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Original Research Article

A Population-Based Incidence and Prognosis of Various Eye Diseases in End Stage Renal Disease Patients and Kidney Transplant Recipients

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Abstract

Aim: The aim of the present study was to assess the Nationwide Glaucoma incidence in end stage renal disease patients and kidney transplant recipients.

Methods: The primary objective of the project was to investigate the effect of KT on the national population-based incidence and prognosis of various eye diseases, including age-related macular degeneration, retinal vein occlusion, and glaucoma.

Results: The mean age of the subjects was 46.4 ± 11.6 years and majority of subjects were men. There was a significant difference in income among the study groups ($P < 0.0001$). A larger proportion of KTRs and ESRD patients had a history of underlying chronic disease such as DM, HTN, and dyslipidemia when compared with healthy control (all Ps < 0.0001). Among the ESRD patients, 76% of the patients under- went hemodialysis, 20% underwent peritoneal dialysis, and 4% underwent mixed dialysis. Among the KTRs, 30% had no dialysis history, 44% underwent hemodialysis, and 16% underwent peritoneal dialysis before KT. For KTRs, 96% of the recipients received induction medication. Almost all the KTRs were prescribed calcineurin inhibitor for maintenance therapy and 14% of the KTRs experienced desensitization.

Conclusion: In conclusion, the present nationwide population-based cohort study showed that there was no significant association of POAG incidence risk in ESRD patients and KTRs after controlling for multiple confounding factors. However, the PACG risk was significantly increased in ESRD patients. Interestingly, KT reduced the risk of PACG in ESRD patients to a level similar to that in healthy controls.

Keywords: Chronic kidney disease, Optic nerve diseases, Epidemiology

Introduction

Glaucoma is one of the major causes of irreversible blindness. The number of people with glaucoma has been increasing worldwide, rising rapidly over the previous decade by 27.9%, and is estimated to reach 111.8 million by 2040. [1] Moreover, glaucoma contributes substantially to health burden in terms of disability adjusted life years (DALYs). [2] chronic kidney disease (CKD) is another prevalent and progressive disease affecting between 8-16% of the global population, [3] resulting in significant healthcare costs, morbidity and mortality. CKD has been implicated in multiple ocular diseases, including glaucoma. The two diseases share several risk factors such as diabetes, hypertension, and cardiovascular disease. [4] In addition, they involve common pathogenic pathways, such as microvascular damage and ischemia, endothelial dysfunction, inflammation and oxidative stress. [4]

Despite emerging evidence to suggest the relationship between glaucoma and CKD, [5-7] there have also been studies reporting no association between them, [8,9] with existing literature on the subject being inconclusive. Additionally, it remains to be elucidated if demographics, socioeconomic status, and comorbidities are confounders of this relationship. Previously, Tham et al. conducted a pooled-analysis of multiple Asian population-based studies, suggesting association between primary open angle glaucoma (POAG) and CKD in East Asians. [10]

Recent, well-designed studies [11] have demonstrated that subjects with moderate or severe renal impairment (creatinine clearance < 60 mL/minute/1.73 m2) are approximately 3-fold more likely to undergo cataract surgery relative to subjects with normal or mildly impaired renal function (creatinine clearance ≥ 60 mL/minute/1.73 m2) in younger adults below 60 years of age. Nevertheless, a large-scale Asian nationwide cohort study on ophthalmic disorders in a population with ESRD has not been undertaken because ESRD is relatively rare.

The aim of the present study was to assess the Nationwide Glaucoma incidence in end stage renal disease patients and kidney transplant recipients.

Materials and Methods

This retrospective study was undertaken to investigate the effect of KT on the population-based incidence and prognosis of various eye diseases, including age-related macular degeneration, retinal vein occlusion, and glaucoma.

The present study excluded subjects based on the following criteria: (1) KT recipients (KTRs) who were not matched to ESRD patients, (2) subjects with a history of glaucoma before enrollment, (3) subjects with a history of multiple organ transplantations or (4) subjects younger than 19 years. Finally, an equal number of KTRs, ESRD patients (5000) and healthy controls (5000) were enrolled in the present study.

Requirement for informed consent was waived because of the retrospective study design and absence of any additional medical intervention on the study participants. The study was conducted as per tenets of the latest version of the Declaration of Helsinki.

The ICD-10 codes were used to define the comorbidities and causes of kidney disease. During the study period, KT was newly performed in the recipients who were identified by the ICD-10 codes R3280 (KT) or V005 (KT related treatment, V code for Korean rare incurable diseases). In Korea, these patients routinely take postoperative immunosuppressants and corticosteroids throughout their life as a maintenance therapy to prevent graft rejection. [12,13] ESRD patients were filtered from the dataset based on CKD diagnosis (N18-19) and history of dialysis for more than 3 months (Z49, Z99.2, and O7011-7020 [hemodialysis] or O7071-7075, and V003 [peritoneal dialysis]). Patients with ESRD were 1:1 matched with KTRs for age, sex, duration of renal replacement therapy, and history of underlying HTN and DM. Healthy controls without any history of CKD were also 1:1 matched with KTRs for age, sex, and year of inclusion.

The medication history of subjects obtained from the NHIS database and ICD-10 codes were used to identify the comorbidities. Patients with ICD-10 codes of HTN (I10-I15, I159, I151, and I1528) or those with a history of antihypertensive medication use for more than two times within a year before KT were considered to have HTN. Patients with ICD-10 codes of DM (E109, E119, E139, E149, E101, E111, E131, E141, E105, E115, E135, and E145) or those with history of taking oral hypoglycemic agents or insulin were considered to have DM. Dyslipidemia was defined by the ICD-10 code of dyslipidemia (E78) or medication history of taking lipid lowering agents. [14]

The diagnosis of POAG or PACG was confirmed when a diagnosis of ICD-10 codes, H40.1 or H40.2, respectively, was made at least three times within one year. H40.1 included unspecified open-angle glaucoma (H4010), POAG (H4011), low-tension glaucoma (H4012), pigmentary glaucoma (H4013), capsular glaucoma with pseudo exfoliation of lens (H4014), and residual stages of open-angle glaucoma (H4015). H40.2 included unspecified primary angle-closure glaucoma (H4020), acute angle-closure glaucoma (H4021), chronic angle-closure glaucoma (H4022), intermittent angle-closure glaucoma (H4023), and residual stage of angle-closure glaucoma (H4024).

Data Collection

Demographic data, including age, sex, income level, dialysis modality, duration of dialysis, date of KT, medications used for induction therapy, history of desensitization, and Charlson comorbidity index (CCI), were obtained from the NHIS database. CCI is a useful indicator for assessing the severity of a patient's comorbidity. The CCI was modified to four categories (0, 1–2, 3–4, and ≥ 5) to adjust subjects' current status: 1-year mortality rate of 12% for "0"; 26% for "1–2"; 52% for "3–4"; 85% for "≥ 5."[14] During the study period, information of immunosuppressant use, such as tacrolimus, cyclosporine, and corticosteroids, were collected and analyzed.

Statistical Analysis

All statistical analyses were performed using the SPSS 20 program. Statistical significance was determined at the level of $P < 0.05$.

Results

Table 1: Subject demographics

	Healthy control (n =5000)	ESRD (n = 5000)	KTR (n = 5000)	*P*-value
Age, years (%)	46.4 ± 11.6	47.3 ± 12.8	46.7 ± 11.5	1
20–29	350	400	380	
30–39	1000	950	980	
40–49	1600	1640	1680	
50–59	1500	1550	1550	
60–69	400	420	350	
≥ 70	150	40	60	
Male sex, n (%)	3000	3010	3020	1
Diabetes mellitus, n (%)	1200	2000	2020	< 0.0001
Hypertension, n (%)	800	4500	4600	< 0.0001
Dyslipidemia, n (%)	600	2100	2800	< 0.0001
Income, quartile, n (%)				< 0.0001
Aid	100	1100	1800	
Q1	1200	1300	750	
Q2	1200	1000	900	
Q3	1100	800	1000	
Q4	1400	800	550	
Dialysis modality, n (%)				< 0.001
No Dialysis History	5000	0 (0)	1500	
Hemodialysis	0 (0)	3800	2200	
Peritoneal dialysis	0 (0)	1000	800	
Mixed dialysis	0 (0)	200	500	
Dialysis duration, years	0 ± 0	2.86 ± 3.03	2.82 ± 3.21	< 0.0001
< 3 months	5000	1000	1600	< 0.0001
3 months-1 year	0 (0)	1600	600	
1–2 years	0 (0)	700	400	
2–3 years	0 (0)	500	400	
3–4 years	0 (0)	350	300	
4–5 years	0 (0)	300	350	
> 5 years	0 (0)	550	1350	
Induction medication, n (%)				< 0.0001
No use	5000	5000	200	
Antithymocyte glubulin	0 (0)	0 (0)	400	
Baxiliximab	0 (0)	0 (0)	4400	
Desensitization, n (%)				< 0.0001
No	5000	5000	4300	
Yes	0 (0)	0 (0)	700	
CNI for maintenance therapy, n (%)				< 0.0001
None	5000	5000	100	
Tacrolimus	0 (0)	0 (0)	4200	
Cyclosporin	0 (0)	0 (0)	700	

The mean age of the subjects was 46.4 ± 11.6 years and majority of subjects were men. There was a significant difference in income among the study groups (P < 0.0001). A larger proportion of KTRs and ESRD patients had a history of underlying chronic disease such as DM, HTN, and dyslipidemia when compared with healthy control (all Ps < 0.0001). Among the ESRD patients, 76% of the patients under- went hemodialysis, 20% underwent peritoneal dialysis, and 4% underwent mixed dialysis. Among the KTRs, 30% had no dialysis history, 44% underwent hemodialysis, and 16% underwent peritoneal dialysis before KT. For KTRs, 96% of the recipients received induction medication. Almost all the KTRs were prescribed calcineurin inhibitor for maintenance therapy and 14% of the KTRs experienced desensitization. The KTRs took postoperative immunosuppressant and

corticosteroid as a maintenance therapy to prevent graft rejection.

Table 2: POAG incidence in ESRD patients, KTRs, and healthy controls

Group	N	POAG Incidence	Duration (person-years)	Incidence rate (/1,000 person-years)	Unadjusted		Model 1		Model 2	
					HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Healthy Control	5000	77	64,358.35	1.20	1 (Ref.)		1 (Ref.)		1 (Ref.)	
ESRD	5000	180	53,507.48	3.36	2.83 (2.17–3.70)	< 0.0001	2.95 (2.26–3.85)	< 0.0001	1.43 (0.97–2.12)	0.07
KTR	5000	200	62,107.74	3.22	2.69 (2.07–3.50)	< 0.0001	2.72 (2.09–3.54)	< 0.0001	1.41 (0.96–2.07)	0.08
ESRD	5000	180	53,507.48	3.36	1 (Ref.)		1 (Ref.)		1 (Reference)	
KTR	5000	200	62,107.74	3.22	0.95 (0.78–1.17)	0.65	0.928 (0.76–1.14)	0.47	1.02 (0.83–1.26)	0.84

When adjusted for age and sex (Model 1), ESRD patients (HR = 2.95, P < 0.0001) and KTRs (HR = 2.72, P < 0.0001) had increased risk of POAG than healthy controls. How- ever, there were no significant increase in the risks of POAG neither in ESRD patients (P = 0.07) nor KTRs (P = 0.08) when adjusted for age, sex, DM, HTN, dyslipidemia, income, and CCI (Model 2). There was no significant difference in POAG incidence rates between ESRD patients and KTRs.

Table 3: PACG incidence in ESRD patients, KTRs, and healthy controls

Group	N	PCAG incidence	Duration (person-years)	Incidence rate (/1000 person-years)	Unadjusted		Model 1		Model 2	
					HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Healthy Control	5000	9	64,358.35	0.14	1 (Ref.)		1 (Ref.)		1 (Ref.)	
ESRD	5000	22	53,507.48	0.41	2.84 (1.31–6.18)	0.008	3.00 (1.38–6.52)	0.006	3.50 (1.08–11.31)	0.036
KTR	5000	8	62,107.74	0.13	0.92 (0.35–2.38)	0.86	0.93 (0.36–2.42)	0.89	1.20 (0.33–4.40)	0.78
ESRD	5000	22	53,507.48	0.41	1 (Ref.)		1 (Ref.)		1 (Ref.)	
KTR	5000	8	62,107.74	0.13	0.95 (0.78–1.17)	0.65	0.32 (0.14–0.72)	0.006	0.35 (0.15–0.82)	0.015

The incidence rate of PACG was significantly greater in ESRD patients (0.41/1,000 person-years) than in healthy controls (0.14/1,000 person-years, P = 0.008). However, there was no significant difference in PACG incidence rate between KTRs (0.13/1,000 person-years) and healthy controls (P = 0.86). This outcome remained unchanged even when the subjects were adjusted for age and sex (Model 1), or age, sex, DM, HTN, dyslipidemia, income, and CCI (Model 2).

Discussion

Glaucoma is one of the leading causes of irreversible blindness, and the number of glaucoma patients is estimated to increase to 111.8 million by 2040. [15,16] The worldwide prevalence of primary open-angle glaucoma (POAG) and primary angle-closure glaucoma (PACG) is estimated to be 3.54% and 1.09%, respectively. [16] Although PACG is estimated to affect approximately 26% of the entire glaucoma population, it is responsible for nearly half the cases of glaucoma-related blindness worldwide. [15] Considering that Asia accounts for approximately 60% of world's population and has a rapidly aging society, the burden of glaucoma is expected to increase disproportionately in Asia. [16,17]

The mean age of the subjects was 46.4 ± 11.6 years and majority of subjects were men. There was a significant difference in income among the study groups (P < 0.0001). A larger proportion of KTRs and ESRD patients had a history of underlying chronic disease such as DM, HTN, and dyslipidemia when compared with healthy control (all Ps < 0.0001). Among the ESRD patients, 76% of the patients under- went hemodialysis, 20% underwent peritoneal dialysis, and 4% underwent mixed dialysis. Among the KTRs, 30% had no dialysis history, 44% underwent hemodialysis, and 16% underwent peritoneal dialysis before KT. For KTRs, 96% of the recipients received induction medication. CKD and major eye diseases are assumed to share common risk factors, including age, smoking, DM, HTN, obesity, and dyslipidemia. Moreover, it is well known that the risk of vision threatening diseases such as age-related macular degeneration and diabetic retinopathy increases in CKD patients. [18,19] However, whether the risk of developing POAG in CKD patients increases remains

controversial. A study of 3,280 Malaysian adults reported that IOP was higher in CKD patients than in those without CKD; however, the study reported no association between CKD and glaucoma. [20]

Almost all the KTRs were prescribed calcineurin inhibitor for maintenance therapy and 14% of the KTRs experienced desensitization. The KTRs took postoperative immunosuppressant and corticosteroid as a maintenance therapy to prevent graft rejection. There was no significant difference in POAG incidence rates between ESRD patients and KTRs. Approximately 30% of KTRs are known to experience acute kidney transplant rejection [21,22] and the mainstay of treatment for graft rejection is high-dose steroid pulse therapy. [23]

The incidence rate of PACG was significantly greater in ESRD patients (0.41/1,000 person-years) than in healthy controls (0.14/1,000 person-years, P = 0.008). However, there was no significant difference in PACG incidence rate between KTRs (0.13/1,000 person-years) and healthy controls (P = 0.86). This outcome remained unchanged even when the subjects were adjusted for age and sex (Model 1), or age, sex, DM, HTN, dyslipidemia, income, and CCI (Model 2). The reported effect of hemodialysis on IOP in the existing literature is inconsistent: the IOP can rise, decrease, or may not change. [24] Hemodialysis can cause complex hemodynamic changes in the ocular structure. During hemodialysis, the rapid decrease in plasma osmolality and relative increase in intracellular urea concentration results in a gradient between plasma and ocular compartments. [25] The present results revealed that PACG risk was significantly greater in ESRD patients. Hemodialysis can alter the angle structure or anterior chamber depth (ACD). Rever et al [26] reported significant decrease of ACD during acetate hemodialysis, but not with bicarbonate hemodialysis.

Conclusion

In conclusion, the present nationwide population-based cohort study showed that there was no significant association of POAG incidence risk in ESRD patients and KTRs after controlling for multiple confounding factors. However, the PACG risk was significantly increased in ESRD patients. Interestingly, KT reduced the risk of PACG in ESRD patients to a level similar to that in healthy controls. Thus, it would be prudent to monitor the onset of PACG in high-risk ESRD patients. Furthermore, as ESRD and POAG share common risk factors, it is important to monitor ESRD patients for the development of POAG.

References

1. Tham YC, Li X, Wong TY, Quigley HA, Aung T, Cheng CY. Global prevalence of glaucoma and projections of glaucoma burden through 2040: a systematic review and meta-analysis. Ophthalmology. 2014;121(11):2081–2090.
2. Kyu HH, Abate D, Abate KH, et al. Global, regional, and national disability-adjusted life-years (DALYs) for 359 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990−2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet North Am Ed. 20 18;392(10159):1859–1922.
3. Chen TK, Knicely DH, Grams ME. Chronic kidney disease diagnosis and management: a review. JAMA. 2019;322(13):1294–1304.
4. Wong CW, Wong TY, Cheng CY, Sabanayagam C. Kidney and eye diseases: common risk factors, etiological mechanisms, and pathways. Kidney Int. 2014;85(6):1290–1302.
5. 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):1981–1988.
6. Wang TJ, Wu CK, Hu CC, Keller JJ, Lin HC. Increased risk of comorbid eye disease in patients with chronic renal failure: a population-based study. Ophthalmic Epidemiol. 2012;19(3):137–143.
7. Park SJ, Byun SJ, Park JY, Kim M. Primary open-angle glaucoma and increased risk of chronic kidney disease. J Glaucoma. 2019;28 (12):1067–1073.
8. Nongpiur ME, Wong TY, Sabanayagam C, Lim SC, Tai ES, Aung T. Chronic kidney disease and intraocular pressure: the Singapore Malay Eye Study. Ophthalmology. 2010;117 (3):477–483.
9. 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. EBio Medicine. 2016;5:193–197.
10. 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):1298–1303.
11. Miglior S, Bergamini F, Migliavacca L, Marighi P, Orzalesi N. Metabolic and social risk factors in a cataractous population. InRisk Factors for Cataract Development 1989 (Vol. 17, pp. 158-164). Karger Publishers.
12. Kasiske BL, Zeier MG, Chapman JR, Craig JC, Ekberg H, Garvey CA, Green MD, Jha V, Josephson MA, Kiberd BA, Kreis HA, McDonald RA, Newmann JM, Obrador GT, Vincenti FG, Cheung M, Earley A, Raman G, Abariga S, Wagner M, Balk EM; Kidney Disease: Improving Global Outcomes. KDIGO clinical practice guideline for the care of kidney

transplant recipients: a summary. Kidney Int. 2010 Feb;77(4):299-311.
13. Park S, Kim M, Kim JE, Kim K, Park M, Kim YC, Joo KW, Kim YS, Lee H. Characteristics of kidney transplantation recipients over time in South Korea. Korean J Intern Med. 2020 Nov;35(6):1457-1467.
14. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: develop ment and validation. J Chronic Dis. 1987; 40(5):373-83.
15. Quigley HA, Broman AT. The number of people with glaucoma worldwide in 2010 and 2020. Br J Ophthalmol. 2006 Mar;90(3):262-7.
16. Tham YC, Li X, Wong TY, Quigley HA, Aung T, Cheng CY. Global prevalence of glaucoma and projections of glaucoma burden through 2040: a systematic review and meta-analysis. Ophthalmology. 2014 Nov;121(11): 2081-90.
17. Chan EW, Li X, Tham YC, Liao J, Wong TY, Aung T, Cheng CY. Glaucoma in Asia: regional prevalence variations and future projections. Br J Ophthalmol. 2016 Jan;100 (1) :78-85.
18. Deva R, Alias MA, Colville D, Tow FK, Ooi QL, Chew S, Mohamad N, Hutchinson A, Koukouras I, Power DA, Savige J. Vision-threatening retinal abnormalities in chronic kidney disease stages 3 to 5. Clin J Am Soc Nephrol. 2011 Aug;6(8):1866-71.
19. Nusinovici S, Sabanayagam C, Teo BW, Tan GSW, Wong TY. Vision Impairment in CKD Patients: Epidemiology, Mechanisms, Differential Diagnoses, and Prevention. Am J Kidney Dis. 2019 Jun;73(6):846-857.
20. Nongpiur ME, Wong TY, Sabanayagam C, Lim SC, Tai ES, Aung T. Chronic kidney disease and intraocular pressure: the Singapore Malay Eye Study. Ophthalmology. 2010 Mar; 117(3):477-83.
21. Go J, Ko K, Jun D, Kwon SK, Han S, Kim YH, Kim MH, Jun KW, Hwang J, Kim SD, Park SC, Kim JI, Yun SS, Moon I. A Half-Century 3000 Cases of Kidney Transplant Experiences in a Single Hospital: the Longest Registry in Korea. Transplant Proc. 2019 Oct; 51(8):2559-2567.
22. Koo EH, Jang HR, Lee JE, Park JB, Kim SJ, Kim DJ, Kim YG, Oh HY, Huh W. The impact of early and late acute rejection on graft survival in renal transplantation. Kidney Res Clin Pract. 2015 Sep;34(3):160-4.
23. Kasiske BL, Zeier MG, Chapman JR, Craig JC, Ekberg H, Garvey CA, Green MD, Jha V, Josephson MA, Kiberd BA, Kreis HA, McDonald RA, Newmann JM, Obrador GT, Vincenti FG, Cheung M, Earley A, Raman G, Abariga S, Wagner M, Balk EM; Kidney Disease: Improving Global Outcomes. KDIGO clinical practice guideline for the care of kidney transplant recipients: a summary. Kidney Int. 2010 Feb;77(4):299-311.
24. Levy J, Tovbin D, Lifshitz T, Zlotnik M, Tessler Z. Intraocular pressure during haemodialysis: a review. Eye (Lond). 2005 Dec;19(12):1249-56.
25. SITPRIJA V, HOLMES JH, ELLIS PP. CHANGES IN INTRAOCULAR PRESSURE DURING HEMODIALYSIS. Invest Ophthalmol. 1964 Jun;3:273-84.
26. Rever B, Fox L, Christensen R, Bar-Khayim Y, Nissenson AR. Adverse ocular effects of acetate hemodialysis. Am J Nephrol. 1983 Jul-Aug;3(4):199-204.