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Association between Dry Age-Related Macular Degeneration, Chronic Kidney Disease and Hypertension: a Retrospective Chart Review Study

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Abstract

Background: Chronic kidney disease (CKD) and age-related macular degeneration (AMD) are two global health concerns that cause significant disability in the elderly. These two diseases share common risk factors and pathological mechanisms. This study investigates the association between hypertension (HTN), CKD and dry AMD in a diverse racial population.

Methods: Data from 8,837 participants aged 40-100 years was retrieved for this retrospective chart review study. Subjects were identified for HTN, CKD and dry AMD, using ICD-10 codes, from the database of University of Texas Medical Branch, Galveston. Patient demographics and their metabolic panels pertaining to kidney and HTN were collected. Logistic regression models were performed to study the association between HTN, CKD and dry AMD after adjusting for age, gender, race and smoking habits.

Results: The logistic regression model for the prevalence of dry AMD with HTN and CKD, excluding an interaction, but without adjustment for demographics (age, gender, race and smoking) suggest positive significant association between HTN and CKD. The coefficients of the model suggest that the odds of dry AMD is 1.4 folds higher for patients with CKD (p=007), and 1.6 folds higher in patients with HTN (p<0001). However, this relationship loses its significance after adjusting for demographic variables suggesting that the effect of CKD and HTN on dry AMD is mediated by age, gender and race. Logistic regression model stratified by race, relating prevalence of dry AMD to the presence of CKD after controlling for effects due to age, gender and HTN show no association of race with HTN. A significant association between dry AMD and CKD in the Hispanic population was noted; with odds of dry AMD being 2.4 folds higher than those without (OR 2.35, 95% 1.21-4.57; p=0.01).

Conclusion: Hypertension is a common risk factor for both dry AMD and CKD and therefore should be controlled at the primary care level so as to reduce the burden of concomitant diseases. Dry AMD is associated with CKD in Hispanic population, needs further studies. Nonetheless, yearly fundoscopic examination should be recommended for patients with HTN and CKD for early detection of dry AMD.

Keywords: Dry Age-related Macular Degeneration; Chronic Kidney Disease; Hypertension; Hispanics; Race

Abbreviations: HTN: Hypertension; CKD: Chronic Kidney Disease; AMD: Age-Related Macular Degeneration; GFR: Glomerular Filtration Rate; UTMB: University of Texas Medical Branch.

Introduction

Chronic kidney disease (CKD) and age-related macular degeneration (AMD) are major public health concerns in the recent years. This is due to the increasing prevalence of CKD and AMD in the aging population worldwide. In the US alone, the prevalence of CKD is projected to increase from 14.4% in 2020 to 16.7% in 2030; while the prevalence of AMD is estimated to double by 2050 [1]. CKD is usually defined as decreased glomerular filtration rate (GFR) of less than 60 mL/min per 1.73 m^2, or by markers of kidney damage e.g. proteinuria and elevated creatinine for at least 3 months [2]. Unfortunately, many cases of kidney failure go largely undiagnosed due to the lack of recognizable symptoms and in turn lead to premature death [3]. On the other hand, AMD is the leading cause of blindness in the elderly, especially those aged 50 and older [4]. Dry AMD, the more common form of the disease, is characterized by the accumulation of lipoprotein deposits called drusen under the retinal pigment epithelial (RPE) cells. Drusen accumulation further causes photoreceptor/RPE cell death, choroidal vascularization, and scarring leading to subsequent loss of vision [5]. Often, AMD has been noted to coexist with CKD and thus has led many investigators to study the relationship between the two diseases.

Both AMD and CKD share common risk factors such as hypertension [2,6], smoking [2,7], and obesity [2,8]. Besides the traditional risk factors, oxidative stress and endothelial dysfunction are also involved in the pathogenesis of both CKD and AMD [2,9]. Endothelial dysfunction due to atherosclerosis causes microvasculature damage and can occur both in kidney and the eyes [10-13]. In addition, an association between low eGFR rate, a marker for CKD and increased risk of late AMD has also been reported [14]. Hypertension, a major risk factor for CKD can cause atherosclerosis which in turn contributes to risk for AMD [15,16]. Because of this common pathogenesis, it is likely that there may be an association between HTN, CKD and AMD.

Although a relationship has been made between AMD and CKD in selected populations, the associated link with HTN remains elusive. The Beaver Dam Eye Study found an association between CKD and early AMD, but did not find an association with exudative AMD or with Geographic Atrophy [17]. In Taiwanese population, patients that have mild to moderate CKD are at a higher risk of developing AMD than those without CKD [18]. On the other hand, Korean subjects with CKD are twice as likely to have AMD or drusen compared to subjects without CKD. Similar conclusion was drawn from a meta-analysis pooled data from 12 studies, where higher rate of AMD in CKD population was found [19]. Indeed, these studies focused on a homogenous population of the Asia-Pacific region, which makes it challenging to generalize the results across other races. These studies also failed to consider comorbid diseases or diagnostic blood/urine parameters that may play a considerable role in AMD disease manifestation. In the current study we intend to elucidate the relationship between HTN, dry AMD and CKD using data from a population that comprises of diverse racial cohorts. Because, race may play a role in increased risk for AMD, we further explored if there could be an association between race, CKD and dry AMD. This study will help increase understanding of the prospective link between HTN, CKD and dry AMD triad so that when a diagnosis of CKD is made, ophthalmologic surveillance may be initiated.

Methods

Study Population

Patient data of enrolled subjects in this population based, cross-sectional study was retrieved from the database of University of Texas Medical Branch (UTMB) in Galveston from year 2009 to 2018. The chart review study was granted a waiver of informed consent by the Institutional Review Board in accordance with the tenets of the Declaration of Helsinki. The Galveston population comprises a diverse ethnicity and includes Caucasians, Hispanics, African Americans, and Asians. In brief, 8,837 participants between the of age 40-100 years old were identified by their visit for a comprehensive eye exam and also had a metabolic panel in the medical records for general health check at the UTMB hospital system.

Study Design and Clinical Data Retreival

Data was retrieved using the International Classification of Diseases, Tenth Revision (ICD-10) codes from the EPIC (electronic medical record) system. Eligible subjects included patients of any race and gender, aged 40-100 years of age who had a diagnosis of dry AMD (H35.31XX) irrespective of their disease stage, and/or chronic kidney disease (N18.X), including kidney failure due to genetic disease or due to an idiopathic cause and/or those with essential hypertension (I10). Patients with diagnosis of diabetes or exudative AMD were excluded from the study. Data collected from patient records included.

a) Demographics: age in years, gender, race, BMI, and smoking status (never, former, or current).

b) Lipid levels: triglycerides, HDL and LDL cholesterol.

c) Blood levels: serum albumin, eGFR (African American), BUN, creatinine.

d) Urinalysis for protein. v. Systolic and diastolic blood pressures.

Statistical Analysis

Patient characteristics were grouped by dry AMD status and are presented as mean and standard deviation or counts and percentages, with differences among groups assessed by t-test, or Chi-square test, as appropriate. Presence of dry AMD was modeled by logistic regression with relation to presence of CKD and HTN. The interaction between HTN and CKD was also tested. This model was further extended to include demographic characteristics. Stratified logistic regression models by HTN and race were also analyzed for presence of dry AMD. All reported p-values were two-sided with $p<0.05$ considered statistically significant. All statistical computation was performed using SAS version 9.4 (SAS Inc., Cary, North Carolina).

Results

Demographic Baseline and Clinical Characteristics

Table 1 shows the baseline characteristics of participants stratified by dry AMD status. A total of 8,837 subjects (mean age 72±11.1years) were enrolled in this study and were mostly Caucasians (63%), African Americans (18%) and Hispanic population (15%) followed others that consisted of Asians or of unknown race. Subjects with dry AMD were predominantly Caucasian, older in age, females, and former smokers and were likely to have hypertension (7.6% vs.4.6%) and CKD (9.6% vs. 6.1%). Based on clinical diagnosis, 58.9% of enrolled subjects were hypertensive, 482 (5.45%) had some form of dry AMD and 792 (8.96%) had CKD. Even though a large proportion of subjects were hypertensive, their systolic and diastolic means were lower than their non-hypertensive counter groups (P<.001). In addition, dry AMD patients tend to have lower diastolic BP, BMI, triglycerides, eGFR and serum albumin.

Characteristics	Category	Total	Dry AMD	No Dry AMD	p-value
			N (%)	N (%)	
CKD	No	7961	482 (6.1)	7479 (93.9)	<.0001
	Yes	876	84 (9.6)	792 (90.4)	
HTN	No	3631	168 (4.6)	3463 (95.4)	<.0001
	Yes	5206	398 (7.6)	4808 (92.4)	
Gender	Female	5558	384 (6.9)	5174 (93.1)	0.012
	Male	3279	182 (5.6)	3097 (94.4)	
Race/Ethnicity	Caucasians	5600	397 (7.1)	5203 (92.9)	<.0001
	Hispanics	1294	78 (6.0)	1216 (94)	
	African Americans	1583	66 (4.2)	1517 (95.8)	
	Other	360	25 (6.9)	335 (93.1)	
Smoking status	Never	4606	282 (6.1)	4324 (93.9)	<.0001
	Former	2382	196 (8.2)	2186 (91.8)	
	Current	1842	88 (4.8)	1754 (95.2)	
			Dry AMD	No dry AMD	
			Mean (SD)	Mean (SD)	
Age			75.1 (11.3)	64.2 (12.9)	<.0001
BMI			26.2 (5.6)	28.5 (6.4)	<.0001
Diastolic BP			76.5 (5.9)	78.0 (6.6)	<.0001
Systolic BP			135.0 (11.1)	131.8 (11.5)	<.0001
HDL			58.3 (17.8)	55.9 (16.8)	0.0021
LDL			109 (28.9)	110.8 (29.1)	0.1766

TRIGLYCERIDE			123.8 (55.8)	131.7 (69.0)	0.0114
BUN			17.5 (6.5)	16.2 (6.0)	<.0001
CREATININE			0.92 (0.4)	0.92 (0.6)	0.8979
ALBUMIN			4.1 (0.3)	4.2 (0.3)	<.0001
eGFR			92.5 (27.1)	96.9 (27.2)	<.0001
Urinary protein			11.2 (28.8)	9.41 (27.6)	0.1751

Table 1: Demographic variables of the study population stratified by dry AMD and no dry AMD.
All values are either % in brackets mean ± standard deviation. BMI, body mass index in kg/m^2; HDL, high-density lipoprotein; LDL, low-density lipoprotein; eGFR, estimated glomerular filtration rate;

Association between dry AMD, CKD and Hypertension

The logistic regression model for analyzing the prevalence of dry AMD with HTN and CKD, but without adjustment for demographics (age, gender, race and smoking) suggest positive significant association between dry AMD, HTN and CKD. However, when including interaction of dry AMD with HTN and CKD there was no significance (p=0.51). The coefficients of the model summarized in (Table 2, Model 1) suggest that the odds of dry AMD is 1.4 timeshigher for patients with CKD (p=.007), and 1.6 times higher in patients with HTN (p<.0001). However, this relationship loses its significance after adjusting for the demographic variables, (Table 2, Model 2), suggesting that the effect of CKD and HTN on dry AMD is mediated by age, gender and race. The odds of having dry AMD increases by 7% with each additional year of age (OR 1.07 95% CI 1.06-1.08; p<.0001), and is 0.7 times lower for males than females (OR 0.73 CI 95% 0.60 0.88; p=.001), and almost 2 times more prevalent in Caucasians (OR 0.54 CI 95% 0.41 0.71; p<.0001) than African Americans.

	Model 1	P value	Model 2	P value
	OR (95%CI)		OR (95%CI)	
Age			1.07 (1.06-1.08)	<.0001
Gender Male vs Female			0.73 (0.60-0.88)	0.0012
Race, Caucasians vs African Americans Hispanics Other			0.54 (0.41-0.71)	<.0001
			0.96 (0.74-1.24)	0.7343
			1.58 (1.01-2.45)	0.0428
Smoking, Never vs Former Current			1.06 (1.82-1.37)	0.5437
			1.06 (1.77-1.30)	0.6714
CKD (Yes)	1.41 (1.10-1.81)	0.0066	1.02 (0.78- 1.33)	0.8819
HTN	1.62 (1.34-1.96)	<.0001	1.08 (0.88 -1.32)	0.4557

Table 2: Multivariate logistic regression modeling the presence or absence of dry AMD.
Model 1: Is crude analysis and shows significant association of dry AMD with CKD and HTN and
Model 2: Shows loss of significance after adjustment for age, gender, race and smoking. OR, odds ratio; CI, confidence interval; CKD, chronic kidney disease, HTN, hypertension; dry AMD, dry age-related macular degeneration.

The prevalence of dry AMD for patients with or without HTN was also analyzed by age, gender, race, smoking habit and CKD (Table 3). Presence or absence of HTN did not show a significant association between dry AMD and CKD. However, when isolated the patients without HTN, the coefficients suggest that the odds of dry AMD increased with age (OR 1.089, CI 95% 1.07 1.10; p<001), were lower for males than females (OR.47, CI95% 0.32 .69; p<0001) and higher for Caucasians than African Americans (p=01). Additionally, the association with gender, lost significance in patients with HTN alone, however, age and Caucasian race vs African Americans continued to hold significance (OR 1.06 CI 95% 1.05 1.07; OR .58 CI 95% 0.43 0.78, p<001). Though not significant, the trend for gender agrees with that of prior models, with males trending lower in prevalence of dry AMD than females (OR 0.84 CI 95% 0.67 1.05, P=14).

	HTN Patients only OR (95%CI)	P value	Non-HTN Patients only OR (95%CI)	P value
Age	1.06 (1.05-1.07)	<0.001	1.089 (1.07-1.11)	<0.001
Gender (male)	0.85 (0.68-1.06)	0.1431	0.47 (0.32-0.69)	<.0001
Race: Caucasians vs African Americans Hispanics Other	0.58 (0.43-0.78)	<0.001	0.34 (0.15-0.78)	0.0115
	0.93 (0.66- 1.28)	0.6611	1.05 (0.66-1.67)	0.8346
	1.30 (0.71- 2.38)	0.39	2.26 (1.18-4.34)	0.0137
CKD (Yes)	1.00 (0.78-1.32)	0.9976	1.30 (0.55-3.05)	0.5543
Smoking Never vs Current vs Former	1.02 (0.75-1.40)	0.912	1.15 (0.72-1.83)	0.552
	1.17 (0.92-1.48)	0.1936	0.79 (0.53-1.17)	0.2427

Table 3: Logistic regression analysis for association of dry AMD with and without HTN.
In non-HTN patients, age, gender and Caucasian race vs. African Americans show significant association with dry AMD, whereas in the presence of HTN the significance of gender is lost. OR, odds ratio; CI, confidence interval; CKD, chronic kidney disease; HTN, hypertension; dry AMD, dry age-related macular degeneration.

Because, Caucasian race has correlated with higher prevalence of dry AMD consistently, we wanted to explore further if race had any associtaion with increased risk of dry AMD in CKD patients. Logistic regression model stratified by race, relating prevalence of dry AMD to the presence of CKD after controlling for effects due to age, gender and HTN is shown is Table 4. While the data show no association of race with HTN, the odds of dry AMD increases with age (p<.001) and is lower for males than females across all races (p<.05). However, in the Hispanic population there was a significant association between dry AMD and CKD with odds of dry AMD being 2.4 folds higher than those without (OR 2.35, 95% 1.21 4.57; p=.01).

	African Americans		Caucasians		Hispanics		Others	
	OR (CI % 95)	P	OR (CI % 95)	P	OR (CI % 95)	P	OR (CI % 95)	P
Age	1.04 (1.02-1.06)	<.001	1.08 (1.07-1.09)	<.0001	1.07 (1.05-1.09)	<.0001	1.06 (1.03-1.10)	0.0012
Gender (male)	0.43 (0.22-0.84)	0.0132	0.80 (0.64-0.10)	0.0485	0.48 (0.27-0.85)	0.0116	1.28 (0.51-3.35)	0.5991
CKD (Yes)	0.96 (0.53-1.75)	0.9	0.86 (0.63-0.24)	0.4746	2.35 (1.21-4.57)	0.0118	1.05 (0.19-5.71)	0.9558
HTN (Yes)	2.11 (0.88-5.07)	0.092	1.07 (0.84-1.35)	0.5987	0.90 (0.52-1.56)	0.7049	0.79 (0.31-2.01)	0.623
Smoking Never vs Current Former	0.86 (0.41-1.82)	0.695	1.11 (0.82-1.50)	0.4929	0.97 (0.43-2.18)	0.9471	2.15 (0.44-10.6)	0.345
	1.68 (0.95-2.97)	0.073	0.92 (0.74-1.17)	0.152	1.33 (0.77-2.31)	0.3054	2.12(0.7- 6.28)	0.1735

Table 4: Association of dry AMD with CKD stratified by race.
Logistic regression model stratified by race, relating prevalence of dry AMD to the presence of CKD after controlling for effects due to age, gender and HTN is shown. OR, odds ratio; CI, confidence interval; CKD, chronic kidney disease; HTN, hypertension; dry AMD, dry age-related macular degeneration.

Discussion

In this cross-sectional population-based study, we investigated the association between HTN, CKD and dry AMD. Though we did not find a significant association between the dry AMD, CKD and hypertension, significant independant effects due to CKD and HTN were noted. Only few studies have addressed the systemic effects of HTN in manifestation of either AMD or CKD alone, this preliminary study highlights the odds of having dry AMD in

the scenario of coexisting HTN and CKD. Previous studies show data correlating HTN with CKD and/or AMD, but with discrepancies between their findings. For example, studies by Deva R, et al. [3,20]; concluded that age and renal failure but not hypertension were determinants for AMD [20]. Both Framingham Heart and Eye and Beaver Dam Eye studies show an association between AMD and hypertension [21,22]. Along the same lines, a correlation has been shown between the duration of arterial hypertension and increase in count and size of drusen in monkeys [23]. Also, an isolated study linked increased diastolic blood pressure to exudative AMD, however, in the current study we did not include subjects with exudative AMD [24]. Due to the limited number of studies available, further evidence based clinical trials are needed to validate the negative impact of uncontrolled HTN in a setting of CKD patients. While our aim in this study was to find if HTN increased the risk of dry AMD in CKD patients, we acknowledge a few limitations in the study design that may have led to skewed outcomes. For instance, we did not segregate various grades of dry AMD and CKD, nor did we classify HTN patients with respect to their blood pressure control, medication types and compliance, in the study design. In addition, patients with a diagnosis of HTN may technically not be hypertensive, as many would have been on treatment resulting in hypertension control. Exclusion of such parameters may have altered the outcome of this study and therefore should be addressed in any future study. The authors would like to emphasize that the preliminary findings from this exploratory study should not be considered conclusive by any means, but instead lead researchers to investigate further.

Another exciting finding of our study was noted when we stratified subjects by race due to the diverse ethical presence in the study population. We report a positive association between dry AMD and CKD in the Hispanic population after adjusting for confounders. Specifically, we found that Hispanics are 2.35 times more likely to present with dry AMD in the presence of CKD when compared to those without. To our knowledge, this is the only study to report such an association with racial preference in manifesting of comorbid diseases like dry AMD and CKD. While an association between CKD and AMD has been reported previously, many of those studies have solely focused on homogenous population largely involving the Asia-Pacific geographic region. Therefore, extrapolating their findings universally may not be appropriate. In addition, variability between population-based studies also exists in design, methodology and statistical analysis. Specifically, there are significant differences between inclusion criteria, study populations, biomarkers for CKD, CKD severity, and AMD grading. Furthermore, studies utilized different effect estimates to document the relationship between CKD and AMD (Incidence, prevalence, crude odds ratio, multivariate odds ratio, etc). Lastly, depending on the study, different confounding factors were included for their multivariate adjustment [19]. While the findings of this racial disparity on dry AMD and CKD is a novel finding, studies are warranted to further define this relationship.

It is not new to the readers that racial disparity may influence AMD and CKD disease differently. In review, Caucasians have a higher risk of developing AMD, and African Americans and Hispanics are at a higher risk for developing CKD [25-27]. However, sadly, since 2000, the number of Hispanics with kidney failure have increased by more than 70 percent compared to non-Hispanics. Hispanics are almost 1.3 times more likely to be diagnosed with kidney failure [28]. The reason behind this disparity is not well understood, but is suggestive of an association with lower socio-economic status and lack of health insurance or access to preventive care [29]. Other factor that may add negative impact on the health of Hispanic Americans is their reduced physical activity and overall sedentary lifestyle. Another study found that 44% of Hispanic Americans were not taking their blood pressure medication despite a diagnosis of HTN [30]. The fact that CKD is a major public health concern with marked variability in disease progression with respect to age, gender and race; information from this study advocates nephrology health care providers to act as sentinels for early detection of other concomitant diseases like dry AMD.

In summary, we present a positive correlation between dry AMD, CKD, and HTN without adjusting for age, gender and race. Like any population-based study, this study is not free of limitations:

- Due to possible selection bias as we used the ICD-10 codes for data retrieval.
- We did not account for the grade/severity of either CKD or dry AMD, which may have limited our ability to correlate HTN with the severity of either disease.

Nonetheless, the observation presented here does not undermine the risk of HTN in dry AMD and CKD disease manifestations. Both CKD and AMD are multifactorial disease and HTN is a common modifiable risk factor and therefore needs to be managed stringently at the primary health care level. While, we also report an incidental but novel finding of Hispanic race correlating to higher prevalence for dry AMD in CKD patients, this needs further definition with studies solely focused on racial disparity. The meaningful findings from this study not only initiates an area of research for future exploration, in addition it may guide clinicians to increased awareness of such relationships so that they may educate patients on routine health exams, lifestyle changes and potential vitamin supplementation when appropriate. Additionally, dry AMD may progress to the exudative form, which may result in irreversible loss of vision and blindness,

particularly in patients with other vascular risk factors, and increased surveillance would improve visual outcomes in these patients.

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