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The Common Antidiabetic Drug Metformin Reduces Odds of Developing Age-Related Macular Degeneration

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Purpose. AMD is the leading cause of irreversible blindness in older individuals in the Western world, and there are currently no therapies to halt disease progression. Studies suggest that the commonly prescribed antidiabetic drug, metformin, is associated with decreased risk of several ocular diseases, but no work has investigated the effect of metformin use on development of AMD. Thus, we aim to investigate whether metformin use is associated with decreased risk of developing AMD.

Methods. In this retrospective case-control study, we used medical records from patients older than 55 who have visited a University of Florida health clinic. Three controls were matched for every AMD case, defined by *International Classification of Diseases, Ninth Revision* code, based on the Charlson Comorbidity Index to ensure comparable baseline overall health status. Univariate and conditional multivariable logistic regressions were used to determine the association between a variety of covariates, including metformin use, and AMD diagnosis.

Results. Metformin use was associated with decreased odds of developing AMD, independently of the other covariates investigated, with an odds ratio of 0.58 and a 95% confidence interval of 0.43 to 0.79. Other medications assessed were not associated with decreased odds of developing AMD.

Conclusions. Patients who had taken metformin had decreased odds of developing AMD, suggesting that metformin may have a therapeutic role in AMD development or progression in those who are at risk. Further work should include clinical trials to investigate prospectively whether metformin has a protective effect in those at risk for developing AMD.

Keywords: AMD, metformin, case controlled study

AMD is the leading cause of vision loss in individuals older than 55 in the Western world.[1] There are two forms of AMD: dry (also known as atrophic or nonexudative), which is characterized by a slow progressive loss of vision, and wet (also known as neovascular or exudative), which is characterized by neovascularization from the choroid. In approximately 10% to 15% of patients with dry AMD, the disease progresses to the wet form. The first treatments developed for wet AMD were inhibitors of VEGF,[2–4] which are effective treatments for end-stage wet AMD. The Age-Related Eye Disease Study (AREDS) identified that supplementation with high levels of antioxidants and zinc can delay advanced AMD.[5,6] However, an ideal therapy would be one that prevents onset or delays progression of early dry AMD.

Genetic studies have suggested that dysregulation of the complement system and extracellular matrix metabolism are strongly linked to both forms of AMD.[7–9] Other studies have shown that elevated levels of oxidative stress,[10–12] increased mutations in mitochondrial DNA,[13,14] and accumulation of lipids and lipofuscin[15] may be associated with the early dry forms of the disease, suggesting that photoreceptor and retinal pigment epithelium (RPE) metabolism are defective in early AMD.

In support of the metabolic hypothesis for early disease, recent studies have reported that dysregulation of retinal metabolism is a contributing factor to initial stress events and disease progression in several preclinical animal models.[14,16–19] In a recent study, our group has found that the drug metformin, a biguanide commonly used to lower serum glucose levels in patients with non–insulin-dependent diabetes mellitus, was able to stimulate glucose metabolism in the retina and protect retinal photoreceptors and RPE from inherited mutations or oxidative stress in preclinical mouse models.[20] We further showed that metformin was protective through activation of 5′ adenosine monophosphate-activated protein kinase (AMPK) in the retina. Conversely, AMPK mutations in the neuroretina result in retinal degeneration and accelerated aging phenotypes in mice.[21] AMPK is a critical cellular energy sensor involved in detecting increases in the ratios of ADP:ATP and AMP:ATP, which increase under cellular energy stress.[22–24] This suggests that activating AMPK results in metabolic reprogramming that can be protective to tissues undergoing cellular and metabolic stress. Based on this evidence, we hypothesize that targeting AMPK could also be protective against development of AMD.

TABLE 1. Distribution of Variables Used for Matching, Before and After Matching

Variable	Before Matching			After Matching		
	Case	Control	Difference	Case	Control	Difference
Age, mean	77	68.21	8.79	77	75.09	1.91
CCI, mean	4.26	4.04	0.22	4.26	4.29	−0.03
Hypertension, %	81.61	81.19	0.42	81.61	81.41	0.2
Anemia, %	5.19	7.48	−2.29	5.19	4.91	0.28

Mean age, CCI, percentage of patients with hypertension, and percentage of patients with anemia in control (without AMD) and case (with AMD) groups before and after matching based on these variables and the difference between these variables in cases and controls. Each case was matched to three controls.

Because metformin is a widely prescribed drug known to activate AMPK, we performed a retrospective case-control study to determine whether metformin use is associated with decreased odds of developing AMD. Our study suggests that taking metformin is associated with reduced odds of developing AMD, whereas use of other antihyperglycemic drugs, statins, or other common medications are not.

METHODS

Study Population

De-identified patient data were obtained from the Integrated Data Repository from the University of Florida, for patients who visited locations in Gainesville, Florida, or Jacksonville, Florida, between June 1, 2011, and June 1, 2017. *International Classification of Diseases, Ninth Revision* (ICD-9) codes were used for identification of diagnoses. These codes are used as standardized identifiers of patient diagnosis for the purposes of payer claims reimbursement. In this study, cases were those who received a diagnosis of AMD based on ICD-9 diagnostic code of 362.5 for macular degeneration and who had visited the clinic at least four times before their diagnosis. Because cases must have had at least four visits before a diagnosis of AMD, cases are incident, and thus information before the diagnosis of AMD is available.

Cases include ICD-9 codes for both wet (ICD-9 code 362.52, exudative senile macular degeneration) and dry (ICD-9 code 362.51, nonexudative senile macular degeneration) forms of AMD, as well as codes for AMD in which wet or dry form was not specified (ICD-9 codes 362.50 [macular degeneration (senile), unspecified] and 362.53 [cystoid macular degeneration]). All cases had at least four prior visits to a University of Florida health clinic before the diagnosis of AMD between June 1, 2011, and June 1, 2017. Patients who had at least four visits during this time period but did not receive a diagnosis of AMD were considered controls.

Study Design

All procedures were approved by the University of Florida Institutional Review Board (IRB) under protocol number IRB201602561. All patient information obtained for this study was de-identified by the University of Florida Integrated Data Repository and therefore the ethics committee approved a Full Waiver of Informed Consent for this study. The data in the University of Florida Integrated Data Repository (https://www.ctsi.ufl.edu/research-initiatives/completed-projects/integrated-data-repository/) is open for use for those with an approved IRB protocol. Therefore, those seeking to reproduce the results can access the same data. All procedures adhered to the tenets of the Declaration of Helsinki.

As the data contained mostly ICD-9 codes; all ICD-10 codes were first converted into corresponding ICD-9 codes. We used the General Equivalence Mapping tools developed by the Centers for Medicaid and Medicare Services to convert ICD-10 into ICD-9 codes.[25] Although missing categories may arise during the process of conversion due to new concepts in ICD-10 that are not present in ICD-9, to our knowledge there are no missing categories in the variables we included in our analysis.

In this retrospective case-control study, controls were matched to cases using a propensity score (PS) algorithm based on the Charlson Comorbidity Index (CCI), which measures the comorbidities of an individual's hospital visits over time and can be used to predict 10-year survival in patients with multiple comorbidities. The CCI is calculated using ICD-9 codes from each individual's medical history.[26,27] The variables considered when calculating the CCI include myocardial infarction, congestive heart failure, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatologic disease, peptic ulcer disease, mild liver disease, diabetes, diabetes with chronic complications, hemiplegia or paraplegia, renal disease, any malignancies, moderate or severe liver disease, metastatic solid tumors, and AIDS. CCI calculation with the corresponding ICD-9 codes was performed as described by Deyo et al.[27]

To ensure the two groups (cases and controls) are comparable with regard to baseline health and age, propensity score matching (PSM) was performed. The variables used for PSM included age, CCI (to control for baseline overall health), hypertension, and anemia. Other factors known to be associated with AMD, such as body mass index (BMI) and sex were not used for PSM because we were interested in identifying their independent effects on AMD to validate our patient population. The PSM was performed in R using the MatchIt package.[28] Specifically, we fitted a logistic regression using AMD as the outcome variable and age, CCI, hypertension, and anemia as covariates to generate the logistic probabilities of PS for the two comparison groups (metformin yes versus no) using the "nearest neighbor" method. Cases and controls were matched on the PS with a 1:3 ratio.

Statistical Analysis

P values of 0.05 were considered statistically significant for all tests. Demographic characteristics collected from the medical records of patients include age, sex, insurance status, and race/ethnicity. We included variables that are known risk factors to AMD in the conditional multivariate logistic regression to control the potential confounding effects on the association between metformin and AMD. Additional variables included in the conditional multivariable logistic regression model were BMI, hypertension, and prior diagnosis with ICD-9 codes for drusen deposits, retinal hemorrhaging, retinal edema, retinal ischemia, macular cysts, or macular puckering (as listed in Table 2). Medication information and corresponding RxNorm IDs, including metformin, were extracted.

TABLE 2. Descriptive Statistics of Study Population

Covariate	Total Patients Without AMD (Control), $n = 5841$	Total Patients With AMD (Case), $n = 1947$	P*	Bonferroni-Corrected P
Age, median (SD)	75 (8.55)	77 (10.10)		
	Number (%)			
Sex			<0.001	0.031
Female	3039 (52.03)	1197 (61.48)		
Male	2802 (47.97)	750 (38.52)		
Race/Ethnicity			<0.001	0.028
Caucasian	4431 (75.86)	1583 (81.3)		
Black/African American	983 (16.83)	245 (12.58)		
Other racial minority	384 (6.57)	119 (6.11)		
Unknown	43 (0.74)	0		
Insurance Status			<0.001	0.031
Governmental	4382 (75.02)	1497 (76.89)		
Other/Unknown	894 (15.31)	213 (10.94)		
Private	283 (4.85)	108 (5.55)		
Self-Pay	282 (4.83)	129 (6.63)		
Clinical comorbidities [ICD-9 Code]				
CCI, mean (SD)	4.29 (3.59)	4.26 (3.71)	0.76†	1
BMI, mean (SD)	29.44 (6.51)	28.23 (6.52)	<0.001†	0.031
Diabetes mellitus [250]	4110 (70.36)	837 (42.99)	<0.001	0.031
Ocular comorbidities [ICD-9 Code]				
Detached retina [361.0]	3 (0.05)	37 (1.9)	<0.001	0.031
Macular cyst, hole, or pseudohole [362.54]	42 (0.72)	79 (4.06)	<0.001	0.031
Puckered macula [352.56]	192 (3.29)	265 (13.61)	<0.001	0.031
Drusen [362.57]	32 (0.55)	110 (5.65)	<0.001	0.031
Retinal hemorrhage [362.81]	8 (0.14)	50 (2.57)	<0.001	0.031
Retinal exudates or deposits [362.82]	1 (0.02)	9 (0.46)	<0.001	0.031
Retinal edema [362.83]	30 (0.51)	162 (8.32)	<0.001	0.031
Retinal ischemia [362.84]	8 (0.14)	19 (0.98)	<0.001	0.031
Medications				
Metformin	610 (10.44)	85 (4.37)	<0.001	0.031
Alpha inhibitors	3 (0.05)	0 (0)	0.578	1
DPP4 inhibitors	169 (2.82)	19 (0.98)	<0.001	0.031
Meglitinides	5 (0.09)	0 (0)	0.341	1
SGLT2 inhibitors	21 (0.36)	2 (0.1)	0.117	1
Thiazolidinediones	4 (0.07)	1 (0.05)	1	1
Serotonin modulators and simulators	3 (0.05)	1 (0.05)	1	1
Serotonin-norepinephrine reuptake inhibitors	8 (0.14)	1 (0.05)	0.466	1
SSRI	67 (1.15)	28 (1.44)	0.34	1
Tetracyclic antidepressants	64 (1.10)	32 (1.64)	0.075	1
Statins	973 (16.66)	270 (13.87)	0.004	0.124

Summary statistics with number and percentage of patients with each covariate or diagnosis in control (without AMD) and case (with AMD) groups.

* Indicates *P* value from χ^2 or Fisher exact test.

† Indicates *P* value from a *t*-test rather than from X^2 or Fisher exact test.

Significant associations between AMD diagnosis and the listed demographic and clinical covariates were determined using univariate and conditional multivariable logistic regression, adjusted for age, sex, and BMI. BMI was calculated as the average of BMI from every hospital visit of each individual. For controls, similar strategies were used to determine the association between the controls and the covariates.

Chi-square tests, Fisher's exact tests, and Student's *t*-tests were used to identify statistically significant associations between the clinical and demographic covariates and AMD diagnosis. To adjust for multiple testing, a Bonferroni-corrected *P* value was used. Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were then calculated to quantify the magnitude of the covariates' effects on the odds of AMD diagnosis using univariate and conditional multivariable logistic regression models. We performed the conditional multivariable logistic regression in a 10-fold cross-validation setting to test the goodness of fit and predictive value, cut point selected using Youden's J. We assessed the association between metformin and AMD in a subgroup consisting of only diabetic patients, using χ^2 tests and ORs and corresponding 95% CIs using univariate and conditional multivariable logistic regression. All statistical analyses were performed in R (R Core Team 2018, Vienna, Austria; https://www.R-project.org/).

RESULTS

Participant Demographics

There were 26,152 patient records collected from the University of Florida electronic health record database of patients who were older than 55 and visited from June 1, 2011,

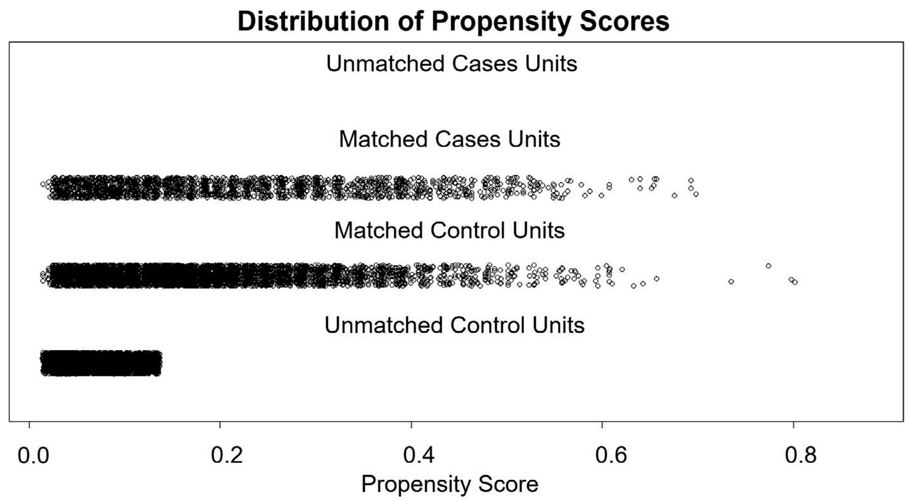

FIGURE 1. Distribution of PSs between cases and controls before and after matching on age (mean), CCI, hypertension (%), and anemia (%).

to June 1, 2017. After excluding patients who had fewer than four visits, there were a total of 5841 patients without AMD (controls) and 1947 patients with AMD (cases), as defined by ICD-9 code, which fit our inclusion criteria. Three controls were matched to each case based on several variables including age, CCI, hypertension, and anemia. The CCI is a measure of overall health status and is calculated considering a variety of diagnoses, as described in the methods section. To ensure matching was successful, we assessed the distribution of these variables before and after matching. Table 1 displays the distribution of these variables among the cases and controls before and after matching, and the differences between the two groups. Figure 1 shows the distribution of the PSs before matching (unmatched) and after matching (matched) for the cases and controls.

Of the AMD cases, 505 patients had dry AMD (ICD-9 code 362.51), 112 patients had wet AMD (ICD-9 code 362.52), and the remaining 1133 patients had unspecified macular degeneration, and, therefore, it was not possible to determine whether these patients had wet or dry AMD. For this reason, we considered all cases to be those with any AMD diagnosis of ICD-9 code 362.5. Of the controls, 610 (10.44%, $P < 0.031$) patients had a history of taking metformin, whereas 85 (4.37%) of the cases had a history of taking metformin (Fig. 2; Table 2).

To assess whether any protective effect may be coming from other prescribed medications, we examined use of several other commonly prescribed drugs or drugs that have been previously investigated as potential therapies for AMD, in our patient population. These included dipeptidyl peptidase 4 (DPP4) inhibitors, selective serotonin reuptake inhibitors (SSRI), tetracyclic antidepressants, and statins. We found that many of the patients in our population were also prescribed these drugs (Table 2). We also examined the use of several other drugs, including meglitinides, alpha inhibitors, sodium-glucose cotransporter-2 (SGL2) inhibitors, thiazolidinedione, serotonin modulators and stimulators, and serotonin and

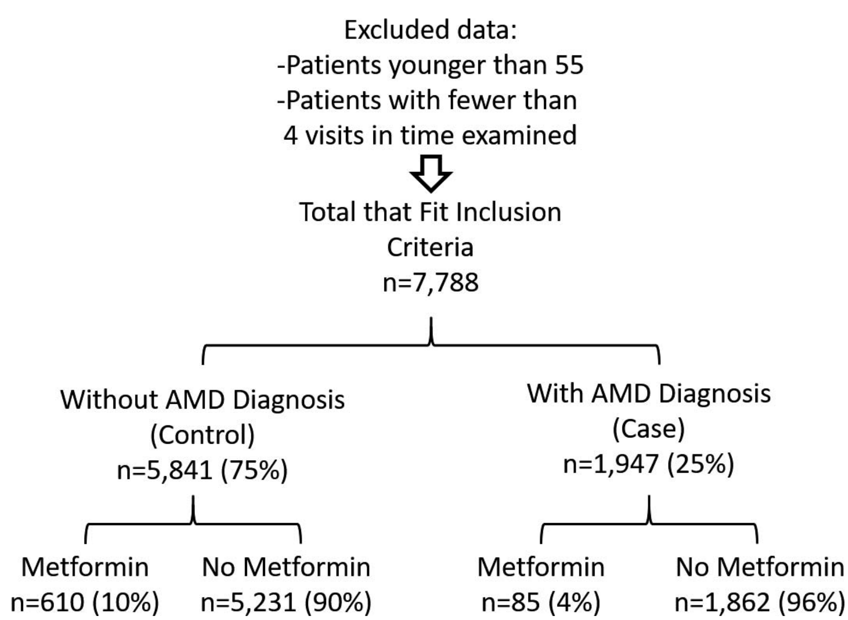

FIGURE 2. Population: cases and controls and metformin use with number of patients and percentage of total of previous group for each arm.

TABLE 3. Univariate and Conditional Multivariable Logistic Regression Models Assessing Risk of Developing AMD

Covariate	Univariate Analysis OR (95% CI)	*P*	Bonferroni-Adjusted *P* Value	Multivariable Analysis OR (95% CI)	*P*
Age	1.02 (1.01–1.03)	<0.0001	0.0037	1.02 (1.08–1.10)	<0.0001
Sex					
Female	1 [Reference]	–	–	1 [Reference]	–
Male	0.68 (0.61–0.75)	<0.0001	0.0037	0.71 (0.63–0.80)	<0.0001
Race/Ethnicity					
Caucasian	1.43 (1.23–1.67)	<0.0001	0.0037	1.41 (1.15–1.69)	0.0002
Black/African American	1 [Reference]	–	–	1 [Reference]	–
Other racial minority	1.2 (0.93–1.54)	0.152	1	1.23 (0.90–1.65)	0.152
Unknown	0.46 (0.16–1.08)	0.111	0.0037	5.23 (0.18–1.26)	0.190
Insurance status					
Governmental	0.75 (0.60–0.93)	0.0082	0.3034	0.60 (0.46–0.78)	0.0001
Other/Unknown	0.52 (0.40–0.67)	<0.0001	0.0037	0.49 (0.63–0.92)	<0.0001
Private	0.83 (0.61–1.13)	0.243	1	0.82 (0.58–1.16)	0.276
Self-pay	1 [Reference]	–	–	1 [Reference]	–
Clinical comorbidities					
CCI	1 (0.99–1.01)	0.756	0.0037	–	–
BMI	0.97 (0.96–0.98)	0.0603	1	1 (0.99–1.01)	0.820
Diabetes	0.32 (0.29–0.35)	<0.0001	0.0037	0.32 (0.28–0.36)	<0.0001
Ocular comorbidities [ICD-9 Code]					
Detached retina [361.0]	37.7 (13.61–156.3)	<0.0001	0.0037	25.89 (8.7–111.67)	<0.0001
Macular cyst, hole, or pseudohole [362.54]	5.84 (4.03–8.59)	<0.0001	0.0037	3.46 (2.23–5.42)	<0.0001
Puckered macula [352.56]	4.64 (3.82–5.63)	<0.0001	0.0037	2.95 (2.35–3.70)	<0.0001
Drusen [362.57]	11.82 (8.08–17.8)	<0.0001	0.0037	10.01 (6.61–15.72)	<0.0001
Retinal hemorrhage [362.81]	19.22 (9.63–43.91)	<0.0001	0.0037	19.67 (9.28–46.83)	<0.0001
Retinal exudates or deposits [362.82]	27.12 (5.09–500.32)	0.002	0.074	4.5 (0.45–11.86)	0.271
Retinal edema [362.83]	17.58 (12.05–26.53)	<0.0001	0.0037	23.56 (15.58–36.70)	<0.0001
Retinal ischemia [362.84]	7.19 (3.25–17.45)	<0.0001	0.0037	6.06 (2.33–16.61)	0.0002
Medications					
Metformin	0.39 (0.31–0.49)	<0.0001	0.0037	0.58 (0.43–0.79)	0.0005
DPP4 inhibitors	0.34 (0.20–0.53)	<0.0001	0.0037	0.80 (0.45–1.34)	0.420
SSRI	1.26 (0.79–1.94)	0.312	1	1.73 (1.02–2.88)	0.037
Tetracyclic antidepressants	1.51 (0.97–2.29)	0.060	1	1.93 (1.17–3.15)	0.009
Statins	0.81 (0.69–0.93)	0.004	0.148	0.99 (0.82–1.21)	0.997

Analysis of covariates using univariate and conditional multivariable logistic regression analysis, showing the ORs and 95% CIs. An OR greater than 1 indicates increased odds of developing AMD, whereas an OR less than 1 indicates decreased odds of developing AMD.

norepinephrine reuptake inhibitors. As the number of patients on these medications was too small, we did not include them in further analysis.

Association of AMD Diagnosis and Metformin Use: Univariate and Conditional Multivariable Logistic Regression

To assess the odds of developing AMD, we used univariate regression, which examines the covariate and its relationship with an AMD diagnosis or lack of AMD diagnosis. We also used conditional multivariable logistic regression, which takes into account all of the variables put into the model simultaneously with the outcome variable, presence or absence of AMD diagnosis. When using conditional multivariable logistic regression, we can estimate the unique contribution of risk that each covariate gives us by considering the other covariates of the patients.

We found that metformin use was associated with statistically significant decreased odds of developing AMD when using univariate analysis (OR, 0.39; 95% CI, 0.31–0.49) and conditional multivariable logistic regression (OR, 0.58; 95% CI, 0.43–0.79) (Table 3). Because metformin was associated with decreased odds of developing AMD, we wanted to rule out the possibility of the protective effect coming from other antidiabetic drugs. To do this, we examined DPP4 inhibitors, which are used to treat diabetes. Univariate logistic regression models showed that DPP4 inhibitors were associated with statistically significant decreased odds for developing AMD (OR, 0.34; 95% CI, 0.20–0.53) (Table 3). However, when using conditional multivariable logistic regression, DDP4 inhibitors did not have a significant association with AMD (OR, 0.80; 95% CI, 0.45–1.34) (Table 3).

In addition to diabetic medications, we wanted to examine the effect of several commonly prescribed medications that may have an association with AMD to rule out any effect from these drugs. Studies suggest that statins, a class of medications used to lower lipid levels, may be associated with decreased odds of developing AMD.[29,30] To examine this possibility, we used univariate logistic regression to assess the association of statin use with AMD. We found that statins were associated with a slight, but statistically significant reduction in odds of developing AMD when using univariate analysis (OR, 0.81; 95% CI, 0.69–0.93), but conditional multivariable logistic regression analysis showed that statins were not associated with development of AMD (OR, 0.99; 95% CI, 0.82–1.21) (Table 3).

Studies in preclinical animal models have previously reported that some medications often used as antidepressants may protect against retinal degeneration.[31–34] To investigate this possibility, we examined drugs in the SSRI and tetracyclic

Table 4. Subgroup Analysis of Metformin Treatment Effects in Patients With Diabetes

	Number (%)	
	Without AMD + Diabetes (Control), *n* = 4110	**With AMD + Diabetes (Case), *n* = 837**
Metformin	576 (14.01)	84 (10.04)
No Metformin	3534 (85.99)	753 (89.96)

Subgroup analysis in diabetic patients to handle the potential effect of diabetes on AMD. Demographic characteristics of the subgroup, including number of controls and cases with diabetes and the number and percentage of those patients with metformin use.

antidepressant classes. Using univariate analysis, we found use of tetracyclic antidepressants did not have a significant association with AMD using univariate analysis (OR, 1.51; 95% CI, 0.97–2.29); however, the use of tetracyclic antidepressants was associated with an increased risk of developing AMD when using conditional multivariable logistic regression (OR, 1.93; 95% CI, 1.17–3.15) (Table 3). SSRIs were also associated with increased odds of developing AMD when using conditional multivariable logistic regression (OR, 1.73; 95% CI, 1.02–2.88) (Table 3).

Interestingly, diabetes was associated with statistically significant decreased odds for developing AMD when using both univariate (OR, 0.32; 95% CI, 0.29–0.35) and conditional multivariable logistic regression analyses (OR, 0.32; 95% CI, 0.28–0.36) (Table 3). Our analysis suggests that the effect of metformin is independent of diabetes diagnosis; this is further addressed in the next section.

To confirm this data set is representative of an AMD diagnosis, we examined several clinical criteria for AMD. These included macular cyst, hole, or pseudo hole (OR, 3.46; 95% CI 2.23–5.42), puckered macula (OR, 2.95; 95% CI, 2.35–3.70), drusen (OR, 10.01; 95% CI, 6.61–15.72), retinal hemorrhaging (OR, 19.67; 95% CI, 9.28–46.83), retinal edema (OR, 23.56; 95% CI, 15.58–36.70), and retinal ischemia (OR, 6.06; 95% CI, 2.33–16.61) (Table 3). These clinical risk factors associated with AMD diagnosis were associated with increased odds of developing AMD in our data set and were all statistically significant using conditional multivariable logistic regression, suggesting that our patient population properly represents an AMD diagnosis.

In addition, we were able to confirm that our data set agrees with other known risk factors for AMD, including sex. Using conditional multivariable logistic regression, we found that being male was associated with statistically significant decreased odds of developing AMD (OR, 0.71; 95% CI, 0.63–0.80) (Table 3).

From the cross-validation analysis, we obtained an average area under the receiver operating characteristic curve of 0.85 with sensitivity of 0.69 and specificity of 0.94, demonstrating good predictive value of the risk factors and predictors included in the analysis.

Association of AMD Diagnosis and Metformin Use: Subgroup Analysis in Diabetic Patients

Because metformin is mainly prescribed to treat type II diabetes, we wanted to account for the potential effect of confounding by indication for diabetes. To do this, we performed a subgroup analysis containing only patients with diabetes. There were 4110 non-AMD control patients with diabetes. Of these, 576 (14.01%) were taking metformin (Table 4). There were 837 patients with AMD who also had diabetes, and of these, 84 (10.04%) were also taking metformin (Table 4). We next performed univariate logistic regression analysis on the subgroup of diabetic patients and found that metformin use was associated with decreased odds of developing AMD (OR, 0.68; 95% CI 0.53–0.87, $P = 0.002$) (Table 5). Metformin use was also associated with decreased odds of developing AMD in this subgroup of diabetic patients using conditional multivariable logistic regression (OR, 0.70; 95% CI 0.49–0.98, $P = 0.043$) (Table 5).

Table 5. Univariate and Conditional Multivariable Logistic Regression Analysis of the Subgroup, Showing ORs for AMD, 95% CIs, and Corresponding *P* Values

	Univariate Analysis OR (95% CI)	***P***	**Multivariate Analysis OR (95% CI)**	***P***
Metformin	0.68 (0.53–0.87)	0.002	0.70 (0.49–0.98)	0.043

Discussion

This study suggests that metformin is associated with decreased odds of developing AMD. To our knowledge, we are the first group to perform an observational study to examine the association of metformin and AMD. Other groups have found that metformin use, but not use of other diabetic medications, is associated with decreased odds of glaucoma,[35] retinal vein occlusions in diabetes mellitus,[36] and diabetic retinopathy.[37] These results are similar to our findings that metformin, but not other medications, are associated with decreased odds of AMD. These findings suggest that metformin itself, and not other medications, has an important protective role.

AMD includes two forms, dry AMD and wet AMD. Although AMD is the leading cause of vision loss of older individuals in the Western world, there are no disease-altering therapies for dry AMD, which comprises approximately 90% of all cases of AMD. There is an incomplete understanding of mechanisms of disease pathogenesis of AMD, which is a barrier to developing effective therapies. Recent studies using preclinical models suggest that metabolic dysregulation may play an important role in AMD pathogenesis.[19,38–40] The retina is one of the most metabolically active tissues in the body with one of the highest energy demands.[41] Recent work from our group suggests that systemic treatment with metformin activates AMPK in the retina and results in an increase in mitochondrial DNA copy number and ATP production in the retina.[20] There also has been evidence of mitochondrial dysfunction in the RPE of AMD patients,[14,16,17] suggesting that metabolic dysfunction could be a disease mechanism in patients with AMD. Therefore, we hypothesized that activation of AMPK in humans may be protective against AMD.

In our study, we used patient data from a large-scale academic research institution to assess whether metformin use may be associated with decreased odds of developing AMD. Data from our patient population confirmed well-established findings, suggesting that our data are representative of other AMD populations.[42] Interestingly, we found that metformin, but not other medications, was associated with decreased odds of developing AMD.

We also found that diabetes diagnosis was associated with decreased odds of developing AMD (OR, 0.32; 95% CI, 0.29–0.35). To assess the potential effect of diabetes in our analysis, we performed a subgroup analysis among diabetic individuals with and without AMD. We also found that metformin was associated with decreased odds of developing AMD in this population (OR, 0.70; 95% CI, 0.49–0.98), suggesting that this effect is independent of diabetes. Other studies that have assessed the association of metformin use and AMD have had similar findings.[43] However, some studies have found that diabetes is associated with increased odds of developing AMD.[44–46] These studies differ in study design and focused on diabetes mellitus in general, whereas our study largely focuses on patients with type 2 diabetes. Of the patients with diabetes, 10.67% have type 1 diabetes (as defined by ICD-9 codes, 250.01, 250.11, 250.13, 250.41, 250.43, 250.51, 250.53, 250.61, 250.63, 250.71, 250.73, 250.91, 250.93).

Due to limitations in data, we were not able to take metformin dosage or length of time on metformin in to account. A previously published study showed that for every cumulative increase of metformin dose by 1 g, there is a 0.16% reduction in the odds for developing open angle glaucoma.[35] This study also found that those in the group with the highest metformin usage (>1110 g over a 2-year period) experienced the highest reduction in odds, a 25% reduction, of developing open angle glaucoma when compared with nonusers. It is possible that patients taking higher doses for longer durations may have lower ORs, which will be addressed in future studies.

ICD billing codes were used as the criteria for defining cases, controls, and identifying covariate diagnoses, which may not be a perfect proxy for some diseases. Cases were those with any diagnosis of AMD, ICD-9 code 362.5. Because for a large number of patients (1333 of a total of 1947 cases) it was not specified whether the macular degeneration was wet or dry, we were unable to form conclusions about each form of AMD. Although the patients in our population have a high BMI, evidence suggests that this is common of adult populations in Florida.[47] In addition, our study did not include any interaction terms in our model to account for nonlinearities in the data. There could be additional confounding factors that were not considered in our analysis. We have included most known risk factors for AMD from literature in the multivariate regression model; however, other risk factors such as family history, smoking, or genetics were not accounted for because they are not collected in the data we used. As smoking and genetics are important risk factors for AMD, the inability to account for these variables could lead to residual confounding. In addition, we used RxNorm IDs from existing medical records as an indication of drug use. This method does not provide us with information about treatment adherence, which could influence our results.

This is a retrospective study and a causal relationship cannot be established; future work using directed acyclic graphs may assist in elucidating the causal pathways. The effects of metformin on AMD incidence or severity should be tested prospectively in large multicenter clinical trials. One phase II, single-blind, randomized, clinical trial is currently under way to evaluate the safety and efficacy of metformin use to decrease geographic atrophy progression in a small group of nondiabetic patients with dry AMD (ClinicalTrials.gov Identifier: NCT02684578). Future prospective studies should further investigate the protective effect of metformin on AMD in large-scale multicenter clinical trials.

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