segment alterations or disruptions were excluded from the review.

We also did not include studies investigating patients who underwent keratoplasty before 1990 because the operation techniques of keratoplasty and postoperative corticosteroid treatment, which are both likely to influence the development of OHT, have changed throughout the years. Patients used to be treated with highly potent corticosteroids for a prolonged period of time, which led to a high incidence of corticosteroid-induced OHT. However, with the development of lamellar operating techniques, the duration of exposure and the potency of the used corticosteroids decreased, lowering the incidence of corticosteroid-induced OHT.[22,23]

Within the included studies, the indication for surgery was investigated extensively as a risk factor for the development of OHT. However, various indications were used as a reference, which led to the identification of a great number of indications that had only been investigated in 1 study. Because of the lack of evidence, most indications were judged to be not associated. To obtain meaningful results, we compared all indications with 1 reference category, that is, keratoconus. This had been investigated in most studies, and in contrast to other indications such as Fuchs endothelial dystrophy (FED), it has not been associated with the development of glaucoma.[24] Transplants performed for the treatment of keratoconus are also known to have a high graft survival rate.[25] Because we did not have the complete databases of the studies, it was only possible to recalculate the univariate results.

To our knowledge, Wu et al[8] performed the only meta-analysis investigating risk factors for the development of OHT after PKP. They also defined OHT as an IOP >21 mmHg; however, they did not specify a time point of

IOP measurement. Similar to the study of Wu et al, we found preexisting glaucoma to have one of the highest correlations with an increase in IOP. In addition, we found that solely a higher preoperative IOP was definitely correlated with the development of OHT and glaucoma in the contralateral eye (in cases without glaucoma in the investigated eye) was probably associated. Wu et al did not investigate these risk factors.

In the study of Wu et al and in this study, aphakic and pseudophakic bullous keratopathy were analyzed as 1 category. Wu et al found this to be significantly associated with the development of OHT. In our study, bullous keratopathy is probably associated when compared with keratoconus and when compared with other indications (risk factor bullous keratoplasty yes vs. no). The more robust result found by Wu et al might be because of the fact that they also included studies published before 1990 (starting from 1972). Most older studies did not differentiate between FED and bullous keratopathy. It has been suggested that FED is associated with the development of glaucoma, which might explain why Wu et al found a higher correlation between developing OHT and bullous keratoplasty.[24] Within our study, we could not find a clear association between FED and the development of OHT after keratoplasty. However, only 2 studies investigated FED separately from other corneal dystrophies. Therefore, further investigation for this risk factor is indicated.

Within this review, a preoperative lens status of both aphakia and pseudophakia was possibly associated with an increased risk, which was mainly because of the heterogeneity in the evidence tables. In cases where the preoperative or postoperative lens status was not defined, aphakia was found to be definitely associated. For pseudophakia, there was no difference in the association of the risk and the operative status. Despite the fact that Wu et al did not make a distinction between preoperative and postoperative lens status, they also found aphakia to be significantly associated and pseudophakia to be not significantly associated. Because within this study preoperative and postoperative aphakic lens status seem to differ in the risk for developing OHT, this might suggest that keratoplasty combined with cataract extraction is associated with the development of OHT when compared with keratoplasty only. However, we found that the risk was not increased when comparing pseudophakic lens status preoperatively and postoperatively. A triple procedure, defined as keratoplasty combined with cataract extraction and IOL implantation in our study, was not associated. This finding was confirmed by the study of Wu et al as well. The only combined surgery that we found to be definitely associated was keratoplasty combined with IOL removal or exchange. The risk factor combined surgery in general was judged to be probably associated as well; however, as its name already indicates, it contains a wide range of types of surgery and detailed information is lacking.

Wu et al also described a moderate association for regrafting. This risk factor was judged to be possibly associated in our study as well; however; its evidence table showed a considerable amount of heterogeneity.

Furthermore, Wu et al found trauma to be related with the development of OHT, although they indicated that this result should be interpreted conservatively because more robustness of the analysis was suggested. We could not find an association of trauma with the development of OHT when compared with keratoconus. Herpes simplex keratitis was not found to be significantly associated in neither the study of Wu et al nor our study.

The use of olopatadine 0.1% or cyclosporine (any dosage) before transplantation was found to be probably associated. This might be because of a secondary effect as patients treated with these drugs often have an allergic eye disease for which they possibly use or have used corticosteroids as well. Corticosteroids are known to cause IOP elevation by inducing molecular alterations in the trabecular meshwork which increase the outflow resistance.[26,27] This effect is known for all types of corticosteroids; however, we found that using prednisolone acetate 1% is probably associated with a higher risk for developing OHT compared with dexamethasone 0.1%. This is mainly because of the fact that the penetration of topical concentrations through the cornea is higher for prednisolone, causing higher concentrations in the aqueous humor.[28] Unfortunately, because of a lack of evidence, we could only find a possible association for prednisolone acetate 1% versus loteprednol etabonate 0.5% and prednisolone acetate 1% versus fluorometholone 0.1%, of which previous research showed that loteprednol etabonate and fluorometholone are weaker topical corticosteroids and are therefore associated with a lower risk for the of development of OHT.[29–31] In addition, based on the data of the study by Vajaranant et al[33], a longer duration of exposure has also been shown to increase the risk for the development of OHT.[32,33] This article was included in our study; however, because they did not present a *P* value, OR, or hazard ratio regarding this risk factor, we could not include these data in our manuscript. In addition, the two included studies which investigated this risk defined the duration of exposure not homogenously and reported different results. Therefore, we could not find an association with duration based on the current evidence.

It is well known that corticosteroid-induced elevation of the IOP is the most common cause of OHT after keratoplasty.[9–11] Within this review, studies specifically reporting the results for steroid-induced OHT (marked with an asterisk in the evidence tables) do not seem to deviate from studies who reported OHT in general. Nevertheless, further research to identify risk factors for corticosteroid-induced OHT after keratoplasty is needed.

We tried to find associations between type of surgery and risk for developing OHT; however, because of the diversity of the studies regarding the methodology, presentation of results, and definition of OHT, the results are not uniform and are very difficult to interpret. Therefore, additional research concerning the relation between type of keratoplasty and development of OHT is necessary.

Twenty risk factors showed considerable heterogeneity during the judgment procedure. We checked whether this could be explained by different types of surgery, but we could not find any correlation between heterogeneity in the results and type of surgery. The heterogeneity might be because of different study populations or the use of different definitions

for OHT or glaucoma within the studies. Additional investigation is needed to determine the association of these risk factors.

Some issues at the study level need to be addressed. The performed semiquantitative approach does not provide the possibility to differentiate between study differences. Throughout the included studies, multiple IOP measuring devices were used. Published studies report contradictive results on the use of different IOP measurement devices and the IOP values after keratoplasty.[34–36] However, in most of the included studies, the same IOP measurement devices were likely to be used before and/or after surgery and within the subgroups, minimalizing possible measurement differences within a study.

The definition of glaucoma or OHT also differed throughout the studies. As described in the Methods section, we tried to use similar cutoffs and outcome measures. However, if this was not possible, we accepted the criteria set by the investigators. It would be too difficult or even impossible to recalculate the value of OHT according to other criteria. Despite this, our results are confirmed by the meta-analysis of Wu et al[8] and are in line with the clinical expectations.

In addition, we have to note that we defined OHT as an increase of $>$ 21 mmHg, which is a commonly used cutoff in the included articles. However, if a more strict cutoff for OHT was used, some of the risk factors might not have been found to be highly associated anymore. This might also apply to the six-month outcomes on which we focused. Although we could not find a specific example within the study, the use of another time frame might influence the results as well.

In conclusion, this review provides an overview of all investigated risk factors for the development of OHT after keratoplasty and the level of evidence that is available for each risk factor. Based on the evidence tables, factors with a definitive and probable association with an increased risk for OHT have been established. This can help identify patients at risk and individualize patient care concerning the choice of therapy, postoperative treatment, and follow-up. In addition, we have shown that many risk factors still lack sufficient evidence to determine their association and need further investigation.

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