Co-occurrence of chronic kidney disease and glaucoma

Liu, Wei; Guo, Ruru; Huang, Dandan; Ji, Jian; Gansevoort, Ron T.; Snieder, Harold; Jansonius, Nomdo M.

Published in:
Survey of Ophthalmology

DOI:
10.1016/j.survophthal.2022.09.001

Publication date:
2022

Available online at www.sciencedirect.com
ScienceDirect
journal homepage: www.elsevier.com/locate/survophthal

Review article

Co-occurrence of chronic kidney disease and glaucoma: Epidemiology and etiological mechanisms

Wei Liu, MD[a,b,1], *Ruru Guo, MD*[a,1], *Dandan Huang, MD*[c], *Jian Ji, MD*[a], *Ron T. Gansevoort, MD, PhD*[d], *Harold Snieder, PhD*[e], *Nomdo M. Jansonius, MD, PhD*[b,*]

[a] *Tianjin Key Laboratory of Retinal Functions and Diseases, Tianjin Branch of National Clinical Research Center for Ocular Disease, Eye Institute and School of Optometry, Tianjin Medical University Eye Hospital, Tianjin, China*
[b] *Department of Ophthalmology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands*
[c] *Department of Ophthalmology, Taihe Hospital, Hubei University of Medicine, Shiyan, Hubei, China*
[d] *Division of Nephrology, Department of Internal Medicine, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands*
[e] *Department of Epidemiology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands*

ARTICLE INFO

Article history:
Received 6 March 2022
Revised 26 August 2022
Accepted 2 September 2022
Available online xxx

Keywords:
Chronic kidney disease
Estimated glomerular filtration rate
Glaucoma
Primary open-angle glaucoma
Uric acid

ABSTRACT

As the histology, physiology, and pathophysiology of eyes and kidneys show substantial overlap, it has been suggested that eye and kidney diseases, such as glaucoma and chronic kidney disease (CKD), may be closely interlinked. We review the relationship between CKD and various subtypes of glaucoma, including primary open-angle glaucoma, primary angle-closure glaucoma, normal tension glaucoma, pseudoexfoliation syndrome, and several glaucoma endophenotypes. We also discuss the underlying pathogenic mechanisms and common risk factors for CKD and glaucoma, including atherosclerosis, the renin-angiotensin system, genes and genetic polymorphisms, vitamin D deficiency, and erythropoietin. The prevalence of glaucoma appears elevated in CKD patients, and *vice versa*, and the literature points to many intriguing associations; however, the associations are not always confirmed, and sometimes apparently opposite observations are reported. Glaucoma and CKD are complex diseases, and their mutual influence is only partially understood.

* Corresponding author: Nomdo M. Jansonius, MD, PhD, Department of Ophthalmology, University Medical Center Groningen, P.O.Box 30.001, 9700 RB Groningen, The Netherlands.
E-mail address: n.m.jansonius@umcg.nl (N.M. Jansonius).
[1] Contributed equally.

0039-6257/$ – see front matter © 2022 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/)
https://doi.org/10.1016/j.survophthal.2022.09.001

Please cite this article as: Wei Liu, Ruru Guo, Dandan Huang et al., Co-occurrence of chronic kidney disease and glaucoma: epidemiology and etiological mechanisms, Survey of Ophthalmology, https://doi.org/10.1016/j.survophthal.2022.09.001

1. Introduction

Chronic kidney disease (CKD) is defined as a glomerular filtration rate (GFR) of less than 60 mL/min per 1.73 m^2 of body surface area or a urinary albumin excretion greater than 30 mg/g that exists for longer than 3 months and that has implications for health.[108] CKD is a serious worldwide public health problem that affects many people and is associated with adverse cardiovascular and kidney outcomes as well as premature death.[32,56,59,78,123,126,193] The prevalence of CKD increases rapidly with aging of the population in both Western and Asian groups. In the United States, the CKD prevalence in adults 30 years of age or older is estimated to be 14.4% in 2020 and 16.7% in 2030.[72] In Singapore, the age- and sex-standardized prevalence of CKD was reported to be 12.8% (11.4%, 18.6%, and 17.6% in Chinese, Malays, and Indians, respectively).[148] In China, the overall prevalence of CKD was found to be 11.4% in adults over 60 years of age.[81] Also other organs than the cardiovascular system experience deleterious health effects from the presence of CKD, such as the brain.[115]

Glaucoma is the worldwide leading cause of irreversible blindness. The global prevalence of glaucoma for the age range 40-80 years is between 3 and 4%, which will result in approximately 110–120 million glaucoma patients in 2040.[170] Glaucoma is characterized by retinal ganglion cell (RGC) degeneration and, related to that, optic nerve head cupping.[184] Glaucoma is related to an increase in intraocular pressure (IOP), but its etiology and pathophysiology are poorly understood, and other factors play a role as well. Examples of other factors are vascular deficits,[1,34] genetic factors,[80,188] increased trans-lamina cribrosa pressure,[82] oxidative stress,[122,150] *Helicobacter pylori* infections,[151] and metabolic diseases, including CKD.

As there is substantial overlap in the histology, physiology, and pathophysiology of eyes and kidneys, it has been suggested that eye and kidney diseases may be closely interlinked.[190] For example, the glomerulus and choroid show structurally similar extensive vascular networks, and similar mechanisms are involved in the development of CKD and many eye diseases, such as oxidative stress, inflammation, atherosclerosis, endothelial dysfunction, and vascular remodeling.[131] Associations were reported between CKD and many eye disorders, including vision impairment,[131,189,204] diabetic retinopathy,[20,22,36,43,48,55,63,117,125,138,149,191,201] age-related macular degeneration,[23,24,27,116,128,183] cataract,[119,189] retinal vein occlusion,[4,37,96,157] ocular surface disease,[18,95,133,168] and–last but not least–glaucoma.

We review the relationship of CKD with the various subtypes of glaucoma, including primary open-angle glaucoma (POAG), primary angle-closure glaucoma (PACG), normal tension glaucoma (NTG), and pseudoexfoliation syndrome (PEX), and several glaucoma endophenotypes, including IOP, disc hemorrhage, and retinal nerve fiber layer defects. We also discuss the possible underlying mechanisms and common risk factors.

2. Relationships between chronic kidney disease and glaucoma

Findings on the relationship between CKD and glaucoma are summarized in Table 1 and discussed in detail below.

2.1. *Chronic kidney disease and primary open angle glaucoma*

2.1.1. *Population-based studies*

Several population-based, cross-sectional studies explored the relationship between CKD and POAG. In the 2010–2011 Korea National Health and Nutrition Examination Survey (KNHANES),[159] there were 5,971 participants of at least 40 years of age who were investigated for the relationship between kidney function and POAG. KHANES showed that a low estimated GFR (eGFR) level (<45 mL/min per 1.73 m^2) was independently (i.e., after adjusting for age, sex, low serum high density lipoprotein cholesterol, high blood glucose, high blood pressure, and IOP) associated with POAG (odds ratio [OR] 2.88, 95% confidence interval [CI] 1.44–5.76). CKD (defined as eGFR <60 mL/min per 1.73 m^2) was also associated with POAG, but this association was no longer significant after controlling for the confounding variables listed above. Other studies found no independent association between CKD and POAG. For instance, in the Beijing Eye Study, which included 1,598 Northern Chinese individuals, a higher prevalence of CKD was not associated with glaucoma.[84] In the Singapore Malay Eye Study[130] the distribution of glaucoma by CKD status was not significant, and there was no association between CKD and glaucoma. In another study from Singapore,[189] although the prevalence of glaucoma was significantly higher in persons with CKD (5.8%) than those without (3.2%), there was no significant association between CKD and glaucoma after adjusting for age, gender, ethnicity, education status, current smoking, alcohol consumption, diabetes status, systolic blood pressure, body mass index, triglyceride levels, low density lipoprotein cholesterol, and cardiovascular disease (OR 0.81, 95% CI 0.6–1.1, P=0.18). In a large consortium of multiple Asian population-based studies,[171] the authors pooled 28,925 participants from nine population-based studies (from China, India, Korea, Russia, and Singapore) and examined the association between kidney function and POAG. There was no significant association between eGFR and POAG after adjusting for age, gender, study group, hypertension, diabetes, hyperlipidemia, body mass index, smoking status, and IOP. Presence of CKD had no significant association with POAG either. There was a weakly significant association between lower eGFR and POAG in the subgroup of East Asians (combined Korean and Chinese individuals; OR 1.09 (per 10 mL/min/1.73 m^2 decrease in eGFR), 95% CI 1.00–1.18, P=0.048). Differences in study population, study design, medical infrastructure, risk profile and prevalence of CKD, management of diseases, as well as survival bias may explain the discrepancies between the different studies. Notably, the only study that showed a significant association between glaucoma and kidney function was the only study conducted in East Asians and found the significance

Please cite this article as: Wei Liu, Ruru Guo, Dandan Huang et al., Co-occurrence of chronic kidney disease and glaucoma: epidemiology and etiological mechanisms, Survey of Ophthalmology, https://doi.org/10.1016/j.survophthal.2022.09.001

Table 1 – Summary of findings on the relationship between CKD and glaucoma.

Author (year)	Study Design	Ethnicity	Sample Size	Definition of CKD	Calculation of eGFR	Main Findings
Population-based studies						
Nongpiur (2010)	Population-based, cross-sectional	Malays	3,280	Defined as an eGFR value <60 mL/min/1.73 m^2 or presence of micro/macroalbuminuria	Based on MDRD equation	• CKD was associated with higher IOP. • No association between CKD and glaucoma.
Wong (2016)	Population-based, cross-sectional	Chinese, Malays and Indians	9,434	Defined as an eGFR value <60 mL/min/1.73 m^{22}	Based on CKD-EPI equation	• Prevalence of glaucoma was significantly higher in persons with CKD (5.8%) than those without (3.2%). • No significant association between CKD and glaucoma.
Shim (2016)	Population-based, cross-sectional	Korean	5,971	Defined as an eGFR value <60 mL/min/1.73 m^2	Based on Cockcroft-Gault formula	• CKD was not associated with POAG after controlling for confounding variables. • Lower eGFR (<45 mL/min/1.73m^2) was significantly associated with POAG. • No association between proteinuria and POAG.
Jonas (2017)	Population-based, cross-sectional	Chinese	1,598	Defined as an eGFR value <60 mL/min/1.73 m^2	Based on MDRD and CKD-EPI equation equation	• No association between CKD and glaucoma.
Tham (2020)	pooled-analysis of multiple population-based studies	Chinese, Indians, Korean, Russian and Singaporean	28,925	Defined as an eGFR value <60 mL/min/1.73 m^2	Based on CKD-EPI equation	• Association between CKD and POAG was only present in East Asians but not in the overall Asian population.
POAG in CKD patients						
Gao (2011)	Cross-sectional	Chinese	9,644	Defined as an eGFR value <60 mL/min/1.73 m^2 and/or proteinuria.	Based on CKD-EPI equation	• CKD patients had higher prevalence of glaucoma suspects (defined as cup/disc ratio ≥0.6) as compared to patients without CKD (3.1% vs 1.8%).
Wang (2012)	Cross-sectional	Chinese	36,596 (9,149 CKD cases; 27,447 controls)	Based on ICD-9-CM codes	Not mentioned	• CKD patients had higher prevalence of glaucoma (7.56%) as compared to patients without CKD (5.70%). • Presence of CKD was associated with glaucoma.
Djordjevic-Jocic (2014)	Cross-sectional	Serbian	328 CKD patients	Defined as kidney damage or an eGFR value <60 mL/min/1.73m^2 for ≥3 months	Based on MDRD equation	• The prevalence of glaucoma was 10.1%, which is much higher than that in general population. • CKD stage was correlated with the severity of glaucoma.
Zhu (2020)	Cross-sectional	American	5,518	Defined as an eGFR value <60 mL/min/1.73 m^2	Based on CKD-EPI equation	• Participants with CKD had a significantly higher prevalence of glaucoma (5.2%) than those without (1.7%). • No association between CKD and glaucoma after multivariable adjustments.

(*continued on next page*)

Please cite this article as: Wei Liu, Ruru Guo, Dandan Huang et al., Co-occurrence of chronic kidney disease and glaucoma: epidemiology and etiological mechanisms, Survey of Ophthalmology, https://doi.org/10.1016/j.survophthal.2022.09.001

Table 1 (*continued*)

Author (year)	Study Design	Ethnicity	Sample Size	Definition of CKD	Calculation of eGFR	Main Findings
Cho (2021)	nationwide, population-based, retrospective, longitudinal cohort	Korean	3,640 CKD patients and 17,971 controls	Based on Korean Classification of Disease	Not mentioned	• Glaucoma developed in 4.3% in CKD group and 2.8% in control group. • CKD increased the risk of glaucoma development.
Ro (2022)	nationwide, population-based, retrospective, longitudinal cohort	Korean	4,260 CKD patients and 21,300 controls	Based on Korean Classification of Disease	Not mentioned	• The risk of developing OAG was significantly higher in the CKD group. •The risk of OAG increased with the severity of CKD.
CKD in POAG patients						
Chou (2018)	nationwide, observational, propensity score matched cohort	Chinese	15,185 POAG patients and 15,185 controls	Based on ICD-9-CM codes	Not mentioned	• Patients with POAG had higher risks of acute renal failure and end-stage renal disease than those without ocular disorders.
Park (2019)	nationwide, population-based, longitudinal, retrospective cohort	Korean	4,78,303	Based on Korean Classification of Disease	Not mentioned	• POAG was associated with an increased risk of CKD development.

CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; IOP = intraocular pressure; POAG = primary open angle glaucoma.

only in a subgroup defined using a more strict criterion (eGFR < 45 mL/min/1.73m^2; Table 1).[159] Some studies adjusted for IOP (aiming for an IOP-independent effect of CKD on POAG), whereas others did not, but this difference could not explain the apparent inconsistent observations.

2.1.2. *Primary open-angle glaucoma in chronic kidney disease patients*

Although the relationship between CKD and POAG appears to be inconsistent in population-based studies, there is some evidence that the prevalence of glaucoma is higher in patients with known CKD. In a large-scale study on ophthalmic disorders in a population with CKD from Taiwan,[180] patients with CKD had a significantly higher prevalence of glaucoma (7.6%) compared to patients without CKD (5.7%; P<0.001). Also, after adjusting for potential confounders (monthly income, geographic region, level of urbanization of the patients' community, and hypertension), patients with CKD had higher odds of glaucoma than patients without CKD (OR 1.35, 95% CI 1.23–1.48). The authors did not subclassify POAG and PACG in this study. In a cohort of 328 CKD patients from southeast Serbia,[45] the prevalence of glaucoma (defined according to the ISGEO criteria as suggested by Foster and coworkers[52]) was 10.1%, which is much higher than the prevalence in the general population of similar age. In multivariable regression analysis, eGFR was significantly related to visual field mean deviation (MD), visual field pattern standard deviation, and cup-to-disc ratio, indicating that CKD stage was related to glaucoma severity. In a cross-sectional study from China,[55] participants with CKD had a higher prevalence of glaucoma suspected optic discs (defined as a cup-to-disc ratio of 0.6 or higher) than participants without CKD (3.1% versus 1.8%; P=0.004). In the National Health and Nutrition Examination Survey 2005–2008,[204] participants with CKD had a significantly higher prevalence of glaucoma (5.2%) than those without (1.7%). This difference, however, disappeared after adjustment for age, sex, race/ethnicity, education level, income level, and marital status. In this study, glaucoma classification was based on fundus images. Cho and coworkers studied the risk of glaucoma development in CKD in a retrospective cohort.[26] They identified 3,640 newly diagnosed CKD patients and 17,971 controls between January, 2001, and December, 2007, from the Korean National Health Insurance Service dataset. Newly diagnosed glaucoma and CKD were included on the basis of the Korean Classification of Disease codes. After 11 years of follow-up, glaucoma had developed more frequently in subjects with newly diagnosed CKD (4.3%) than in those without CKD (2.8%; P<0.0001). The hazard ratio (HR) was 1.63 (95% CI 1.34–1.98) after adjusting for age, sex, comorbidities (hypertension, diabetes mellitus, hyperlipidemia and stroke), residence, household income, and the year of enrollment. Because of the use of disease codes, glaucoma was not subclassified according to subtypes in this study. Recently, Ro and coworkers investigated the risk of developing OAG after CKD diagnosis using a representative sample of approximately 1.1 million South Koreans from the National Health Insurance Service-National Sample Cohort 2002–2015.[145] They identified 4,260 newly diagnosed CKD patients and 21,300 non-CKD controls. During a 12-year follow-up, the risk of developing OAG was significantly higher in the CKD group than in the control group (HR 1.55, 95% CI 1.36–1.75, P<0.001, adjusted for age, sex, income, residential area, diabetes mellitus, hypertension, hyperlipidemia, and ischemic stroke). They also found that the risk of OAG increased with the severity of CKD

(CKD stage 1–3: HR 1.28, 95% CI 1.08–1.52, P=0.005; CKD stage 4–5: HR 1.86, 95% CI 1.59–2.18, P<0.001).

2.1.3. *Chronic kidney disease in primary open-angle glaucoma patients*

In a cohort including 478,303 beneficiaries in the 2002–2013 Korean National Health Insurance database,[137] POAG was associated with an increased risk of CKD development (HR 7.63, 95% CI 5.89–9.87). This result is consistent with that of another nationwide, observational cohort study[29] that showed a higher risk of acute kidney injury (HR 2.58, 95% CI 1.88–3.55, P<0.001) and end-stage kidney failure (HR 4.84, 95% CI 3.02–7.77, P<0.001) in new POAG patients compared to patients without ocular disorders, after adjustment for age, sex, index date, diabetes, hypertension, hyperlipidemia, modified Charlson Comorbidity Index score, and baseline use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers, nonselective and selective β-blockers, calcium-channel blockers, loop diuretics, sulfonylurea, biguanides, α-glucosidase inhibitors, thiazolidinedione, meglitinide, insulin, aminoglycosides, statins, and antiplatelet drugs.

2.1.4. *Uric acid and primary open-angle glaucoma*

Uric acid, the end product of purine metabolism, is excreted predominantly by the proximal tubules in the kidney. Uric acid plays an important role in the pathophysiology of kidney disease, is linked to the development of CKD, and can be considered a marker of CKD.[50,58] A few researchers explored the association between serum uric acid and POAG. Elisaf and coworkers found that serum uric acid levels were significantly higher in 49 POAG patients without a known history of diabetes compared to 72 age- and sex-matched individuals without glaucoma (6.2±1.9 mg/dL versus 5.0±1.2 mg/dL; P=0.006)[49]; however, in a prospective, cross-sectional case-control study, including 163 POAG patients and 103 controls, both the serum uric acid level and the uric acid/creatinine ratio were significantly lower in the POAG patients than in the control group.[113] Stratification revealed a negative association between uric acid levels and POAG severity in male patients. The intriguing role of uric acid will be discussed below (Section 2.5), after having reviewed it also for primary angle-closure glaucoma (2.2), normal tension glaucoma (2.3), and pseudoexfoliation syndrome (2.4).

2.1.5. *Albuminuria and primary open-angle glaucoma*

Albuminuria is the other parameter besides eGFR that defines chronic kidney disease.[108,178] In a cross-sectional study of 3009 Chinese adults aged 40–80 years, a higher urinary albumin-to-creatinine ratio (UACR) was independently associated with POAG (OR 1.04 per 50 mg/g increase, 95% CI 1.01–1.07, P=0.003) after adjusting for age, sex, IOP, diabetes mellitus, hyperlipidemia, hypertension, antihypertensive medication, history of cardiovascular disease, current smoking status, alcohol intake, body mass index, and eGFR.[118] After stratification according to albuminuria level, macroalbuminuria was independently associated with POAG whereas microalbuminuria was not. In a cross-sectional study of 4186 nondiabetic participants aged 19 years or older from the 2011–2012 KNHANES,[91] albuminuria, even low-grade, was significantly associated with POAG (based on the ISGEO criteria), and the subjects in the upper tertile of UACR showed a higher prevalence of POAG than those in the lower UACR tertile after adjusting for demographic factors (age, sex, education level, ever-smoker status), laboratory parameters (serum triglyceride level, serum high-density lipoprotein cholesterol level), mean arterial pressure, kidney function (eGFR), and IOP (OR 1.96, 95% CI 1.07–3.60, P=0.03). In another study from the 2010–2011 KNHANES with participants aged 40 years or older, however,[159] proteinuria (defined as a score greater than +1 on a semiquantitative scale measured by a dipstick test) was not associated with POAG. This may be explained by the different study participants' demographics (especially age) and different measurement methods, with qualitative dipstick measurement of albuminuria being less sensitive and less precise when compared to actual quantitative albuminuria measurement by nephelometry.

2.2. *Chronic kidney disease and primary angle-closure glaucoma*

We identified no studies concerning the relationship between CKD and PACG and only 2 studies concerning the relationship between uric acid and PACG, from the same research group from China. Li and coworkers included 886 PACG patients and 994 controls in a retrospective case-control study.[114] The level of uric acid was significantly lower in PACG patients (0.286±0.082 mmol/L) compared to controls (0.295±0.085 mmol/L; P=0.025). The level of uric acid was lowest in the severe PACG group followed by the moderate and mild PACG group, indicating a dose-response effect, strengthening a possible role of uric acid in the pathogenesis of PACG. In their prospective cohort study,[112] they investigated the relationship between pretreatment serum uric acid levels and the progression of newly diagnosed PACG. They enrolled 64 newly diagnosed PACG patients and followed them for a mean period of 13 months; progression was determined by two criteria: (1) a clinical diagnosis of medically uncontrollable IOP and (2) a continued decline of the visual field. They found that the baseline uric acid values were significantly higher in nonprogressing subjects than in progressing subjects. In their multivariable model, a decreased baseline serum uric acid level was associated with an increased risk for progressing PACG, both in male (HR 6.09, 95% CI 1.16–31.86, P=0.03) and female (HR 3.57, 95% CI 1.13–11.24, P=0.03) subjects, again suggesting that a high serum uric acid level may have a protective role against PACG and could slow disease progression (see Section 2.5 for discussion).

2.3. *Chronic kidney disease and normal tension glaucoma*

We did not identify studies demonstrating an association between CKD and NTG. Regarding uric acid, Yuki et al enrolled 47 NTG patients and 44 controls and compared, cross sectionally, the uric acid levels between the two groups.[199] The level of uric acid was higher in NTG patients than in controls (5.8±1.5 mg/dL vs 4.9 ± 1.4 mg/dL, P=0.01).

Please cite this article as: Wei Liu, Ruru Guo, Dandan Huang et al., Co-occurrence of chronic kidney disease and glaucoma: epidemiology and etiological mechanisms, Survey of Ophthalmology, https://doi.org/10.1016/j.survophthal.2022.09.001

Table 2 – Serum uric acid levels in different types of glaucoma.

Author (year)	Ethnicity	Participants	Case Group			Control Group			P Value
			n	Age (years)	Serum UA level (mg/dL)	n	Age (years)	Serum UA level (mg/dL)	
Elisaf (2001)	Greek	POAG vs controls †	49	65.0±9.0	6.2±1.9	72	63.0±8.0	5.0±1.2	0.006
Yuki (2010)	Japanese	NTG vs controls*	47	59.5±10.2	5.8±1.5	44	62.7±14.8	4.9±1.4	0.01
Simavlı (2015)	Turkish	PEX vs controls	31	73.6±14.1	5.3±1.2§	34	70.1±12.7	5.1±1.5§	0.56
Li (2017)	Chinese	PACG vs patients without glaucoma*	886	63.2±10.7	4.8±1.4	994	63.3±10.1	5.0±1.4	0.025
Li (2019)	Chinese	POAG vs controls†	163	50.0±17.2	5.4±1.4	103	51.4±16.1	6.1±0.9	<0.001
Li (2019)	Chinese	progressive vs nonprogressive PACG‡	32	59.8±15.2	4.3±1.2	32	58.1±15.3	5.3±1.2	0.002

UA = uric acid; POAG = primary open angle glaucoma; PACG = primary angle closure glaucoma; NTG = normal tension glaucoma; PEX = pseudoexfoliation syndrome.

* groups were reported to be similar in age and gender.

† groups were reported to be similar in age, gender, BMI, and blood pressure.

‡ groups were reported to be similar in age, gender, BMI, blood pressure, and several ocular parameters (intraocular pressure, vertical cup-to-disc ratio, central corneal thickness, anterior chamber depth, axial length, and mean deviation of the visual field).

§ the authors wrote mg/mL where values suggest mg/dL.

2.4. *Chronic kidney disease and pseudoexfoliation syndrome*

Up to now, there is no evidence that CKD is related to PEX. In an age-matched case-control study,[129] the prevalence of PEX was similar in CKD patients who did not need dialysis (4.7%; n=106), dialysis patients (6.9%; n=101), and controls (5.9%; n=117). In another cross-sectional study,[200] the prevalence of CKD was higher in controls (11.7%, n=94) than in PEX (3.5%, n=86, P=0.05) and POAG (3.3%, n=91, P=0.049), but this difference could be attributed to a higher prevalence of diabetes mellitus in the control group; the significance disappeared after adjusting for diabetes mellitus and age, using multivariable analysis. In a prospective, case-control study,[62] the biochemical (serum creatinine, urea, blood urea nitrogen, creatinine clearance, and microalbumin) and ultrasonographic (kidney volume, resistive index and pulsatility index) parameters indicative for CKD did not differ between PEX patients (n=49) and controls (n=42). In a population-based cross-sectional study assessing the prevalence of PEX and its associations in a Russian population (n=5,451), there was no association between PEX and CKD.[13] Theoretically, uric acid level could be elevated in PEX, because xanthine oxidase, which produces uric acid, was reported to be increased in PEX;[194] however, in a case-control study including 31 PEX patients and 34 controls, serum uric acid levels were similar in both groups.[161] The authors argued that an increased oxidative stress in PEX might cause a decrease in uric acid and lead to similar uric acid levels between PEX patients and controls. Of note, all the studies mentioned above referred to PEX rather than PEX glaucoma (glaucoma secondary to PEX). We did not identify any study that addressed the relationship between CKD and PEX glaucoma.

2.5. *Uric acid in the various glaucoma subtypes*

Table 2 summarizes the identified studies on serum uric acid levels in different subtypes of glaucoma. Although 5 of 6 studies showed a significant outcome, there was no consistent direction of the effect, not even within the different subtypes of glaucoma. Possible explanations for this apparent inconsistency are differences in ethnicity (All studies in which uric acid was reported to be protective were from China) or differences in unknown confounding factors. It could also be the case that uric acid is involved in two, opposite, mechanisms. The first mechanism is uric acid being a marker of CKD, a presumed harmful process. The second mechanism is related to the observation that low uric acid serum levels have been associated with neurodegenerative disease, possibly via the fact that uric acid has a strong antioxidant capacity.[14] These opposite mechanisms could lead to variable outcomes in seemingly similar studies, since glaucoma pathophysiology has both vascular and neurodegenerative components.

2.6. *Chronic kidney disease and glaucoma endophenotypes*

2.6.1. *Chronic kidney disease and intraocular pressure*

Although many factors play a role in the pathogenesis of glaucoma, IOP is the most important one. In the Singapore Malay Eye Study (n=3,280),[130] CKD was associated with higher IOP (P<0.0001), independent of age, diabetes, corneal thickness, and glaucoma status. The difference in IOP between persons with and without CKD, however, was small (0.3 mm Hg). Possible mechanisms by which CKD might be associated with higher IOP include a breakdown in the homeostasis of body fluids leading to fluid overload, accumulation of toxic metabolites, and impaired aqueous outflow through the trabecular meshwork. In the Ural Eye and Medical Study performed in a Russian population (n=5,899),[12] higher IOP was associated with higher blood urea concentration. In 2011 KNHANES (n=402),[28] higher IOP was associated with higher urinary albumin excretion (non-glaucomatous type 2 diabetes population without impaired kidney function). On the other hand, in the Asian Eye Epidemiology Consortium (n=28,925) and the 2010–2011 KNHANES (n=5,971),[171,159] IOP was not associated

with eGFR. The most obvious difference between the above-mentioned studies was the kidney function variable that was associated with IOP (Singapore Malay Eye Study: CKD; Ural Eye and Medical Study: blood urea concentration; 2011 KNHANES: urinary albumin excretion; Asian Eye Epidemiology Consortium and the 2010–2011 KNHANES: eGFR as a continuous variable), and this might explain the divergent findings.

Systemic medications commonly used in CKD patients may also influence IOP; however, the influence of these medications on IOP is not unambiguous. In the *posthoc* analysis of the Singapore Epidemiology of Eye Disease study (8,063 participants), systemic β-blocker use was independently associated with an IOP reduction of 0.45 mm Hg (95% CI 0.25–0.65 mm Hg reduction, P<0.001) whereas a higher IOP was found in participants using ACE inhibitors (0.33 mm Hg higher, 95% CI 0.08–0.57 mm Hg, P=0.008), angiotensin receptor blockers (0.40 mm Hg higher, 0.05–0.75 mm Hg, P=0.02), statins (0.21 mm Hg higher, 0.02–0.40 mm Hg, P=0.03), and sulfonylureas (0.34 mm Hg higher, 0.05–0.63 mm Hg, P=0.02), after adjustment for concurrent use of other medications and age, sex, body mass index, ethnicity, systolic blood pressure, low-density lipoprotein cholesterol levels, and diabetes.[71] In the Gutenberg Health Study (13,527 participants), however, none of the cardiovascular medications (selective or non-selective β-blockers, ACE inhibitors, angiotensin receptor blockers, renin-angiotensin blockers, calcium channel blockers, diuretics, nitrates, other antihypertensives, peripheral vasodilators, aspirin, and statins) was associated with IOP after adjustment for age, sex, body mass index, systolic blood pressure, and central corneal thickness.[73]

2.6.2. *Chronic kidney disease and disc hemorrhage*

Disc hemorrhage (DH) is a specific sign of and risk factor for glaucoma and glaucoma progression.[11,17] The prevalence of DH is higher in glaucoma or ocular hypertension patients (from 2% to 33.4%) than in the general population (from 0% to 1.4%).[44,46,67] In a cross-sectional study including a large number of subjects (n=149,719), kidney function was significantly associated with the presence of DH.[105] Subjects with a higher serum creatinine level showed a higher prevalence of DH (P<0.003), and subjects in the lowest eGFR quartile showed a significantly higher risk of having a DH compared to subjects in the highest quartile (OR 1.96, 95%CI 1.22–3.14) after adjusting for age, sex, hypertension, diabetes, and hyperlipidemia. The authors proposed that a common angiopathic mechanism might contribute to kidney dysfunction and DH because the glomeruli of the kidney and retina of the eye have the most abundant microvascular networks in the body, and a decreased kidney function might stimulate the development of DH through vascular dysregulation, vascular endothelial dysfunction, or autonomic dysfunction.

2.6.3. *Chronic kidney disease and retinal nerve fiber layer thickness*

A reduced retinal nerve fiber layer (RNFL) thickness is an indication of RGC loss and can thus be considered a clinical sign of (early) glaucoma.[83,163] Four case-control studies addressed the association between RNFL thickness and CKD. In the first study, the mean RNFL thickness in 33 patients with chronic kidney failure requiring hemodialysis or peritoneal dialysis was found to be significantly decreased compared to the RNFL thickness in 20 controls (87.1 versus 106.3 μm; P<0.01).[42] This was confirmed in a second study, in which specifically the temporal superior RNFL was found to be significantly thinner in end-stage kidney failure patients undergoing hemodialysis (n=32) compared to controls (n=38).[86] In this study subjects with preexisting glaucoma, macular degeneration, diabetic retinopathy or uncontrolled hypertension, and patients who had previously undergone laser coagulation were excluded, thus highlighting the direct association between CKD and RNFL. It should be noted that hemodialysis has been associated with an increase in IOP, and this increase might explain the observed thinning of the RNFL.[21] The reported increase in IOP, however, was associated exclusively with acetate dialysate hemodialysis, which was mainly used before 1986 and entirely replaced by bicarbonate hemodialysis in 2005.[21] This suggests that the RNFL thinning reported in the two studies cited above (published in 2009 and 2020) is an IOP-independent finding. Also in a third study, including 171 CKD patients and 40 controls, the RNFL of CKD patients was significantly thinner than that of controls (94.1 versus 99.9 μm, P<0.001).[192] Finally, in a fourth study, no difference in RNFL thickness was found in CKD patients (n=50) compared with both healthy (n=50) and hypertensive subjects (n=50)[10]; the authors suggested that RNFL thinning could be a feature of late CKD.

Potentially, the pattern of RNFL loss may differ between glaucoma and CKD.[25,85] If so, this difference could be related to the fact that RNFL thinning in CKD patients seems primarily related to IOP-independent factors and secondarily, to an increase in IOP (see 2.6.1). In glaucoma the opposite is the case. An IOP-independent factor that could link CKD and RNFL thinning is retinal ischemia, which is common in CKD and its associated systemic disorders like diabetes mellitus, hypertension, atherosclerosis, hyperlipidemia, etc, and may cause RNFL thinning.[106,107,165] Other possible factors are increased inflammation and oxidative stress, dysregulation of the renin-angiotensin system, and presence of uremic toxins.[42,192]

3. Possible underlying mechanisms

CKD and glaucoma share vascular, genetic, and hormonal pathways. The major mechanisms that contribute to CKD include atherosclerosis, activation of the renin-angiotensin system, genetic polymorphisms, and vitamin D and erythropoietin deficiency, most of which are also implicated in glaucoma.[190] These mechanisms are summarized in Fig. 1 and will be discussed in detail in the following paragraphs.

3.1. *Atherosclerosis*

The association between CKD and accelerated atherosclerosis was described more than 40 years ago, and it has been suggested recently that even in early CKD stages the risk of atherosclerosis is increased.[176] CKD accelerates atherosclerosis via various mechanisms, among which an increase in serum homocysteine,[146] an increase in lipoprotein concentrations,[16] a decrease in transforming growth factor beta 1 levels,[166] and an increase in oxidative stress. Atherosclerosis

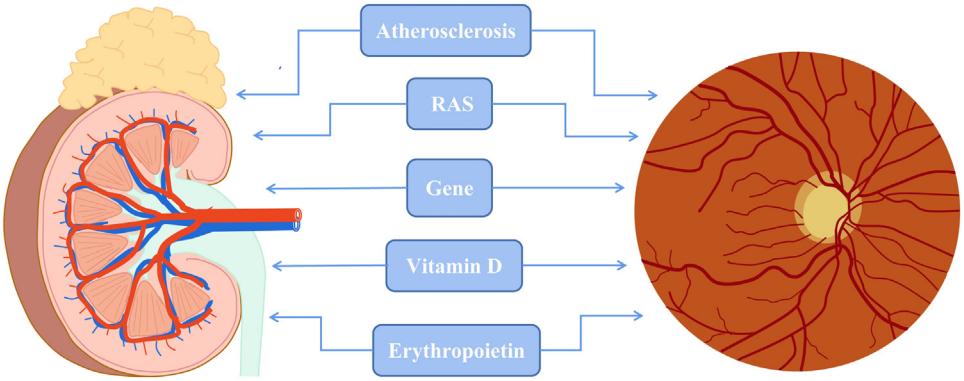

Fig. 1 – Possible pathogenic mechanisms and common risk factors for CKD and glaucoma.

plays a major role in many age-related eye diseases, including diseases of the optic nerve.[66] Population-based data on the relationship between atherosclerosis and glaucoma are scarce and inconclusive.[40] Shim and coworkers performed a case-control study in a clinical setting and reported that increased systemic arterial stiffness, which is related to atherosclerosis, was an independent risk factor for glaucoma.[158] Arteriosclerosis and increased systemic arterial stiffness may result in blood vessels with small lumens, increased peripheral vessels resistance, endothelial dysfunction, decreased oxygenation, and eventually an alteration in circulatory hemodynamics and disruption of ocular autoregulation. The impaired autoregulation hampers adequate perfusion, thus relating glaucoma development or aggravation to atherosclerosis. When arterial hypertension is taken as a proxy for atherosclerosis, these circulatory effects have been shown, among others, with mathematical models combined with laser speckle flowgraphy.[134,135] Likewise, the relationship between arterial hypertension and glaucoma has been shown in many studies,[6,147,162] as is the case for the relationship between arterial hypertension and CKD[47,64]; however, the relationship between arterial blood pressure and glaucoma is complex. For example, not only arterial hypertension, but also low blood pressure have been reported as a potential risk factor for the development and progression of glaucoma.[79,90,109,172] Low blood pressure has been associated with thinning of inner retinal layers, mediated by a decrease in ocular blood flow, in apparently healthy subjects from the general population with blood pressure values in the lower tail of the population-based blood pressure distribution,[134,135] supporting a role for low blood pressure in glaucoma. To the best of our knowledge, CKD has not been associated with low blood pressure.

3.2. *Renin-angiotensin system*

The renin-angiotensin system (RAS), known for over a century, is a hormone system that regulates blood pressure and extracellular volume homeostasis. Dozens of angiotensin peptides and peptidases and at least six receptors are involved in the RAS, such as angiotensinogen (AGT), renin, ACE, and the angiotensin II (Ang II) type 1 and type 2 receptors (AT1 and AT2).[203] The RAS cascade mainly consists of two axes: (1) the recently described angiotensin (1–7), angiotensin converting enzyme 2, and Mas receptor axis (ACE2-Ang(1–7)-MasR), and (2) the classical angiotensin II, angiotensin converting enzyme 1, and angiotensin II type 1 receptor axis (ACE1-AngII-AT1R).[74] Apart from the well-known systemic RAS, occurrence of a local RAS has been documented in multiple tissues, including the kidney. The intrarenal activation of RAS plays a pivotal role in the pathogenesis and progression of CKD through blood pressure-dependent and independent mechanisms and pathways, including (pro)renin receptor, Wnt/β-catenin signaling, the PGE_2/EP_4 pathway, Klotho, vitamin D receptor, liver X receptor, and others.[30,196]

A local RAS has also been found in the eye and implicated in the pathogenesis of glaucoma.[31,70,76,175] RAS components in cultured human nonpigmented ciliary epithelial cells were reported to be responsible for aqueous humor formation and secretion,[38] and Ang II was found to diminish trabecular aqueous outflow by inducing cellular proliferation and increased deposition of collagen in the trabecular meshwork.[155] This indicates that the ocular RAS may be implicated in the formation and drainage of aqueous humor and regulation of IOP. ACE inhibitors have been shown to halt progression of visual field loss in glaucoma patients,[69] decrease POAG suspect conversion,[136] and lowering IOP both in patients and animal models,[35,154] suggesting a role of the ACE1-AngII-AT1R axis in the pathogenesis of glaucomatous optic neuropathy. These inhibitors can increase the uveoscleral outflow by decreasing Ang II levels in aqueous humor[77] and slow down aqueous humor formation by lowering blood flow in the ciliary body.[142] ACE inhibitors also act through the kallikrein-kinin system. By preventing the breakdown of bradykinin, ACE inhibitors can promote prostaglandin synthesis and then increase uveoscleral outflow of aqueous humor.[120] Furthermore, the Mas receptor and ACE2 are also expressed in the ocular tissues, which may also regulate the ocular physiology through the ACE2-Ang(1-7)-MasR axis.[31] Diminazene aceturate, an ACE2 activator, showed beneficial effects on glaucoma by neuroprotection and increasing aqueous humor drainage, indicating ACE2 is a potential therapeutic target in glaucoma treatment.[53]

3.3. *Genetic polymorphisms*

The Klotho gene was first identified as an antisenescence gene; a defective Klotho gene results in aging phenotypes

such as hypokinesis, arteriosclerosis, and short lifespan in mice.[101] Basic and clinical studies have indicated that Klotho, an enzyme encoded by the Klotho gene, is a pathogenic factor in the development and progression of CKD via its influence on phosphate and vitamin D metabolism, as well as soft tissue and vascular calcification.[205] Ahoor et al found that aqueous and serum levels of Klotho are decreased in both PEX and PEX glaucoma patients, and this decrease was more significant in the latter group.[2] Yamamoto and coworkers suggested that Klotho fragments might contribute to the attenuation of axonal injury-induced calpain activation and oxidative stress, thereby protecting the RGCs against neuronal degeneration.[195] Collectively, these results indicate that Klotho may be implicated in age-related disease in the eye, such as glaucoma, through its pathogenic pathways similar to the aging processes occurring elsewhere in the human body.

Mutations of the complement factor H (*CFH*) gene, a fluid-phase regulator in the alternative complement pathway, have been associated with atypical hemolytic uremic syndrome and mesangial proliferative glomerulonephritis. The complement pathway was also found to be implicated in eye diseases. A genetic polymorphism (Y402H) in the *CFH* gene was associated with AMD in a genome-wide association study (GWAS)[97] and confirmed in virtually all GWAS thereafter.[15] Although the *CFH* gene is not convincingly linked to glaucoma in GWAS, it has been reported that complement components are synthesized and terminal complement complex is formed in the glaucomatous retina, and uncontrolled complement activation may contribute to the degeneration of retinal ganglion cells and their synapses and axons in glaucoma.[100,164] Findings of another study suggest that the classical complement cascade may be involved in synapse elimination during neurodegenerative injury.[167] In a clinical study, a significant increase in the complement C3a/C3 ratio was observed in progressive POAG patients, both in the aqueous humor and in the serum, and there was a significant correlation between disease progression and the C3a/C3 ratio.[75] These findings suggest that the complement system is activated during neurodegenerative injury in the glaucomatous retina and indicate, although not confirmed in GWAS, that the *CFH* gene may play a role in the pathogenesis and progression of glaucoma.[169]

In a case-control study from Japan including 190 POAG patients, 268 NTG patients, and 240 controls, angiotensin II receptor gene polymorphisms were associated with glaucoma, indicating a RAS-related genetic background of glaucoma.[65] Myocilin, a 55–57 kD glycoprotein of the olfactomedin family, is highly expressed in the trabecular meshwork and aggregation of aberrant mutant myocilin is closely associated with glaucoma pathogenesis.[179] In rats with experimental mesangioproliferative glomerulonephritis, myocilin was found to be expressed in podocytes of the kidney and induced in mesangial cells.[60] The specific function of myocilin in the kidney is not clear, but in a parallel to functions of other olfactomedin proteins, it might have a role in cell-cell adhesion and/or signaling processes. All these results indicate that kidney disease and glaucoma may share a common genetic background; however, thus far no significant genetic associations are found between POAG and eGFR in GWAS data.[156]

3.4. *Vitamin D deficiency*

Vitamin D plays a pivotal role in calcium and phosphorus homeostasis, and vitamin D status is reflected by serum total 25-hydroxyvitamin D (25(OH)D) concentrations. Among individuals with CKD, the prevalence of vitamin D deficiency may be up to 80%, and low serum levels of vitamin D have been reported to be associated with the development and progression of CKD.[54,132]

Vitamin D may have a protective effect on glaucoma, by regulating IOP,[102] affecting immunomodulation in the pathogenesis of glaucoma,[121] regulating neurotrophic factors and oxidative stress in the central nervous system,[9,41,93,121,177] and improving ocular blood flow.[51,139] Studies relating vitamin D and glaucoma directly, however, are limited and inconsistent.[141] Krefting and coworkers reported no association between vitamin D and IOP.[98] Yoo and coworkers found a reverse J shaped association between 25(OH)D levels and the risk of OAG, while Kim and coworkers found lower 25(OH)D levels were significantly associated with an elevated risk of glaucoma only in females.[197,92] Wiggs[187] reported that the risk of PEX glaucoma was associated with vitamin D, but decreased vitamin D levels were not found in PEX glaucoma patients in another study.[7] Goncalves and coworkers found that decreased 25(OH)D was associated with the presence but not the severity of POAG,[61] whereas the severity of POAG was associated with lower serum vitamin D levels in patients of African descent.[8] Finally, no significant difference in serum vitamin D levels between POAG patients and controls was detected in a meta-analysis.[111] Apparently, the associations between vitamin D levels and glaucoma are thus far inconclusive.

3.5. *Erythropoietin*

Erythropoietin (EPO), a glycoprotein hormone, is synthesized predominantly in the kidney and is secreted in response to tissue hypoxia. The primary function of EPO is to stimulate erythrocyte formation in the bone marrow; EPO also has angiogenic and neuroprotective properties.[33,94,144,152,182] EPO can regulate neuroprotection through a variety of mechanisms that include the inhibition of apoptosis, a reduction in glutamate and/or reactive oxygen species, a reduction in proinflammatory cytokines, the recruitment of stem cells, and the maintenance of vascular autoregulation.[57]

EPO has been reported to protect RGCs in different models of neurodegeneration (including glaucoma) by inhibiting neuronal apoptosis, both *in vitro* and *in vivo*.[89,99,143,153,174,185,198,202] The risk of glaucoma could thus be higher in CKD patients, who have a decreased EPO production.[190] Similarly, EPO is considered to be a potential neuroprotectant in glaucoma.[173] EPO was documented to protect optic nerve function in patients with traumatic optic neuropathy,[87,88] and in patients with chronic kidney failure undergoing peritoneal dialysis, the temporal RNFL thickness was greater in patients receiving EPO (n=15), compared to those who did not receive EPO (n=14; P=0.02).[3]

EPO is not only produced in the kidneys, but also locally, among others sites, in the eye.[68] Several studies documented an increased aqueous humor concentration (rather than serum concentration) of EPO in glaucomatous

Please cite this article as: Wei Liu, Ruru Guo, Dandan Huang et al., Co-occurrence of chronic kidney disease and glaucoma: epidemiology and etiological mechanisms, Survey of Ophthalmology, https://doi.org/10.1016/j.survophthal.2022.09.001

eyes.[39,124,127,181] Glaucoma is often associated with local hypoxia, elevated reactive oxygen species, glutamate, nitric oxide, and free radicals,[5,160,186] and EPO may thus be expressed by the eye compensatorily.[68,87] Apparently, given the findings described in the previous paragraph, a local increase in EPO does not make the effects of systemic EPO irrelevant. One reason for this could be that the glaucomatous process is not limited to the eye, but also affects the optic nerve and - in the end - the entire visual pathways.[19,104,140]

4. Conclusions and future directions

We report on the current stage of knowledge regarding the relationship between CKD and glaucoma. The prevalence of glaucoma appears elevated in CKD patients, and *vice versa*, and the literature points too many intriguing associations, supporting the general idea that CKD and glaucoma share common pathophysiological pathways. Simultaneously, both CKD and glaucoma are complex diseases with pathways that may reinforce or counteract each other, and this may be different in different patients and different disease stages or pathological conditions. As such, it is not unexpected that reported associations are not always confirmed and that sometimes apparently opposite observations are made. An example is the role of uric acid. Here, protective as well as harmful effects have been reported, which may or may not be explained by a neuroprotective effect of uric acid that may surpass the harmful effect of CKD in some but not all patients. Which effect dominates may depend on characteristics of the study population and study design. Analyses in huge population-based data sets, with a careful consideration of confounding and mediating factors for both neurodegeneration and vascular disease, could further our insights here. Another approach could be to focus on more extreme phenotypes than those found in population-based samples.

Another reason why observations might be difficult to align arises if systemic and local (that is, in the eye) effects are compared directly. An example is what has been observed for EPO. Here, systemic EPO is supposed to have neuroprotective effects whereas elevated EPO levels in the eye may be secondary to local damage. Studies considering systemic and local effects in the context of plausible pathophysiological models, should further our understanding of the association between CKD and glaucoma.

Finally, GWAS thus far failed to uncover a common genetic background for CKD and glaucoma. Further studies are needed to convincingly confirm or reject a potential pleiotropic relationship between CKD and glaucoma. One approach to investigate this in more detail is via the construction and application of polygenic risk scores.[103,110]

5. Method of literature search

We performed a comprehensive search in Pubmed, EMBASE, Web of Science, and ScienceDirect for published papers relating to CKD and glaucoma. Articles from January 1980 to June 2021 with the following keywords in various combinations were recruited: glaucoma, open angle glaucoma, angle closure glaucoma, normal tension glaucoma, low tension glaucoma, exfoliation glaucoma, pseudoexfoliation glaucoma, exfoliation syndrome, kidney disease, chronic kidney disease, chronic kidney failure, intraocular pressure, ocular pressure, IOP, disc hemorrhage, retinal nerve fiber layer, uric acid, glomerular filtration rate, eGFR, albuminuria, proteinuria, creatinine, urea nitrogen. The search yielded 445 results; of those, articles relating to the relationships between CKD and various subtypes of glaucoma and glaucoma endophenotypes, and the underlying mechanisms were included in this review. Relevant articles from the reference lists of identified articles were manually searched for additional inclusions. The search was restricted to articles written in English. However, articles written in other languages with at least an English abstract were also considered if adequate information could be retrieved from the abstract. Articles without an English abstract were excluded.

Disclosure

The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article. This work was supported by grants from the Open Project of Tianjin Key Laboratory of Retinal Functions and Diseases (2020tjswmq003), Youth Special Fund of Clinical Research of Tianjin Medical University Eye Hospital (2020QN02), Tianjin Key Medical Discipline (Specialty) Construction Project (TJYXZDXK-037A) and by the University of Groningen Abel Tasman Talent Program (University Medical Center Groningen/Tianjin Medical University). These funding organizations had no role in the design or conduct of this research.

Key references

Reference 171: In a large consortium of multiple Asian population-based studies, the authors pooled participants from nine population-based studies (from China, Hong Kong, India, Korea, Russia, and Singapore) and examined the association between kidney function and POAG. With a sample size of close to 29000 Asian adults, this study is the largest and most comprehensive to date in this aspect.

Reference 190: In this review, the authors explored underlying pathogenic mechanisms and common risk factors for kidney and ocular disease, especially glaucoma.

REFERENCES

1. Aghsaei Fard M, Ritch R. Optical coherence tomography angiography in glaucoma. Ann Transl Med. 2020;8(18):1204.
2. Ahoor MH, Ghorbanihaghjo A, Sorkhabi R, Kiavar A. Klotho and endothelin-1 in pseudoexfoliation syndrome and glaucoma. J Glaucoma. 2016;25(12):919–22.
3. Aktas Z, Unlu M, Uludag K, et al. The effect of systemic erythropoietin treatment on retinal nerve fiber layer parameters in patients with chronic renal failure undergoing peritoneal dialysis. J Glaucoma. 2015;24(3):214–18.
4. Arakawa S, Yasuda M, Nagata M, et al. Nine-year incidence and risk factors for retinal vein occlusion in a general

Japanese population: the Hisayama Study. Invest Ophthalmol Vis Sci. 2011;52(8):5905–9.
5. Arjamaa O, Nikinmaa M. Oxygen-dependent diseases in the retina: role of hypoxia-inducible factors. Exp Eye Res. 2006;83(3):473–83.
6. Asefa NG, Neustaeter A, Jansonius NM, Snieder H. Autonomic dysfunction and blood pressure in glaucoma patients: the lifelines cohort study. Invest Ophthalmol Vis Sci. 2020;61(11):25.
7. Atalay K, Savur FG, Kirgiz A, et al. Serum levels of thyroid hormone, vitamin D, vitamin B12, folic acid, C-reactive protein, and hemoglobin in pseudoexfoliation and primary open angle Glaucoma. J Fr Ophtalmol. 2019;42(7):730–8.
8. Ayyagari R, Chen YI, Zangwill LM, et al. Association of severity of primary open-angle glaucoma with serum vitamin D levels in patients of African descent. Mol Vis. 2019;25:438–45.
9. Balion C, Griffith LE, Strifler L, et al. Vitamin D, cognition, and dementia: a systematic review and meta-analysis. Neurology. 2012;79(13):1397–405.
10. Balmforth C, van Bragt JJ, Ruijs T, et al. Chorioretinal thinning in chronic kidney disease links to inflammation and endothelial dysfunction. JCI Insight. 2016;1(20):e89173.
11. Bengtsson B, Leske MC, Yang Z, Heijl A, Group EMGT. Disc hemorrhages and treatment in the early manifest glaucoma trial. Ophthalmology. 2008;115(11):2044–8.
12. Bikbov MM, Kazakbaeva GM, Zainullin RM, et al. Intraocular pressure and its associations in a Russian population: the ural eye and medical study. Am J Ophthalmol. 2019;204:130–9.
13. Bikbov MM, Zainullin RM, Gilmanshin TR, et al. Prevalence and associated factors of pseudoexfoliation in a Russian population: the Ural Eye and Medical Study. Am J Ophthalmol. 2020;210:158–66.
14. Black CN, Bot M, Scheffer PG, Snieder H, Penninx BWJH. Uric acid in major depressive and anxiety disorders. J Affect Disord. 2018;225:684–90.
15. Black JR, Clark SJ. Age-related macular degeneration: genome-wide association studies to translation. Genet Med. 2016;18(4):283–9.
16. Bostom AG, Shemin D, Lapane KL, et al. Hyperhomocysteinemia, hyperfibrinogenemia, and lipoprotein(a) excess in maintenance dialysis patients: a matched case-control study. Atherosclerosis. 1996;125(1):91–101.
17. Budenz DL, Anderson DR, Feuer WJ, et al. Detection and prognostic significance of optic disc hemorrhages during the Ocular Hypertension Treatment Study. Ophthalmology. 2006;113(12):2137–43.
18. Canellos HM, Cooper J, Paek A, Chien J. Multiple calcified deposits along the eyelid margins secondary to chronic renal failure and hyperparathyroidism. Optometry. 2005;76(3):181–4.
19. Chan JW, Chan NCY, Sadun AA. Glaucoma as neurodegeneration in the brain. Eye Brain. 2021;13:21–8.
20. Chavers BM, Mauer SM, Ramsay RC, Steffes MW. Relationship between retinal and glomerular lesions in IDDM patients. Diabetes. 1994;43(3):441–6.
21. Chen SH, Lu DW, Ku WC, Chuang LH, Ferng SH, Chen YJ, Lu YH, Chai PY. Changes in intraocular pressure during hemodialysis: a meta-analysis. J Glaucoma. 2021;30(9):866–73.
22. Chen YH, Chen HS, Tarng DC. More impact of microalbuminuria on retinopathy than moderately reduced GFR among type 2 diabetic patients. Diabetes Care. 2012;35(4):803–8.
23. Cheng Q, Saaddine JB, Klein R, et al. Early Age-related macular degeneration with cardiovascular and renal comorbidities: an analysis of the national health and nutrition examination survey, 2005-2008. Ophthalmic Epidemiol. 2017;24(6):413–19.
24. Cheung CM, Li X, Cheng CY, et al. Prevalence, racial variations, and risk factors of age-related macular degeneration in Singaporean Chinese, Indians, and Malays. Ophthalmology. 2014;121(8):1598–603.
25. Chihara E, Honda Y. Multiple defects in the retinal nerve fiber layer in glaucoma. Graefes Arch Clin Exp Ophthalmol. 1992;230(3):201–5.
26. Cho HK, Han JC, Choi JA, et al. Association between chronic renal disease and the risk of glaucoma development: a 12-year nationwide cohort study. Invest Ophthalmol Vis Sci. 2021;62(6):27.
27. Choi J, Moon JW, Shin HJ. Chronic kidney disease, early age-related macular degeneration, and peripheral retinal drusen. Ophthalmic Epidemiol. 2011;18(6):259–263.
28. Choi JA, Han K, Kwon HS. Association between urinary albumin excretion and intraocular pressure in type 2 diabetic patients without renal impairment. PLoS One. 2014;9(5):e96335.
29. Chou CL, Hsieh TC, Chen JS, Fang TC. Risks of all-cause mortality and major kidney events in patients with new-onset primary open-angle glaucoma: a nationwide long-term cohort study in Taiwan. BMJ Open. 2018;8(3):e021270.
30. Chou YH, Chu TS, Lin SL. Role of renin-angiotensin system in acute kidney injury-chronic kidney disease transition. Nephrology (Carlton). 2018;23(4):121–5 Suppl.
31. Choudhary R, Kapoor MS, Singh A, Bodakhe SH. Therapeutic targets of renin-angiotensin system in ocular disorders. J Curr Ophthalmol. 2016;29(1):7–16.
32. Matsushita K, van der Velde M, et al., Chronic Kidney Disease Prognosis Consortium Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. Lancet.. 2010;375(9731):2073–2081.
33. Chung H, Lee H, Lamoke F, et al. Neuroprotective role of erythropoietin by antiapoptosis in the retina. J Neurosci Res. 2009;87(10):2365–74.
34. Chung HS, Harris A, Evans DW, et al. Vascular aspects in the pathophysiology of glaucomatous optic neuropathy. Surv Ophthalmol. 1999;43(1):S43–50 Suppl.
35. Constad WH, Fiore P, Samson C, Cinotti AA. Use of an angiotensin converting enzyme inhibitor in ocular hypertension and primary open-angle glaucoma. Am J Ophthalmol. 1988;105(6):674–7.
36. Cruickshanks KJ, Ritter LL, Klein R, Moss SE. The association of microalbuminuria with diabetic retinopathy. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. Ophthalmology. 1993;100(6):862–7.
37. Cugati S, Wang JJ, Rochtchina E, Mitchell P. Ten-year incidence of retinal vein occlusion in an older population: the Blue Mountains Eye Study. Arch Ophthalmol. 2006;124(5):726–32.
38. Cullinane AB, Leung PS, Ortego J, et al. Renin-angiotensin system expression and secretory function in cultured human ciliary body non-pigmented epithelium. Br J Ophthalmol. 2002;86(6):676–83.
39. Cumurcu T, Bulut Y, Demir HD, Yenisehirli G. Aqueous humor erythropoietin levels in patients with primary open-angle glaucoma. J Glaucoma. 2007;16(8):645–8.
40. de Voogd S, Wolfs RC, Jansonius NM, et al. Atherosclerosis, C-reactive protein, and risk for open-angle glaucoma: the Rotterdam study. Invest Ophthalmol Vis Sci. 2006;47(9):3772–6.

Please cite this article as: Wei Liu, Ruru Guo, Dandan Huang et al., Co-occurrence of chronic kidney disease and glaucoma: epidemiology and etiological mechanisms, Survey of Ophthalmology, https://doi.org/10.1016/j.survophthal.2022.09.001

41. DeLuca GC, Kimball SM, Kolasinski J, et al. Review: the role of vitamin D in nervous system health and disease. Neuropathol Appl Neurobiol. 2013;39(5):458–84.
42. Demir MN, Eksioglu U, Altay M, et al. Retinal nerve fiber layer thickness in chronic renal failure without diabetes mellitus. Eur J Ophthalmol. 2009;19(6):1034–8.
43. Deva R, Alias MA, Colville D, et al. Vision-threatening retinal abnormalities in chronic kidney disease stages 3 to 5. Clin J Am Soc Nephrol. 2011;6(8):1866–71.
44. Diehl DL, Quigley HA, Miller NR, et al. Prevalence and significance of optic disc hemorrhage in a longitudinal study of glaucoma. Arch Ophthalmol. 1990;108(4):545–550.
45. Djordjevic-Jocic J, Cukuranovic R, Mitic B, et al. Ocular and systemic factors associated with glaucoma in chronic kidney disease patients. Int Urol Nephrol. 2014;46(11):2191–8.
46. Drance SM. Disc hemorrhages in the glaucomas. Surv Ophthalmol. 1989;33(5):331–7.
47. Duni A, Dounousi E, Pavlakou P, Eleftheriadis T, Liakopoulos V. Hypertension in Chronic Kidney Disease: Novel Insights. Curr Hypertens Rev. 2020;16(1):45–54.
48. Edwards MS, Wilson DB, Craven TE, et al. Associations between retinal microvascular abnormalities and declining renal function in the elderly population: the Cardiovascular Health Study. Am J Kidney Dis. 2005;46(2):214–24.
49. Elisaf M, Kitsos G, Bairaktari E, et al. Metabolic abnormalities in patients with primary open-angle glaucoma. Acta Ophthalmol Scand. 2001;79(2):129–32.
50. Fathallah-Shaykh SA, Cramer MT. Uric acid and the kidney. Pediatr Nephrol. 2014;29(6):999–1008.
51. Flammer J, Orgül S. Optic nerve blood-flow abnormalities in glaucoma. Prog Retin Eye Res. 1998;17(2):267–89.
52. Foster PJ, Buhrmann R, Quigley HA, Johnson GJ. The definition and classification of glaucoma in prevalence surveys. Br J Ophthalmol. 2002;86(2):238–42.
53. Foureaux G, Nogueira JC, Nogueira BS, et al. Antiglaucomatous effects of the activation of intrinsic Angiotensin-converting enzyme 2. Invest Ophthalmol Vis Sci. 2013;54(6):4296–306.
54. Franca Gois PH, Wolley M, Ranganathan D, Seguro AC. Vitamin D deficiency in chronic kidney disease: recent evidence and controversies. Int J Environ Res Public Health. 2018;15(8):1773.
55. Gao B, Zhu L, Pan Y, et al. Ocular fundus pathology and chronic kidney disease in a Chinese population. BMC Nephrol. 2011;12:62.
56. Gansevoort RT, Correa-Rotter R, Hemmelgarn BR, et al. Chronic kidney disease and cardiovascular risk: epidemiology, mechanisms, and prevention. Lancet. 2013;382(9889):339–52.
57. Genc S, Koroglu TF, Genc K. Erythropoietin as a novel neuroprotectant. Restor Neurol Neurosci. 2004;22(2):105–19.
58. Giordano C, Karasik O, King-Morris K, Asmar A. Uric acid as a marker of kidney disease: review of the current literature. Dis Markers. 2015;2015:382918.
59. Go AS, Chertow GM, Fan D, et al. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med. 2004;351(13):1296–305.
60. Goldwich A, Baulmann DC, Ohlmann A, et al. Myocilin is expressed in the glomerulus of the kidney and induced in mesangioproliferative glomerulonephritis. Kidney Int. 2005;67(1):140–51.
61. Goncalves A, Milea D, Gohier P, et al. Serum vitamin D status is associated with the presence but not the severity of primary open angle glaucoma. Maturitas. 2015;81(4):470–4.
62. Gonen T, Gonen KA, Guzel S. What is the effect of pseudoexfoliation syndrome on renal function in patients without glaucoma? Curr Eye Res. 2014;39(2):188–93.
63. Grunwald JE, Alexander J, Maguire M, et al. Prevalence of ocular fundus pathology in patients with chronic kidney disease. Clin J Am Soc Nephrol. 2010;5(5):867–73.
64. Hamrahian SM, Falkner B. Hypertension in chronic kidney disease. Adv Exp Med Biol. 2017;956:307–25.
65. Hashizume K, Mashima Y, Fumayama T, et al. Genetic polymorphisms in the angiotensin II receptor gene and their association with open-angle glaucoma in a Japanese population. Invest Ophthalmol Vis Sci. 2005;46(6):1993–2001.
66. Hayreh SS. The role of age and cardiovascular disease in glaucomatous optic neuropathy. Surv Ophthalmol. 1999;43(Suppl 1):S27–42.
67. Healey PR, Mitchell P, Smith W, Wang JJ. Optic disc hemorrhages in a population with and without signs of glaucoma. Ophthalmology. 1998;105(2):216–23.
68. Hernández C, Simó R. Erythropoietin produced by the retina: its role in physiology and diabetic retinopathy. Endocrine. 2012;41(2):220–6.
69. Hirooka K, Baba T, Fujimura T, Shiraga F. Prevention of visual field defect progression with angiotensin-converting enzyme inhibitor in eyes with normal-tension glaucoma. Am J Ophthalmol. 2006;142(3):523–5.
70. Hirooka K, Shiraga F. Potential role for angiotensin-converting enzyme inhibitors in the treatment of glaucoma. Clin Ophthalmol. 2007;1(3):217–223.
71. Ho H, Shi Y, Chua J, Tham YC, Lim SH, Aung T, Wong TY, Cheng CY. Association of systemic medication use with intraocular pressure in a multiethnic Asian population: The Singapore Epidemiology of Eye Diseases Study. JAMA Ophthalmol. 2017;135(3):196–202.
72. Hoerger TJ, Simpson SA, Yarnoff BO, et al. The future burden of CKD in the United States: a simulation model for the CDC CKD Initiative. Am J Kidney Dis. 2015;65(3):403–11.
73. Höhn R, Mirshahi A, Nickels S, Schulz A, Wild PS, Blettner M, Pfeiffer N. Cardiovascular medication and intraocular pressure: results from the Gutenberg Health Study. Br J Ophthalmol. 2017;101(12):1633–7.
74. Holappa M, Vapaatalo H, Vaajanen A. Many faces of renin-angiotensin system - focus on eye. Open Ophthalmol J. 2017;11:122–42.
75. Hubens WHG, Beckers HJM, Gorgels TGMF, Webers CAB. Increased ratios of complement factors C3a to C3 in aqueous humor and serum mark glaucoma progression. Exp Eye Res. 2021;204:108460.
76. Igić R. Four decades of ocular renin-angiotensin and kallikrein-kinin systems (1977-2017). Exp Eye Res. 2018;166:74–83.
77. Inoue T, Yokoyoma T, Koike H. The effect of angiotensin II on uveoscleral outflow in rabbits. Curr Eye Res. 2001;23(2):139–43.
78. Jager KJ, Kovesdy C, Langham R, Rosenberg M, Jha V, Zoccali C. A single number for advocacy and communication-worldwide more than 850 million individuals have kidney diseases. Kidney Int. 2019;96(5):1048–50.
79. Jammal AA, Berchuck SI, Mariottoni EB, Tanna AP, Costa VP, Medeiros FA. Blood pressure and glaucomatous progression in a large clinical population. Ophthalmology. 2022;129(2):161–70.
80. Janssen SF, Gorgels TG, Ramdas WD, et al. The vast complexity of primary open angle glaucoma: disease genes, risks, molecular mechanisms and pathobiology. Prog Retin Eye Res. 2013;37:31–67.
81. Ji A, Pan C, Wang H, et al. Prevalence and associated risk factors of chronic kidney disease in an elderly population from Eastern China. Int J Environ Res Public Health. 2019;16(22):4383.

Please cite this article as: Wei Liu, Ruru Guo, Dandan Huang et al., Co-occurrence of chronic kidney disease and glaucoma: epidemiology and etiological mechanisms, Survey of Ophthalmology, https://doi.org/10.1016/j.survophthal.2022.09.001

82. Jonas JB, Ritch R, Panda-Jonas S. Cerebrospinal fluid pressure in the pathogenesis of glaucoma. Prog Brain Res. 2015;221:33–47.
83. Jonas JB, Schiro D. Localised wedge shaped defects of the retinal nerve fibre layer in glaucoma. Br J Ophthalmol. 1994;78(4):285–90.
84. Jonas JB, Wang YX, Wei WB, et al. Chronic kidney disease and eye diseases: the Beijing Eye Study. Ophthalmology. 2017;124(10):1566–9.
85. Jung KI, Kim SJ, Park CK. Systemic vascular risk factors for multiple retinal nerve fiber layer defects. Sci Rep. 2018;8(1):7797.
86. Jung S, Bosch A, Ott C, et al. Retinal neurodegeneration in patients with end-stage renal disease assessed by spectral-domain optical coherence tomography. Sci Rep. 2020;10(1):5255.
87. Kashkouli MB, Pakdel F, Sanjari MS, et al. Erythropoietin: a novel treatment for traumatic optic neuropathy-a pilot study. Graefes Arch Clin Exp Ophthalmol. 2011;249(5):731–6.
88. Kawakami M, Sekiguchi M, Sato K, et al. Erythropoietin receptor-mediated inhibition of exocytotic glutamate release confers neuroprotection during chemical ischemia. J Biol Chem. 2001;276(42):39469–75.
89. Kilic U, Kilic E, Soliz J, et al. Erythropoietin protects from axotomy-induced degeneration of retinal ganglion cells by activating ERK-1/-2. FASEB J. 2005;19(2):249–51.
90. Killer HE, Pircher A. Normal tension glaucoma: review of current understanding and mechanisms of the pathogenesis. Eye (Lond). 2018;32(5):924–30.
91. Kim GA, Park SH, Ko J, et al. Albuminuria is associated with open-angle glaucoma in nondiabetic Korean subjects: a cross-sectional study. PLoS One. 2016;11(12):e0168682.
92. Kim HT, Kim JM, Kim JH, et al. The relationship between vitamin D and glaucoma: a Kangbuk Samsung Health Study. Korean J Ophthalmol. 2016;30(6):426–33.
93. Kim JM, Kim YJ, Kim DM. Increased expression of oxyproteins in the optic nerve head of an in vivo model of optic nerve ischemia. BMC Ophthalmol. 2012;12:63.
94. King CE, Rodger J, Bartlett C, et al. Erythropoietin is both neuroprotective and neuroregenerative following optic nerve transection. Exp Neurol. 2007;205(1):48–55.
95. Klaassen-Broekema N, van Bijsterveld OP. Limbal and corneal calcification in patients with chronic renal failure. Br J Ophthalmol. 1993;77(9):569–71.
96. Klein R, Moss SE, Meuer SM, Klein BE. The 15-year cumulative incidence of retinal vein occlusion: the Beaver Dam Eye Study. Arch Ophthalmol. 2008;126(4):513–18.
97. Klein RJ, Zeiss C, Chew EY, et al. Complement factor H polymorphism in age-related macular degeneration. Science. 2005;308(5720):385–9.
98. Krefting EA, Jorde R, Christoffersen T, Grimnes G. Vitamin D and intraocular pressure–results from a case-control and an intervention study. Acta Ophthalmol. 2014;92(4):345–9.
99. Kretz A, Happold CJ, Marticke JK, Isenmann S. Erythropoietin promotes regeneration of adult CNS neurons via Jak2/Stat3 and PI3K/AKT pathway activation. Mol Cell Neurosci. 2005;29(4):569–79.
100. Kuehn MH, Kim CY, Ostojic J, et al. Retinal synthesis and deposition of complement components induced by ocular hypertension. Exp Eye Res. 2006;83(3):620–8.
101. Kuro-o M, Matsumura Y, Aizawa H, et al. Mutation of the mouse klotho gene leads to a syndrome resembling ageing. Nature. 1997;390(6655):45–51.
102. Kutuzova GD, Gabelt BT, Kiland JA, et al. 1α,25-Dihydroxyvitamin D(3) and its analog, 2-methylene-19-nor-(20S)-1α,25-dihydroxyvitamin D(3) (2MD), suppress intraocular pressure in non-human primates. Arch Biochem Biophys. 2012;518(1):53–60.
103. Lambert SA, Abraham G, Inouye M. Towards clinical utility of polygenic risk scores. Hum Mol Genet. 2019;28(R2):R133–R142.
104. Lawlor M, Danesh-Meyer H, Levin LA, Davagnanam I, De Vita E, Plant GT. Glaucoma and the brain: trans-synaptic degeneration, structural change, and implications for neuroprotection. Surv Ophthalmol. 2018;63(3):296–306.
105. Lee JY, Kim JM, Shim SH, et al. Association between optic disc hemorrhage and renal function in South Korea. J Glaucoma. 2018;27(3):251–6.
106. Lee MW, Lee WH, Park GS, Lim HB, Kim JY. Longitudinal changes in the peripapillary retinal nerve fiber layer thickness in hypertension: 4-year prospective observational study. Invest Ophthalmol Vis Sci. 2019;60(12):3914–3919.
107. Lee MW, Lee WH, Ryu CK, Lee YM, Lee YH, Kim JY. Peripapillary retinal nerve fiber layer and microvasculature in prolonged type 2 diabetes patients without clinical diabetic retinopathy. Invest Ophthalmol Vis Sci. 2021;62(2):9.
108. Levey AS, de Jong PE, Coresh J, et al. The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report. Kidney Int. 2011;80(1):17–28.
109. Levine RM, Yang A, Brahma V, Martone JF. Management of blood pressure in patients with glaucoma. Curr Cardiol Rep. 2017;19(11):109.
110. Lewis CM, Vassos E. Polygenic risk scores: from research tools to clinical instruments. Genome Med. 2020;12(1):44.
111. Li S, Li D, Shao M, et al. Lack of Association between serum vitamin B_6, vitamin B_{12}, and vitamin D levels with different types of glaucoma: a systematic review and meta-analysis. Nutrients. 2017;9(6):636.
112. Li S, Shao M, Cao W, Sun X. Association between pretreatment serum uric acid levels and progression of newly diagnosed primary angle-closure glaucoma: a prospective cohort study. Oxid Med Cell Longev. 2019;2019:7919836.
113. Li S, Shao M, Li D, et al. Association of serum uric acid levels with primary open-angle glaucoma: a 5-year case-control study. Acta Ophthalmol. 2019;97(3):e356–63.
114. Li S, Shao M, Tang B, et al. The association between serum uric acid and glaucoma severity in primary angle closure glaucoma: a retrospective case-control study. Oncotarget. 2017;8(2):2816–24.
115. Liabeuf S, Pepin M, Franssen CFM, et al. Chronic kidney disease and neurological disorders: are uraemic toxins the missing piece of the puzzle? Nephrol Dial Transplant. 2021:gfab223.
116. Liew G, Mitchell P, Wong TY, et al. CKD increases the risk of age-related macular degeneration. J Am Soc Nephrol. 2008;19(4):806–11.
117. Liew G, Mitchell P, Wong TY, Wang JJ. Retinal microvascular signs are associated with chronic kidney disease in persons with and without diabetes. Kidney Blood Press Res. 2012;35(6):589–94.
118. Lim ZW, Chee ML, Thakur S, et al. Albuminuria and primary open-angle glaucoma: the Singapore Chinese Eye Study (SCES). Br J Ophthalmol. 2021;105(5):669–73.
119. Liu YT, Hung TY, Lee YK, et al. Association between chronic kidney disease and risk of cataract: a nationwide retrospective cohort study. Am J Nephrol. 2017;45(6):524–31.
120. Lotti VJ, Pawlowski N. Prostaglandins mediate the ocular hypotensive action of the angiotensin converting enzyme inhibitor MK-422 (enalaprilat) in African green monkeys. J Ocul Pharmacol. 1990;6(1):1–7.
121. McKinnon SJ. The cell and molecular biology of glaucoma: common neurodegenerative pathways and relevance to glaucoma. Invest Ophthalmol Vis Sci. 2012;53(5):2485–7.

Please cite this article as: Wei Liu, Ruru Guo, Dandan Huang et al., Co-occurrence of chronic kidney disease and glaucoma: epidemiology and etiological mechanisms, Survey of Ophthalmology, https://doi.org/10.1016/j.survophthal.2022.09.001

122. McMonnies C. Reactive oxygen species, oxidative stress, glaucoma and hyperbaric oxygen therapy. J Optom. 2018;11(1):3–9.
123. Meguid El Nahas A, Bello AK. Chronic kidney disease: the global challenge. Lancet. 2005;365(9456):331–40.
124. Mokbel TH, Ghanem AA, Kishk H, et al. Erythropoietin and soluble CD44 levels in patients with primary open-angle glaucoma. Clin Exp Ophthalmol. 2010;38(6):560–5.
125. Mottl AK, Kwon KS, Garg S, et al. The association of retinopathy and low GFR in type 2 diabetes. Diabetes Res Clin Pract. 2012;98(3):487–93.
126. Muntner P, He J, Hamm L, et al. Renal insufficiency and subsequent death resulting from cardiovascular disease in the United States. J Am Soc Nephrol. 2002;13(3):745–53.
127. Nassiri N, Nassiri N, Majdi M, et al. Erythropoietin levels in aqueous humor of patients with glaucoma. Mol Vis. 2012;18:1991–5.
128. Nitsch D, Evans J, Roderick PJ, et al. Associations between chronic kidney disease and age-related macular degeneration. Ophthalmic Epidemiol. 2009;16(3):181–6.
129. Niyaz L, Ozkurt S, Musmul A. Pseudoexfoliation syndrome in chronic kidney disease patients. Ren Fail. 2015;37(3):456–8.
130. Nongpiur ME, Wong TY, Sabanayagam C, et al. Chronic kidney disease and intraocular pressure: the Singapore Malay Eye Study. Ophthalmology. 2010;117(3):477–83.
131. Nusinovici S, Sabanayagam C, Teo BW, et al. Vision impairment in CKD patients: epidemiology, mechanisms, differential diagnoses, and prevention. Am J Kidney Dis. 2019;73(6):846–57.
132. Obi Y, Hamano T, Isaka Y. Prevalence and prognostic implications of vitamin D deficiency in chronic kidney disease. Dis Markers. 2015;2015:868961.
133. Ohguro N, Matsuda M, Fukuda M. Corneal endothelial changes in patients with chronic renal failure. Am J Ophthalmol. 1999;128(2):234–6.
134. Pappelis K, Choritz L, Jansonius NM. Microcirculatory model predicts blood flow and autoregulation range in the human retina: in vivo investigation with laser speckle flowgraphy. Am J Physiol Heart Circ Physiol. 2020;319(6):H1253–73.
135. Pappelis K, Jansonius NM. U-shaped effect of blood pressure on structural OCT metrics and retinal perfusion in ophthalmologically healthy subjects. Invest Ophthalmol Vis Sci. 2021;62(12):5.
136. Pappelis K, Loiselle AR, Visser S, Jansonius NM. Association of systemic medication exposure with glaucoma progression and glaucoma suspect conversion in the Groningen Longitudinal Glaucoma Study. Invest Ophthalmol Vis Sci. 2019;60(14):4548–55.
137. Park SJ, Byun SJ, Park JY, Kim M. Primary open-angle glaucoma and increased risk of chronic kidney disease. J Glaucoma. 2019;28(12):1067–73.
138. Penno G, Solini A, Zoppini G, et al. Rate and determinants of association between advanced retinopathy and chronic kidney disease in patients with type 2 diabetes: the Renal Insufficiency And Cardiovascular Events (RIACE) Italian multicenter study. Diabetes Care. 2012;35(11):2317–23.
139. Pittas AG, Chung M, Trikalinos T, et al. Systematic review: vitamin D and cardiometabolic outcomes. Ann Intern Med. 2010;152(5):307–14.
140. Prins D, Hanekamp S, Cornelissen FW. Structural brain MRI studies in eye diseases: are they clinically relevant? A review of current findings. Acta Ophthalmol. 2016;94(2):113–21.
141. Ramdas WD, Schouten JSAG, Webers CAB. The Effect of vitamins on glaucoma: a systematic review and meta-analysis. Nutrients. 2018;10(3):359.
142. Reitsamer HA, Kiel JW. Relationship between ciliary blood flow and aqueous production in rabbits. Invest Ophthalmol Vis Sci. 2003;44(9):3967–71.
143. Resende AP, Rosolen SG, Nunes T, et al. Functional and structural effects of erythropoietin subconjunctival administration in glaucomatous animals. Biomed Hub. 2018;3(2):1–11.
144. Rex TS, Wong Y, Kodali K, Merry S. Neuroprotection of photoreceptors by direct delivery of erythropoietin to the retina of the retinal degeneration slow mouse. Exp Eye Res. 2009;89(5):735–40.
145. Ro JS, Moon JY, Park TK, Lee SH. Association between chronic kidney disease and open-angle glaucoma in South Korea: a 12-year nationwide retrospective cohort study. Sci Rep. 2022;12(1):3423.
146. Robinson K, Gupta A, Dennis V, et al. Hyperhomocysteinemia confers an independent increased risk of atherosclerosis in end-stage renal disease and is closely linked to plasma folate and pyridoxine concentrations. Circulation. 1996;94(11):2743–8.
147. Roddy GW. Metabolic syndrome is associated with ocular hypertension and glaucoma. J Glaucoma. 2020;29(9):726–731.
148. Sabanayagam C, Lim SC, Wong TY, et al. Ethnic disparities in prevalence and impact of risk factors of chronic kidney disease. Nephrol Dial Transplant. 2010;25(8):2564–70.
149. Sabanayagam C, Shankar A, Koh D, et al. Retinal microvascular caliber and chronic kidney disease in an Asian population. Am J Epidemiol. 2009;169(5):625–32.
150. Saccà SC, Izzotti A, Rossi P, Traverso C. Glaucomatous outflow pathway and oxidative stress. Exp Eye Res. 2007;84(3):389–99.
151. Saccà SC, Vagge A, Pulliero A, Izzotti A. Helicobacter pylori infection and eye diseases: a systematic review. Medicine (Baltimore). 2014;93(28):e216.
152. Sato T, Kusaka S, Shimojo H, Fujikado T. Vitreous levels of erythropoietin and vascular endothelial growth factor in eyes with retinopathy of prematurity. Ophthalmology. 2009;116(9):1599–603.
153. Sättler MB, Merkler D, Maier K, et al. Neuroprotective effects and intracellular signaling pathways of erythropoietin in a rat model of multiple sclerosis. Cell Death Differ. 2004;11(2):S181–92 Suppl.
154. Shah GB, Sharma S, Mehta AA, Goyal RK. Oculohypotensive effect of angiotensin-converting enzyme inhibitors in acute and chronic models of glaucoma. J Cardiovasc Pharmacol. 2000;36(2):169–75.
155. Shen F, Zhang L, Liu T. [Effects of angiotensin II on the 3H-TdR incorporation and synthesis of collagen in cultured bovine trabecular meshwork cells]. Yan Ke Xue Bao. 2001;17(4):209–12.
156. Shiga Y, Akiyama M, Nishiguchi KM, et al. Genome-wide association study identifies seven novel susceptibility loci for primary open-angle glaucoma. Hum Mol Genet. 2018;27(8):1486–96.
157. Shih CH, Ou SY, Shih CJ, et al. Bidirectional association between the risk of comorbidities and the diagnosis of retinal vein occlusion in an elderly population: a nationwide population-based study. Int J Cardiol. 2015;178:256–61.
158. Shim SH, Kim CY, Kim JM, et al. The role of systemic arterial stiffness in open-angle glaucoma with diabetes mellitus. Biomed Res Int. 2015;2015:425835.
159. Shim SH, Sung KC, Kim JM, et al. Association between renal function and open-angle glaucoma: The Korea National Health and Nutrition Examination Survey 2010-2011. Ophthalmology. 2016;123(9):1981–8.
160. Silva M, Grillot D, Benito A, et al. Erythropoietin can promote erythroid progenitor survival by repressing apoptosis through Bcl-XL and Bcl-2. Blood. 1996;88(5):1576–82.
161. Simavlı H, Bucak YY, Tosun M, Erdurmuş M. Serum uric acid, alanine aminotransferase, hemoglobin and red blood cell

Please cite this article as: Wei Liu, Ruru Guo, Dandan Huang et al., Co-occurrence of chronic kidney disease and glaucoma: epidemiology and etiological mechanisms, Survey of Ophthalmology, https://doi.org/10.1016/j.survophthal.2022.09.001

count levels in pseudoexfoliation syndrome. J Ophthalmol. 2015;2015:914098.
162. Skrzypecki J, Ufnal M, Szaflik JP, Filipiak KJ. Blood pressure and glaucoma: at the crossroads between cardiology and ophthalmology. Cardiol J. 2019;26(1):8–12.
163. Sommer A, Katz J, Quigley HA, et al. Clinically detectable nerve fiber atrophy precedes the onset of glaucomatous field loss. Arch Ophthalmol. 1991;109(1):77–83.
164. Stasi K, Nagel D, Yang X, et al. Complement component 1Q (C1Q) upregulation in retina of murine, primate, and human glaucomatous eyes. Invest Ophthalmol Vis Sci. 2006;47(3):1024–9.
165. Stefanutti C, Mesce D, Pacella F, Di Giacomo S, Turchetti P, Forastiere M, Trovato Battagliola E, La Torre G, Smaldone G, Pacella E. Optical coherence tomography of retinal and choroidal layers in patients with familial hypercholesterolaemia treated with lipoprotein apheresis. Atheroscler Suppl. 2019;40:49–54.
166. Stefoni S, Cianciolo G, Donati G, et al. Low TGF-beta1 serum levels are a risk factor for atherosclerosis disease in ESRD patients. Kidney Int. 2002;61(1):324–35.
167. Stevens B, Allen NJ, Vazquez LE, et al. The classical complement cascade mediates CNS synapse elimination. Cell. 2007;131(6):1164–78.
168. Su DH, Wong TY, Foster PJ, et al. Central corneal thickness and its associations with ocular and systemic factors: the Singapore Malay Eye Study. Am J Ophthalmol. 2009;147(4):709–16 e1..
169. Tezel G, Yang X, Luo C, et al. Oxidative stress and the regulation of complement activation in human glaucoma. Invest Ophthalmol Vis Sci. 2010;51(10):5071–5082.
170. Tham YC, Li X, Wong TY, et al. Global prevalence of glaucoma and projections of glaucoma burden through 2040: a systematic review and meta-analysis. Ophthalmology. 2014;121(11):2081–90.
171. Tham YC, Tao Y, Zhang L, et al. Is kidney function associated with primary open-angle glaucoma? Findings from the Asian Eye Epidemiology Consortium. Br J Ophthalmol. 2020;104(9):1298–303.
172. Topouzis F, Wilson MR, Harris A, Founti P, Yu F, Anastasopoulos E, Pappas T, Koskosas A, Salonikiou A, Coleman AL. Association of open-angle glaucoma with perfusion pressure status in the Thessaloniki Eye Study. Am J Ophthalmol. 2013;155(5):843–51.
173. Tsai JC, Song BJ, Wu L, Forbes M. Erythropoietin: a candidate neuroprotective agent in the treatment of glaucoma. J Glaucoma. 2007;16(6):567–71.
174. Tsai JC, Wu L, Worgul B, et al. Intravitreal administration of erythropoietin and preservation of retinal ganglion cells in an experimental rat model of glaucoma. Curr Eye Res. 2005;30(11):1025–31.
175. Vaajanen A, Vapaatalo H. Local ocular renin-angiotensin system - a target for glaucoma therapy? Basic Clin Pharmacol Toxicol. 2011;109(4):217–24.
176. Valdivielso JM, Rodríguez-Puyol D, Pascual J, et al. Atherosclerosis in chronic kidney disease: more, less, or just different? Arterioscler Thromb Vasc Biol. 2019;39(10):1938–66.
177. van der Schaft J, Koek HL, Dijkstra E, et al. The association between vitamin D and cognition: a systematic review. Ageing Res Rev. 2013;12(4):1013–23.
178. Vart P, Grams ME. Measuring and assessing kidney function. Semin Nephrol. 2016;36(4):262–72.
179. Wang H, Li M, Zhang Z, et al. Physiological function of myocilin and its role in the pathogenesis of glaucoma in the trabecular meshwork (Review). Int J Mol Med. 2019;43(2):671–81.
180. Wang TJ, Wu CK, Hu CC, et al. Increased risk of co-morbid eye disease in patients with chronic renal failure: a population-based study. Ophthalmic Epidemiol. 2012;19(3):137–43.
181. Wang ZY, Zhao KK, Zhao PQ. Erythropoietin is increased in aqueous humor of glaucomatous eyes. Curr Eye Res. 2010;35(8):680–4.
182. Watanabe D, Suzuma K, Matsui S, et al. Erythropoietin as a retinal angiogenic factor in proliferative diabetic retinopathy. N Engl J Med. 2005;353(8):782–92.
183. Weiner DE, Tighiouart H, Reynolds R, Seddon JM. Kidney function, albuminuria and age-related macular degeneration in NHANES III. Nephrol Dial Transplant. 2011;26(10):3159–3165.
184. Weinreb RN, Aung T, Medeiros FA. The pathophysiology and treatment of glaucoma: a review. JAMA. 2014;311(18):1901–1911.
185. Weishaupt JH, Rohde G, Pölking E, et al. Effect of erythropoietin axotomy-induced apoptosis in rat retinal ganglion cells. Invest Ophthalmol Vis Sci. 2004;45(5):1514–22.
186. Wenger RH. Cellular adaptation to hypoxia: O2-sensing protein hydroxylases, hypoxia-inducible transcription factors, and O2-regulated gene expression. FASEB J. 2002;16(10):1151–62.
187. Wiggs JL. The cell and molecular biology of complex forms of glaucoma: updates on genetic, environmental, and epigenetic risk factors. Invest Ophthalmol Vis Sci. 2012;53(5):2467–9.
188. Wiggs JL, Pasquale LR. Genetics of glaucoma. Hum Mol Genet. 2017;26(R1):R21–7.
189. Wong CW, Lamoureux EL, Cheng CY, et al. Increased burden of vision impairment and eye diseases in persons with chronic kidney disease - a population-based study. EBioMedicine. 2016;5:193–7.
190. Wong CW, Wong TY, Cheng CY, Sabanayagam C. Kidney and eye diseases: common risk factors, etiological mechanisms, and pathways. Kidney Int. 2014;85(6):1290–302.
191. Wong TY, Coresh J, Klein R, et al. Retinal microvascular abnormalities and renal dysfunction: the atherosclerosis risk in communities study. J Am Soc Nephrol. 2004;15(9):2469–76.
192. Wu IW, Sun CC, Lee CC, et al. Retinal neurovascular changes in chronic kidney disease. Acta Ophthalmol. 2020;98(7):e848–55.
193. Xie Y, Bowe B, Mokdad AH, et al. Analysis of the global burden of disease study highlights the global, regional, and national trends of chronic kidney disease epidemiology from1990 to 2016. Kidney Int. 2018;94:567–81.
194. Yağci R, Gürel A, Ersöz I, et al. The activities of paraoxonase, xanthine oxidase, adenosine deaminase and the level of nitrite in pseudoexfoliation syndrome. Ophthalmic Res. 2009;42(3):155–9.
195. Yamamoto K, Sato K, Yukita M, et al. The neuroprotective effect of latanoprost acts via klotho-mediated suppression of calpain activation after optic nerve transection. J Neurochem. 2017;140(3):495–508.
196. Yang T, Xu C. Physiology and pathophysiology of the intrarenal renin-angiotensin system: an update. J Am Soc Nephrol. 2017;28(4):1040–9.
197. Yoo TK, Oh E, Hong S. Is vitamin D status associated with open-angle glaucoma? A cross-sectional study from South Korea. Public Health Nutr. 2014;17(4):833–43.
198. Youssoufian H, Longmore G, Neumann D, et al. Structure, function, and activation of the erythropoietin receptor. Blood. 1993;81(9):2223–36.
199. Yuki K, Murat D, Kimura I, et al. Reduced-serum vitamin C and increased uric acid levels in normal-tension glaucoma. Graefes Arch Clin Exp Ophthalmol. 2010;248(2):243–8.

Please cite this article as: Wei Liu, Ruru Guo, Dandan Huang et al., Co-occurrence of chronic kidney disease and glaucoma: epidemiology and etiological mechanisms, Survey of Ophthalmology, https://doi.org/10.1016/j.survophthal.2022.09.001

200. Zakrzewski PA, Mackenzie PJ, Tsai G, et al. Does an association exist between pseudoexfoliation syndrome and chronic kidney disease? J Glaucoma. 2012;21(8):562–6.
201. Zander E, Seidlein I, Herfurth S, et al. Increased prevalence of proliferative retinopathy and cardiovascular autonomic dysfunction in IDDM patients with proteinuria. Exp Clin Endocrinol. 1992;99(2):102–7.
202. Zhong L, Bradley J, Schubert W, et al. Erythropoietin promotes survival of retinal ganglion cells in DBA/2J glaucoma mice. Invest Ophthalmol Vis Sci. 2007;48(3):1212–18.
203. Zhou L, Liu Y. Wnt/β-catenin signaling and renin-angiotensin system in chronic kidney disease. Curr Opin Nephrol Hypertens. 2016;25(2):100–6.
204. Zhu Z, Liao H, Wang W, et al. Visual impairment and major eye diseases in chronic kidney disease: the National Health and Nutrition Examination Survey, 2005-2008. Am J Ophthalmol. 2020;213:24–33.
205. Zou D, Wu W, He Y, et al. The role of klotho in chronic kidney disease. BMC Nephrol. 2018;19(1):285.

Please cite this article as: Wei Liu, Ruru Guo, Dandan Huang et al., Co-occurrence of chronic kidney disease and glaucoma: epidemiology and etiological mechanisms, Survey of Ophthalmology, https://doi.org/10.1016/j.survophthal.2022.09.001