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Association between macular degeneration and mild to moderate chronic kidney disease

A nationwide population-based study

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Abstract

Chronic kidney disease (CKD) and macular degeneration (MD) are 2 grave diseases leading to significant disability secondary to renal failure and blindness. The 2 diseases share not only common risk factors but also similar pathogenic mechanisms to renal and retinal injuries. Previous epidemiological studies indicated association between these 2 diseases. However, this concept is challenged by recent investigations. Patients with mild to moderate CKD (n = 30,696) between January 1, 1995 and December 31, 2005 were selected from the Taiwan National Health Insurance Database. Controls (n = 122,784) were matched by age, gender, diabetes mellitus type 2, and hypertension status (1:4 ratios). The risk of MD was compared between the 2 groups. The mean age of patients was 54.9 ± 15.7 years. The proportion of MD was 2.7% in mild to moderate CKD patients and 1.9% in normal controls ($P < 0.001$); and, 0.39% and 0.26% ($P < 0.001$) in advanced MD. Mild to moderate CKD patients had higher risk for MD [adjusted odds ratio (OR), 1.301; 95% confidence interval (CI), 1.200–1.411; $P < 0.001$] than normal renal function subjects. The association was more pronounced for advanced MD. From all age strata (10 years increase), the presence of CKD in those patients aged less than 40 years had highest OR for all MD (OR = 2.125, 95% CI: 1.417–3.186, $P < 0.001$). The results were consistent in interaction terms, highlighting the importance of CKD in young age patient for risk of MD. The high risk for MD in mild to moderate CKD patients remains significant after adjustment for personal habits (alcohol drinking and smoking, model 1; OR: 1.371; 95% CI: 1.265–1.486; $P < 0.001$), comorbidities (dyslipidemia, cerebrovascular disease, and peripheral vascular disease, model 2; OR: 1.369; 95% CI: 1.264–1.484; $P < 0.001$) and all these factors (model 3; OR: 1.320, 95% CI: 1.218–1.431, $P < 0.001$). This association was consistent in the subanalysis, excluding those patients with diabetic retinopathy. Proper diagnosis and timely intervention should be warranted to retard visual loss of these patients.

Abbreviations: CFH = complement factor H, CI = confidence interval, CKD = chronic kidney disease, eGFR = estimated glomerular filtration rate, ESRD = end-stage renal disease, ICD-9 = International Classification of Diseases, Ninth Revision, LHID 2005 = Longitudinal Health Insurance Database 2005, MD = macular degeneration, MESA = Multi-Ethnic Study of Atherosclerosis, NHANES III = Third National Health and Nutrition Examination Survey, NHI = National Health Insurance, OR = odds ratio.

Keywords: age, chronic kidney disease, eye, macular degeneration

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1. Introduction

The chronic kidney disease (CKD) and macular degeneration (MD) are high prevalent and devastating condition in Taiwan and worldwide. CKD is a global public health dilemma. It is associated with multiple comorbidities, progression to kidney failure, cardiovascular disease, and premature death.[1] MD is the leading cause of adult blindness in industrialized countries and it affects approximately 6 million persons globally.[2] The number of persons having MD or CKD will be expected to double by the year 2020, as a result of aging of the world's population. Both diseases are frequently present in the elderly people and share many common risk factors, such as hypertension,[3,4] obesity,[5] and smoking.[6,7] Patients with CKD have higher risk for many eye diseases, including diabetic retinopathy, glaucoma, and cataract. The association between type 2 membranoproliferative glomerulonephritis and cuticular drusen, a boundary form of age-related MD, has been well established. Both diseases shared high frequency of the genetic polymorphism in the complement factor H (CFH) gene.[8,9] However, the association between CKD and MD remains in debate. The Blue Mountains Eye Study found triple higher risk for development of age-related MD in patients having moderate CKD than normal/mild CKD patients after 5 years of follow-up.[9] A cross-sectional study enrolling matched subsets from Third National Health and Nutrition Examination Survey (NHANES III) participants, found that neither albuminuria nor estimated glomerular filtration rate (eGFR) were significant risk factors for any MD. However, the odds ratio (OR) was 3.05 [95% confidential interval (CI): 1.51–6.13; $P < 0.01$] for "late" MD in patients with eGFR < 60 mL/min.[10] Similarly, a hospital-based case–control study described a greater risk (OR: 1.94, $P = 0.01$) and more severe MD (OR: 11.31, $P < 0.01$) for patients having CKD stage 3 to 5 than stage 1 to 2.[11] More recently, in Multi-Ethnic Study of Atherosclerosis (MESA) Study, the risk of early MD did not increase in renal impaired patients, defined either by Cystatin C or eGFR, except for normotensive patients.[12] In Korean NHANES, serum creatinine was not a risk factor for early or late MD.[13] Because of all these controversies, the relationship between CKD and MD deserves further study to clarify its association.

Emerging evidences indicated that CKD and MD share not only many risk factors but also common pathogenic mechanisms to renal and retinal injuries, including atherosclerosis, endothelial dysfunction, oxidative stress, inflammation, altered genetic polymorphisms, and Klotho gene pathway.[4,8] Considering renal failure as a condition of premature aging, these pathways suggested biologically plausible mechanisms for an increased risk of MD in CKD patients from their early stage of life. It is unclear if MD could develop at a younger age in patients having CKD than normal function people.

Because of the extent, vulnerability and reversibility of organ damage in mild to moderate CKD patients, the unawareness of a diagnosis of MD in these people may impede opportunity to preserve their vision. It is mandatory to clarify this relationship because the coexistence of 2 diseases may adversely affect the quality of life and outcome of patients, and also have important public health implication to redefine the so-called "age-related macular degeneration" in CKD patients. The ascertainment of this association may provide evidence to warrant timely diagnosis and ophthalmologic intervention to retard visual loss in CKD patients. In this population-based study, we aim to elucidate the association between MD and mild to moderate CKD using a nationwide representative sample of patients with comparable baseline characteristics.

2. Materials and methods

2.1. Study design and patient setting

Patients enrolled in this population-based, cross-sectional, matched study were retrieved from the Longitudinal Health Insurance Database 2005 (LHID 2005), which covered almost 99% of the entire population of Taiwan in 2005. Taiwan launched a single-payer National Health Insurance (NHI) program in 1995. Of the 25.56 million individuals enrolled in this registry for the NHI program, the LHID 2005 randomly sampled 1,000,000 enrolled beneficiaries.[14]

Eligible study subjects were adult patients with prevalent CKD who had a diagnosis of CKD recorded in the database [International Classification of Diseases, Ninth Revision (ICD-9) codes 250.4, 274.1, 283.11, 403.1, 404.2, 404.3, 440.1, 442.1, 447.3, 572.3, 580–588, 593, 642.1, 646.2, and 753.1] between January 1, 1995, and December 31, 2005.[15,16] Exclusion criteria were those aged less than 18 years, had advanced CKD, a missing ID link and patients underwent dialysis therapy or renal transplantation. From all patients, 30,696 mild to moderate CKD patients were identified and enrolled for analysis. The reference non-CKD patients were retrieved from the remaining patients (n = 733,807) in the LHID2005. The selected 122,784 participants were matched with those in the CKD cohort (at 1:4 ratio) in terms of age, gender, presence of diabetes mellitus and hypertension (Fig. 1). This study compared the prevalence and risk of MD between CKD and non-CKD patients from homogenous comparable national representative samples. We identified patients having wet MD based on a diagnosis of ICD-9 code of 362.5 (degeneration of macula and posterior pole of retina), 362.50 (MD, senile, unspecified), 362.52 (exudative senile MD), or 362.53 (cystoid macular degeneration). We used ICD-9 code of 362.52 (exudative senile MD) to define neovascular MD and used this condition as surrogate of advanced MD. To increase the validity of diagnoses, we excluded those patients with concomitant diagnosis of central serous chorioretinopathy (ICD-9 code: 362.41) and pathologic myopia (ICD-9 code: 360.21), and only selected those patients if the diagnosis had being made by an ophthalmologist. In Taiwan, MD is meticulously diagnosed based on a review of the patient's medical history and one or more of several clinical examinations. All patients with suspicious of MD are screened with visual acuity, funduscopy, optical coherence tomography, fluorescein angiography, and indocyanine green angiography (if necessary). The ophthalmologist will chose an appropriate ICD-9 code for final diagnosis. Comorbidities, including cerebrovascular disease, myocardial infarction, congestive heart failure, peripheral vascular disease, peptic ulcer disease, dementia, and other neurological disorders were recorded if the diseases were ascertained before CKD diagnosis. This study employed deidentified secondary data from the NHI data set and it was exempted from institutional review board revision and the informed consent.

2.2. Disease definitions

We used codes from the ICD-9 to define diseases. Advanced CKD was defined for those patients with a primary diagnosis of CKD and had received erythropoietin-stimulating agents treatment,

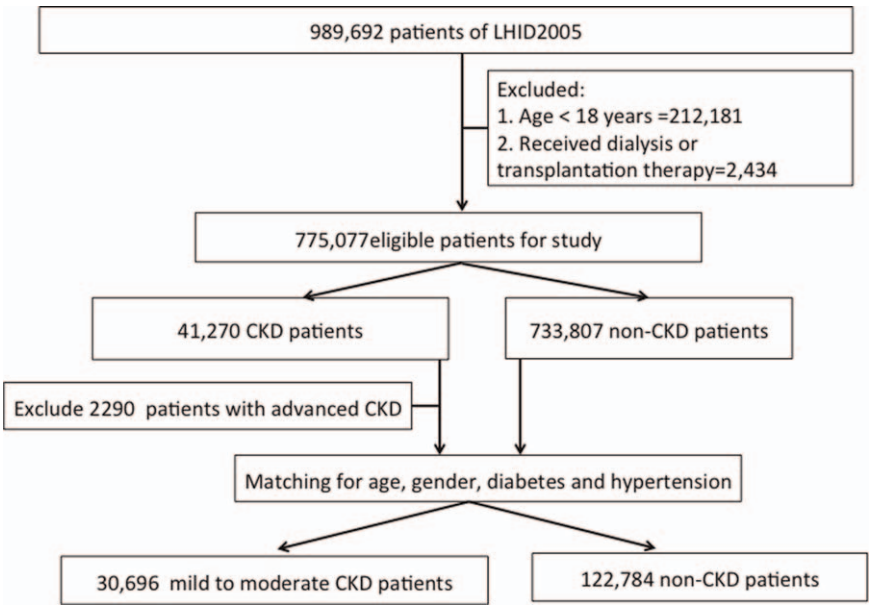

Figure 1. Study schema and patient flow. CKD = chronic kidney disease, LHID = Longitudinal Health Insurance Database.

indicating that their serum creatinine levels were greater than 6 mg/dL and hematocrit levels were less than 28%.[17] Patients with end-stage renal disease (ESRD) receiving dialysis were defined as those who had catastrophic illness registration cards for ESRD (ICD-9 code 585). Comorbidities were defined if the patient had at least three ambulatory claims or at least 1 inpatient claim with diagnosis of ICD-9 code 250 (Type 2 diabetes mellitus); 401 to 405 (hypertension); 272 (dyslipidemia); 430 to 438 (cerebrovascular disease); 410, 412 (myocardial infarction); 428 (congestive heart failure); 441, 443, 785 (peripheral vascular disease); 531 to 534 (peptic ulcer disease); 290 (dementia) or 344, 342 (other neurological disorders).[18]

2.3. Statistical analysis

Descriptive statistics were expressed as mean ± standard deviation or frequency (percentage) where was appropriate. All numerical variables were tested with normality by Kolmogorov–Simirnov test. The Student *t* test was applied to compare continuous variables between groups. Categorical data were tested with Chi-square test. We determined the OR for MD and CKD in every age group. Interaction terms of each cell of the cross-tabulation of age group × CKD were estimated by using the cell of age <40 years without CKD, as reference group. Conditional logistic regression was used to estimate OR and 95% CI associated with MD, followed by multivariate analysis. In addition, 3 multivariate models were considered to adjust for personal habit (alcohol use and smoking, model 1), comorbidities (cerebrovascular disease, myocardial infarction, congestive heart failure, peripheral vascular disease, peptic ulcer disease, dementia and other neurological disorders, model 2) and all of these factors (model 3). To control as possible the selection bias, we have re-sampled a subset of patients from exclusion of patient who had coding of 362.53, as indicative of exudative MD. Conditional logistic regression was applied again in this subanalysis. All statistical tests were 2-tailed, and a *P*-value of <0.05 was considered statistically significant. Data were analyzed using the Statistical Analysis System (SAS 9.2) software for Windows XP.

3. Results

The baseline characteristics of the study population are summarized in Table 1. A total of 153,480 patients were enrolled in this study: 30,696 mild to moderate CKD patients and 122,784 normal renal function subjects. The mean age of patients was 54.9 ± 15.7 years. From all patients, 79,175 (51.59%) were men. The primary etiology of CKD included: hypertension and renovascular, 39.93% (12257); diabetes, 19.58% (6011); chronic glomerulonephritis, 5.96% (1828); genitourinary, 1.53% (470); gout and hyperuricemia, 0.33% (101); polycystic kidney disease, 0.06 (18) and unknown or other cause, 32.61% (10011 patients). The patients having CKD were most likely to have dyslipidemia (28.89% vs 19.1%, $P < 0.001$), smoking (29.99% vs 22.59%, $P < 0.001$) and alcoholic drinking habit (25.78% vs 15.88%, $P < 0.001$) than normals. Mild to moderate CKD patients were also more likely to have the following comorbidities: cerebrovascular disease (12.87% vs 10.35%, $P < 0.001$), myocardial infarction (1.51% vs 1.26%, $P < 0.001$), congestive heart failure (3.38% vs 1.39%, $P < 0.001$), peripheral vascular disease (5.14% vs 3.41%, $P < 0.001$), peptic ulcer disease (37.98% vs 26.75%, $P < 0.001$), dementia (2.09% vs 1.69%, $P < 0.001$), and other neurological disorders (3.13% vs 2.31%, $P < 0.001$). The use of concomitant medication differed between the 2 groups of patients, especially for the use of oral beta-blockers (0.14% of CKD patients vs 0.66% of normal, $P < 0.001$), calcium channel blockers (1.1% vs 0.88%, $P < 0.001$), angiotensin converting enzyme inhibitor or angiotensin receptor blockers (0.43% vs 0.35%, $P = 0.04$) and diuretics (0.06% vs 0.03%, $P = 0.02$).

The proportions of all and advanced MD were greater in patients having mild to moderate CKD than normal renal function subjects (2.7% vs 1.9%, $P < 0.001$ and 0.39% vs 0.26%, $P < 0.001$, respectively, Table 1). Overall, the proportion of MD increased with age; however, mild to moderate CKD patients had higher proportion of MD than normal in all age strata (10 years increase), except for those patients aged greater than 80 years. The increased trend of MD with advance of age was more pronounced in CKD men than CKD women (Table 2).

Table 1

Baseline characteristics of study population.

	All	Normal	Mild to moderate CKD	*P*
Number	153,480	12,2784	30,696	
Age, mean	54.9±15.7	54.9±15.7	54.9±15.7	1
Age group, n (%)				1
<40 y, n (%)	26,690 (17.39%)	21,352 (17.39%)	5338 (17.39%)	
40–49 y, n (%)	32,495 (21.17%)	25,996 (21.17%)	6499 (21.17%)	
50–59 y, n (%)	37,745 (24.59%)	30,196 (24.59%)	7549 (24.59%)	
60–69 y, n (%)	25,030 (16.31%)	20,024 (16.31%)	5006 (16.31%)	
70–79 y, n (%)	21,545 (14.04%)	17,236 (14.04%)	4309 (14.04%)	
>80 y, n (%)	9975 (6.50%)	7980 (6.50%)	1995 (6.50%)	
Male, n (%)	79,175 (51.59%)	63,340 (51.59%)	15,835 (51.59%)	1
Diabetes, n (%)	30,055 (19.58%)	24,044 (19.58%)	6011 (19.58%)	1
Hypertension, n (%)	61,225 (39.89%)	48,980 (39.89%)	12,245 (39.89%)	1
Dyslipidemia, n (%)	32,322 (21.06%)	23,454 (19.1%)	8868 (28.89%)	<0.001
Alcohol drinking, n (%)	27,416 (17.86%)	19,504 (15.88%)	7912 (25.78%)	<0.001
Smoking, n (%)	36,940 (24.07%)	27,734 (22.59%)	9206 (29.99%)	<0.001
Comorbidities				
Cerebrovascular disease	16,665 (10.86%)	12,714 (10.35%)	3951 (12.87%)	<0.001
Myocardial infarction	2006 (1.31%)	1543 (1.26%)	463 (1.51%)	0.005
Congestive heart failure	3481 (2.27%)	2445 (1.39%)	1036 (3.38%)	<0.001
Peripheral vascular disease	5760 (3.75%)	4181 (3.41%)	1579 (5.147%)	<0.001
Peptic ulcer disease	44,508 (29.00%)	32,850 (26.75%)	11,658 (37.98%)	<0.001
Dementia	2711 (1.77%)	2069 (1.69%)	642 (2.09%)	<0.001
Other neurological disorders	3797 (2.47%)	2835 (2.31%)	962 (3.13%)	<0.001
Area				<0.001
North	67,096 (43.72%)	54,835 (44.66%)	12,261 (39.94%)	
Middle	36,291 (23.65%)	28,786 (23.44%)	7505 (24.45%)	
Southern	41,599 (27.10%)	32,563 (26.52%)	9036 (29.44%)	
East	6776 (4.41%)	5754 (4.69%)	1022 (3.33%)	
Land	1051 (0.68%)	815 (0.66%)	236 (0.77%)	
Missing	667 (0.43%)	31 (0.03%)	636 (2.07%)	
Low subsidy, n (%)	1407 (0.92%)	1108 (0.90%)	299 (0.97%)	0.23
Drugs				
Aspirin	551 (0.36%)	408 (0.33%)	143 (0.47%)	0.005
Oral beta blocker	1034 (0.67%)	814 (0.66%)	220 (0.14%)	0.303
Calcium channel blocker	1419 (0.92%)	1082 (0.88%)	337 (1.10%)	0.004
ACEI/ARB	562 (0.37%)	431 (0.35%)	131 (0.43%)	0.049
Diuretics	53 (0.03%)	36 (0.03%)	17 (0.06%)	0.027
Macular degeneration, n (%)	3111 (2.00%)	2289 (1.90%)	822 (2.70%)	<0.001
Advanced MD, n (%)	436 (0.28%)	316 (0.26%)	120 (0.39%)	<0.001

Smoking indicated current and former smoking.

ACEI = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker, CKD = chronic kidney disease, MD = macular degeneration.

Table 2

Proportion of all macular degeneration in both groups by age and gender.

			No. of macular degeneration						
Total	**No. at risk**	**%**	**All**	**%**	**Normal**	**%**	**CKD**	**%**	***P* (normal vs CKD)**
<40 y, n (%)	26,690	17.39	104	0.39	68	0.32	36	0.67	<0.001
40–49 y, n (%)	32,495	21.17	246	0.76	185	0.71	61	0.94	0.05
50–59 y, n (%)	37,745	24.59	466	1.23	335	1.11	131	1.74	<0.001
60–69 y, n (%)	25,030	16.31	684	2.73	486	2.43	198	3.96	<0.001
70–79 y, n (%)	21,545	14.04	1014	4.71	755	4.38	259	6.01	<0.001
>80 y, n (%)	9975	6.50	597	5.98	460	5.76	137	6.87	0.06
Man									
<40 y, n (%)	14,620	18.47	59	0.4	41	0.35	18	0.62	0.04
40–49 y, n (%)	17,020	21.50	162	0.95	123	0.9	39	1.15	0.19
50–59 y, n (%)	18,515	23.38	259	1.4	179	1.21	80	2.16	<0.001
60–69 y, n (%)	11,675	14.75	294	2.52	218	2.33	76	3.25	0.01
70–79 y, n (%)	12,340	15.59	580	4.7	418	4.23	162	6.56	<0.001
>80 y, n (%)	5005	6.32	295	5.89	228	5.69	67	6.69	0.23
Woman									
<40 y, n (%)	12,070	16.24	45	0.37	27	0.28	18	0.75	<0.001
40–49 y, n (%)	15,475	20.83	84	0.54	62	0.5	22	0.71	0.15
50–59 y, n (%)	19,230	25.88	207	1.08	156	1.01	51	1.33	0.09
60–69 y, n (%)	3355	17.97	390	2.92	268	2.51	122	4.57	<0.001
70–79 y, n (%)	9205	12.39	434	4.71	337	4.58	97	5.27	0.20
>80 y, n (%)	4970	6.69	302	6.08	232	5.84	70	7.04	0.15

CKD = chronic kidney disease.

Table 3

Odd ratios for macular degeneration by age groups and its interaction with CKD.

	All-macular degeneration				
	Normal (%)	CKD (%)	OR	95% CI	*P*
Age group, y					
<40	0.32%	0.67%	2.125	1.417–3.186	<0.001
40–49	0.71%	0.94%	1.322	0.988–1.767	0.059
50–59	1.11%	1.74%	1.570	1.284–1.929	<0.001
60–69	2.43%	3.96%	1.656	1.399–1.959	<0.001
70–79	4.38%	6.01%	1.396	1.207–1.614	<0.001
>80	5.76%	6.87%	1.205	0.989–1.469	0.063
Age group, y × CKD					
40–49 × CKD (vs <40 y)			0.622	0.378–1.024	0.062
50–59 × CKD (vs <40 y)			0.741	0.471–1.166	0.194
60–69 × CKD (vs <40 y)			0.779	0.502–1.208	0.265
70–79 × CKD (vs <40 y)			0.657	0.427–1.010	0.056
>80 × CKD (vs <40 y)			0.567	0.361–0.890	0.014

CI = confidence interval, CKD = chronic kidney disease, OR = odd ratios.

The OR of CKD to normal for association of all-MD was analyzed by age group and by interaction terms (age group × CKD, Table 3). The presence of CKD in those patients aged less than 40 years had highest OR for all MD (OR = 2.125, 95% CI: 1.200–1.411, $P < 0.001$). The results were consistent in interaction terms, highlighting the importance of CKD in young age patient for risk of MD. Conditional logistic regression identified the presence of CKD (OR = 1.301, 95% CI: 1.200–1.411, $P < 0.001$), dyslipidemia (OR: 1.257, 95% CI: 1.159–1.363, $P < 0.001$), cerebrovascular disease (OR: 1.238, 95% CI: 1.133–1.351, $P < 0.001$), peripheral vascular disease (OR: 1.169, 95% CI: 1.025–1.334, $P < 0.001$), peptic ulcer disease (OR: 1.218, 95% CI: 1.131–1.313, $P < 0.001$), alcohol drinking (OR: 1.220, 95% CI: 1.120–1.329, $P < 0.001$), and smoking habit (OR: 1.233, 95% CI: 1.143–1.331, $P < 0.001$) as significant independent factors associated with MD (Tables 4 and 5). In multivariate analyses, the association between CKD and MD remained significant after adjusting for personal habits (alcohol drinking and smoking, model 1; OR: 1.371; 95% CI: 1.265–1.486; $P < 0.001$), comorbidities (dyslipidemia, cerebrovascular disease, and peripheral vascular disease, model 2; OR: 1.369; 95% CI: 1.264–1.484; $P < 0.001$) and all these factors (model 3; OR: 1.320, 95% CI: 1.218–1.431, $P < 0.001$; Table 6).

Patients with diabetic retinopathy were also included in the analysis. The fact that the selected 122,784 participants were matched with those in the CKD cohort (at 1:4 ratio) in terms of age, gender, presence of diabetes mellitus and hypertension does not mean that the severity of the diabetic retinopathy was similar

Table 4

Conditional logistic regression of factors associated with all macular degeneration.

	Univariate analysis			Multivariate analysis		
	OR	95% CI	*P*	OR	95% CI	*P*
CKD (vs normal)	1.437	1.327–1.327	<0.0001	1.301	1.200–1.411	<0.001
Age	–					
Male gender (vs woman)	–					
Diabetes (vs no)	–					
Hypertension (vs no)	–					
Low subsidy (vs no)	1.027	0.727–0.727	0.8803			
Dyslipidemia	1.381	1.275–1.275	<0.0001	1.257	1.159–1.363	<0.001
Cerebrovascular disease	1.348	1.236–1.236	<0.0001	1.238	1.133–1.351	<0.001
Myocardial infarction	1.089	0.875–0.875	0.4476			
Congestive heart failure	1.064	0.891–0.891	0.4942			
Peripheral vascular disease	1.335	1.172–1.172	<0.0001	1.169	1.025–1.334	0.01
Peptic ulcer disease	1.373	1.278–1.278	<0.0001	1.218	1.131–1.313	<0.001
Dementia	1.016	0.851–0.851	0.8634			
Alcohol drinking	1.383	1.273–1.273	<0.0001	1.220	1.120–1.329	<0.001
Smoking	1.354	1.257–1.257	<0.0001	1.233	1.143–1.331	<0.001
Aspirin	1.239	0.847–0.847	0.2703			
Calcium channel blocker	0.897	0.673–0.673	0.4584			
ACEI/ARB	1.14	0.672–0.672	0.7048			
Area		—				
Middle	0.981	0.904–0.904	0.6485			
Southern	1.061	0.982–0.982	0.1337			
East	1.063	0.909–0.909	0.4471			
Land	0.907	0.606–0.606	0.6342			

ACEI = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker, CI = confidence interval, CKD = chronic kidney disease, OR = odds ratio.

Table 5

Conditional logistic regression of factors associated with advanced macular degeneration.

	Univariate analysis			Multivariate analysis		
	OR	95% CI	*P*	OR	95% CI	*P*
CKD (vs normal)	1.535	1.244–1.894	<0.0001	1.491	1.203–1.848	<0.001
Age	—					
Male gender (vs woman)	—					
Diabetes (vs no)	—					
Hypertension (vs no)	—					
Low subsidy (vs no)	0.423	0.105–1.699	0.2254			
Dyslipidemia	1.356	1.097–1.677	0.0048	1.194	0.963–1.481	0.107
Cerebrovascular disease	1.085	0.858–1.371	0.497			
Myocardial infarction	0.789	0.425–1.5	0.4837			
Congestive heart failure	0.903	0.551–1.477	0.6833			
Peripheral vascular disease	1.353	0.967–1.894	0.0781			
Peptic ulcer disease	1.291	1.006–1.477	0.043	1.169	0.96–1.423	0.120
Dementia	0.741	0.445–1.233	0.249			
Alcohol drinking	1.322	1.064–1.667	0.0123	1.242	0.986–1.565	0.066
Smoking	1.097	0.899–1.338	0.3629			
Aspirin	0.578	0.144–2.324	0.4399			
Calcium channel blocker	0.993	0.491–2.010	0.9843			
ACEI/ARB	1.098	0.706–1.708	0.6711			
Area						
Middle	0.523	0.405–0.676	<0.0001	0.516	0.399–0.667	<0.001
Southern	0.545	0.428–0.693	<0.0001	0.532	0.417–0.677	<0.001
East	0.678	0.434–1.061	0.0888	0.681	0.435–1.065	0.092
Land	0.832	0.309–2.239	0.7154	0.847	0.314–2.281	0.742

ACEI = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker, CKD = chronic kidney disease, OR = odds ratio.

in both groups. To control as possible the selection bias, we have resampled a subset of patients from exclusion of patient who had coding of 362.53, as indicative of exudative AMD. This condition represented macular edema related to diabetes or to retinal vein occlusions. A total of 595 patients were excluded for subanalysis. Again, the same matching strategy was applied for this subset analysis (n = 151,400; CKD = 30,280 and normal = 121,120). The mean age of resampling subset was 54.8 ± 15.8 years and 49% of them were men. Hypertension was present in 39.8% and diabetes in 19.3% of resampling population. The OR for CKD for all-MD or advanced MD remained significantly high in the resampling subset, after adjustment for personal habit, comorbidities, and combination of all these factors (Table 7).

4. Discussion

In this nationwide population-based study using patients of comparable baseline characteristics, we found that patients with mild to moderate CKD have higher risk for MD than non-CKD patients. The association was more pronounced for advanced MD. This association was independent of common risk factors of MD, including smoking, alcohol use, and comorbidities (dyslipidemia, cerebrovascular disease, and peripheral vascular disease), and, even in the subanalysis, excluding those patients with diabetic retinopathy. A novel finding of the study was the highest risk associated with MD in CKD patients having age less than 40 years, compared with those CKD patients of older age strata. Traditionally, a diagnosis of MD is usually suspected when the age of patient having visual abnormality exceed 50 years old.[19] Given the significant burden of CKD worldwide, especially the mild to moderate stage patients, and the devastating condition associated with MD and consequent blindness; proper diagnosis and timely intervention to these diseases should be warranted. Funduscopic examination should be warranted to all mild to moderate CKD patients with visual impairment, and

Table 6

Multivariate conditional logistic regression analysis for association of CKD with macular degeneration.

	OR	95% CI	*P*
All macular degeneration			
Model 1, adjusted for personal habit	1.371	1.265–1.486	<0.001
Model 2, adjusted for comorbidities	1.369	1.264–1.484	<0.001
Model 3, adjusted for all factors of model 1 and 2	1.320	1.218–1.431	<0.001
Advanced macular degeneration			
Model 1, adjusted for personal habit	1.494	1.209–1.847	<0.001
Model 2, adjusted for comorbidities	1.476	1.194–1.825	<0.001
Model 3, adjusted for all factors of model 1 and 2	1.447	1.169–1.791	<0.001

CKD = chronic kidney disease, OR = odds ratio.

Table 7

Multivariate conditional logistic regression analysis for association of CKD with macular degeneration in the resampling subset.

	OR	95% CI	*P*
All macular degeneration			
Model 1, adjusted for personal habit	1.353	1.246–1.469	<0.001
Model 2, adjusted for comorbidities	1.352	1.245–1.469	<0.001
Model 3, adjusted for all factors of model 1 and 2	1.304	1.200–1.417	<0.001
Advanced macular degeneration			
Model 1, adjusted for personal habit	1.572	1.263–1.956	<0.001
Model 2, adjusted for comorbidities	1.540	1.237–1.917	<0.001
Model 3, adjusted for all factors of model 1 and 2	1.522	1.221–1.897	<0.001

CKD = chronic kidney disease, OR = odds ratio.

a diagnosis of MD should be considered, even in the young age of presentation.

There are emerging studies indicating the association of CKD and MD. The structural, developmental, and physiological pathways of the kidney share similarities with the eye. Both organs have rich vascular networks. A variety of human genetic defects affect both organs causing congenital oculorenal syndromes. The 2 diseases have altered complement pathway, which trigger inflammation and leading to end organ damage among glomerular basement membrane and Bruch membrane of the retina.[20] Especially, the CFH polymorphisms increase the genetic risk of age-related MD and promote dense deposit disease in the kidney.[21] An animal model using transgenic mouse with high expression of CFH, demonstrated a dose-dependent protective effect in the function and structure of both eye and renal abnormalities.[22] In addition, the sharing of common cardiometabolic risks (hypertension, diabetes, dyslipidemia, and tobacco)[23] and pathogenic pathways (atherosclerosis, endothelial dysfunction, oxidative stress, inflammation, altered genetic polymorphisms, complement system dysfunction, and Klotho gene pathway) between these 2 diseases strengthens the supposition of this association.[3–5,8] Clinically, this association has been demonstrated from findings of several epidemiological studies, such as the Blue Mountains Eye Study,[9] case–control subset study of NHANES III,[10] and the Beaver Dam Eye Study.[24] However, this association becomes challenging in recent investigations. Neither the MESA study[12] nor the Korean NHANES[13] could find solid relationship between impaired renal function, expressed by Cystatin C, eGFR or serum creatinine, and MD. The controversies between studies in part could be explained by the difference of age of study population, the baseline comorbidities of involved patients and the methods used to define CKD. The 2 most recent studies[12,13] have enrolled patients with mean age approximately 10 years younger than the previous studies.[9,10,24] The patient enrollment criteria of MESA cohort have excluded participants with cardiovascular disease from the study. The Korean NHANES study found that serum creatinine did not associate with either early or late MD, after adjusting for age, gender, and smoking status.[13] To further clarify the inconsistence between various studies, we have used cohort of patients with matched baseline for important confounders (age, gender, diabetes, and hypertension status). The results of our study, that included a large sample of patients with a gamma of age diversities, have demonstrated the association between MD and mild to moderate CKD in all age strata. These findings may have considerable public and academic impact to diagnose and treat the MD in early stage of CKD patients in timely manner in order to preserve their vision.

The pooled overall prevalence of early and late MD in Asian (6.8% and 0.56%) was similar to Caucasians populations (8.8% and 0.59%) and varied by age groups and disease definition. The increased trend of MD with advance of age observed in our study was similar to previous results.[25] Meta-analysis studies have reported overall prevalence of late MD 2.3% in American white population aged 50 to 97 years[26]; and, 2.4% in United Kingdom population aged 50 or more.[27] Although the age-standardized prevalence of MD in CKD population remains largely unknown, the proportion of any MD among CKD patients could be as high as 29% (stage 1 to 2) to 44% (stage 3 to 5).[11] The risk for MD in our patients having mild to moderate CKD was highest for those aged less than 40 years (Table 3). The possible explanations to the occurrence of MD at early age in renal impaired patients included the defect of heparin sulfate, downregulation of Klotho gene and premature cell senescence associated with CKD. The heparin sulfate is a common proteoglycan of glomerular basement membrane and it is defective in the early kidney damage leading to development of albuminuria. The defect of heparin sulfate is also responsible for CFH polymorphisms observed in MD.[28] Downregulation of Klotho gene was associated with aging-related inflammation and early CKD in senescence-accelerated mice.[29] All these mechanistic evidences and clinical findings suggested younger presentation of MD in patients having renal dysfunction, even at early stage of CKD, than normal renal function subjects. A diagnosis of MD should be considered in all CKD patients having visual impairment, regardless of age of presentation.

The findings of present study may need further confirmations to indicate causal relationship between CKD and MD. Patients with advanced CKD are equivalents of vasculopathy because of the coexistence of many traditional cardiovascular risk factors and uremia-related risk factors. Anemia, acidosis, microinflammation, and malnutrition may have grave impact at different organ system, including the retina. We excluded patients having advanced CKD from the study because the presence of all these factors may obscure and confound the exact association of renal dysfunction with MD. In addition, the use of erythropoietin-stimulating agents in our advanced CKD patients may have effects on the relationship between 2 diseases. The presence of erythropoietin receptors in the retinal layers indicated possible developmental, physiologic, and therapeutic roles of erythropoietin in the eye.[30,31] The erythropoietin seems to have protective effects on the eye and play roles in the biological pathway of many ocular disorders such as diabetic retinopathy, retinopathy of prematurity, glaucoma, age-related MD, optic neuritis, and retinal detachment.[32–34] Recently, the relationship between advanced CKD patients, especially dialysis patients, and MD has been reported using similar national database.[35] Certainly, demonstration of association between mild to moderate CKD and MD will have significant impact because of high burden of early stage CKD worldwide.

Other limitations of generalizability were lined in factors including, homogeneous oriental ethnic group, cross-sectional nature, incomplete biochemistry parameters, use of diagnostic code to define disease (that could in part underestimate diseases with trivial symptoms or conditions occurred outside medical health system) and the lack of fundoscopic survey to evaluate the gravity of MD. Dietary consumptions of fish fatty acid, fish oil, omega-3, lutein, and antioxidants (vitamin A, E, C) have protective effects on the development of MD.[36–38] Unfortunately, dietary records were not available in the database. However, the eating habits of case and control patients may have shared similar racial, cultural, and religion factor since both groups of patients were residents of Taiwan. Topical Dorzolamide-Timolol With Intravitreous Anti-Vascular Endothelial Growth Factor may retard development of MD.[39] These medications were waived from NHI payment and could not be analyzed from database. Ultimately, family predispositions were not present in the database. However, the use of national representative large samples, extensive coverage of age stratum, and clinical risk factors with multiple adjustments sensitivity analyses have strengthened the conjecture of this study. The homogeneous comparable baseline characteristics of 2 groups may minimize the influence of confounding factors to the study. Clear and unbiased definition of disease by careful identification of diagnostic codes (the disease was ascertained if the diagnostic codes appeared at least in 3 ambulatory claims or at least 1 inpatient claim) may

allow accurate identification of patients with CKD or macular disease from registry database. Further prospective cohort study should be conducted to clarify the causality of these 2 diseases.

In conclusion, this nationwide population-based study enrolling comparable baseline characteristics patients (age, gender, diabetes, and hypertension matched cohort), has demonstrated the association of mild to moderate CKD and MD. The risk of MD was highest for CKD patients having age less than 40 years. This relationship was consistent in all age strata and it was independent of smoking, alcohol use, and comorbidities (dyslipidemia, cerebrovascular disease, and peripheral vascular disease). A diagnosis of MD should be considered in all mild to moderate CKD patients with visual impairment, even at young age of life. Additional study should be conducted to evaluate the exact mechanistic pathway underlying in CKD patients for development of MD.

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