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Relationship between oral metformin use and age-related macular degeneration

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Abstract

In a cross-sectional retrospective study of 3120 diabetic patients aged ≥ 60 years, those taking metformin were less likely to have age-related macular degeneration compared with those not taking the drug (OR 0.70, 95%CI 0.55-0.88).

Introduction

Age-related macular degeneration (AMD) comprises a series of degenerative processes affecting the retina, retinal pigment epithelium (RPE), choriocapillaris, and choroid. At present, no medical therapies are approved to slow or halt the progression of AMD from its earliest stages. Metformin is the most widely prescribed medication for type 2 diabetes and is generally safe and well-tolerated.[1] The drug lowers glucose but has numerous other mechanisms that suggest it could have some efficacy against AMD.[2,3] The overlap of these pathways with processes known to be dysregulated in AMD led us to conduct a cross-sectional study of the electronic health record at the University of California, San Francisco (UCSF) to test whether metformin use was associated with less AMD.

Methods

In a retrospective cross-sectional study, the UCSF electronic medical record was queried to identify all diabetic patients (i.e., an ICD-9-CM or ICD-10-CM code of diabetes or diabetic retinopathy) aged 60 years or older with an ophthalmology encounter from April 18, 2012 until August 31, 2019. Billing codes and medications documented in the medical record were used to classify disease and medication status (Tables 1 and 2; available at https://www.ophthalmologyretina.org).

The exposure variable of interest was metformin use prior to or at the first ophthalmology encounter, and the outcome of interest was AMD at the first ophthalmology encounter.

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Conflict of interest: None.

Manual chart review revealed that codes for drusen were unreliable (of 101 patients with a code for drusen only 46 were confirmed on chart review), but codes for non-neovascular (94 of 122 confirmed) and neovascular (23 of 26 confirmed) AMD were acceptable. Consequently we defined AMD with billing codes for non-neovascular or neovascular AMD but not drusen.

Potential confounders were determined *a priori*, and included age in years, smoking (i.e., current vs. non-current smoker), metabolic syndrome, and socioeconomic status.[4] The presence of diabetic retinopathy was used as a proxy for metabolic syndrome, since some patients saw internists at other hospitals and thus would have missing data; insurance status (i.e., private vs. non-private insurance), sex, and race (i.e., White, Black, Asian, Other) were used as proxies of socioeconomic status. Each of these potential confounders was used to create a propensity score for metformin use, and the final statistical analysis employed logistic regression to model patient-level AMD as a function of metformin use, with inverse probability weighting of propensity scores to account for the likelihood of systematic differences in the groups of patients with and without exposure to metformin. For comparison, similar analyses were done for the other common diabetes medications, as well as the outcome of non-neovascular AMD. The significance level of the main metformin analysis was set at 0.05, and all other analyses were deemed exploratory. All analyses were done with the statistical package R version 3.5.2. The study adhered to the principles of the Declaration of Helsinki. Ethical approval was provided by the UCSF Human Research Protection Program.

Results

The electronic medical record extraction identified 3,120 individuals 60 years or older with a diagnosis of diabetes at the time of their first ophthalmology encounter. Of these, 122 (3.9%) had non-neovascular AMD and 26 (0.8%) had neovascular AMD documented at the initial ophthalmology visit. Characteristics of patients with and without AMD are shown in Table 3 (available at https://www.ophthalmologyretina.org), including diabetes medications.

Individuals with documentation of metformin use were significantly less likely to have AMD in the primary cross-sectional analysis (OR 0.70, 95%CI 0.55 to 0.88). In contrast, none of the other commonly used diabetes medications demonstrated a strong inverse correlation with AMD (Table 4). The relationship between metformin and AMD was not significantly modified by race (metformin by race [White vs. non-White] interaction P=0.44) although there was some evidence of a weaker association among those classified as current or former smokers (OR 0.92, 95%CI 0.64-1.31) relative to those classified as never-smokers or unknown smoking status (OR 0.56, 95%CI 0.41-0.77; metformin by smoking interaction P=0.046). A sensitivity analysis including only the 2,642 people on ≥ 1 diabetes medication found consistent results (OR 0.63, 95%CI 0.49-0.82). Analyses modeling non-neovascular AMD were similar to those for the primary AMD outcome, which included both non-neovascular and/or neovascular AMD (Table 4).

Discussion

In this study, metformin was found to be associated with a significantly reduced odds of AMD in a diabetic population. Recently, Brown et al reported that metformin use was associated with decreased odds of AMD in a population of over 77% Whites and 63.5% diabetics, with less than 9% (n = 695) of the total studied population taking metformin.[5] The present study provides additional support for this previous finding in a more racially diverse population of diabetic patients in which approximately one-third were Asian. The association was observed not only for the primary AMD outcome, which included both neovascular and non-neovascular AMD, but also when assessing non-neovascular AMD alone.

There is a strong association between current smoking and AMD.[6] This study provided evidence that the association between metformin use and reduced odds of AMD may be modified by smoking status, since the statistical association was weaker and of a lower magnitude among current and former smokers compared with never-smokers. Other studies have not found attenuated associations of metformin and health outcomes among smokers.[7] Future study is needed.

This study has limitations. Its retrospective design relied upon data entered into the medical record in the context of routine care. Although some amount of data misclassification is likely, our manual chart review provided some confidence in the validity of the data. The observational nature of the study precludes conclusions about causality. The relatively small sample size limited statistical power, preventing certain analyses (e.g. neovascular AMD as a secondary outcome).

In conclusion, this cross-sectional retrospective study demonstrated that oral metformin use was associated with a reduced odds of AMD, with consistent results for the overall AMD outcome and the non-neovascular AMD outcome. Given the current lack of effective therapies for non-neovascular AMD, this study adds to the body of evidence supporting further evaluation of metformin as an intervention for AMD in larger populations and possibly in future prospective trials.

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Table 1:
ICD-9-CM and ICD-10-CM codes used for this study.

For the primary analysis, age-related macular degeneration (AMD) was defined as the codes in the non-neovascular AMD and neovascular AMD categories, and those with only drusen were excluded.

Condition	ICD-9-CM	ICD-10-CM
Diabetes	249.x, 250.x, 362.0x, 648.00, 648.01, 648.02, 648.04	E08.x, E09.x, E10.x, E11.x, E13.x, O24.x
Diabetic retinopathy	362.0x	E08.3x, E09.3x, E10.3x, E11.3x, E13.3x
Drusen	362.57	H35.36x
Non-neovascular AMD	362.50, 362.51	H35.30, H35.31x
Neovascular AMD	362.52	H35.32x

Table 2.

Classification of diabetic drugs queried in the study population

Class	Medication
Biguanides	Metformin
Sulfonylurea	Glipizide, glyburide, glimepiride
Meglitinide	Repaglinide, nateglinide
Alpha-glucosidase inhibitors	Acarbose, miglitol
Thiazolidinediones	Pioglitazone, rosiglitazone
DPP-4 inhibitors	Sitagliptin, saxagliptin, linagliptin, alogliptin
SGLT-2 inhibitors	Canagliflozin, dapagliflozin, empagliflozin, ertugliflozin
Bile acid sequestrants	Colesevelam
Insulins	All insulin preparations

DPP-4 = dipeptidyl peptidase IV; SGLT-2 = sodium-glucose transporter-2

Table 3:
Demographic and clinical characteristics of the study population.

Age-related macular degeneration (AMD) was defined as an ICD-9-CM and/or ICD-10-CM billing code for non-neovascular and/or neovascular macular degeneration, but not drusen.

	60-69y		70-79y		≥80y	
Characteristic	**No AMD N=1455**	**AMD N=31**	**No AMD N=1037**	**AMD N=49**	**No AMD N=480**	**AMD N=68**
AMD subtype						
Non-neovascular	0 (0%)	26 (84%)	0 (0%)	43 (88%)	0 (0%)	53 (78%)
Neovascular	0 (0%)	5 (16%)	0 (0%)	66 (12%)	0 (0%)	15 (22%)
Sex						
Female	741 (51%)	15 (48%)	545 (53%)	28 (57%)	275 (57%)	39 (57%)
Race						
White	466 (32%)	12 (39%)	294 (28%)	21 (43%)	150 (31%)	26 (38%)
Black	174 (12%)	2(6%)	114 (11%)	4 (8%)	36 (8%)	2 (3%)
Asian	456 (31%)	14 (45%)	417 (40%)	17 (35%)	208 (43%)	28 (41%)
Other	359 (25%)	3 (10%)	212 (20%)	7 (14%)	86 (18%)	12 (18%)
Ethnicity						
Hispanic	169 (12%)	1 (3%)	136 (13%)	9 (18%)	54 (11%)	4 (6%)
Insurance						
Medi-Cal	110 (8%)	2 (6%)	43 (4%)	2 (4%)	4 (1%)	2 (3%)
Medicare	914 (63%)	20 (65%)	792 (76%)	42 (86%)	389 (81%)	55 (81%)
Private	393 (27%)	9 (29%)	192 (19%)	4 (8%)	82 (17%)	10 (15%)
Unknown	38 (3%)	0 (0%)	10 (1%)	1 (2%)	5 (1%)	1 (1%)
Smoking history						
Current	76 (5%)	2 (6%)	41 (4%)	2 (4%)	3 (1%)	4 (6%)
Former	492 (34%)	13 (42%)	381 (37%)	17 (35%)	165 (34%)	25 (37%)
Never	862 (59%)	16 (52%)	601 (58%)	30 (61%)	302 (63%)	39 (57%)
Unknown	25 (2%)	0 (0%)	14 (1%)	0 (0%)	10 (2%)	0 (0%)
Diabetes medications*						
None	268 (18%)	9 (29%)	235 (23%)	13 (27%)	118 (25%)	15 (22%)

	60-69y		70-79y		≥80y	
Characteristic	**No AMD N=1455**	**AMD N=31**	**No AMD N=1037**	**AMD N=49**	**No AMD N=480**	**AMD N=68**
Metformin	902 (62%)	12 (39%)	612 (59%)	24 (49%)	225 (47%)	32 (47%)
Insulins	524 (36%)	11 (35%)	322 (31%)	11 (22%)	161 (34%)	24 (35%)
Sulfonylureas	411 (28%)	9 (29%)	323 (31%)	20 (41%)	141 (29%)	21 (31%)
DPP-4 inhibitors	138 (9%)	4 (13%)	90 (9%)	4 (8%)	67 (14%)	8 (12%)
Thiazolidinediones	181 (6%)	1 (3%)	67 (6%)	4 (8%)	35 (7%)	3 (4%)
Meglitinides	33 (2%)	1 (3%)	27 (3%)	3 (6%)	19 (4%)	2 (3%)
Alpha-glucosidase inhibitor	18 (1%)	0 (0%)	14 (1%)	2 (4%)	3 (1%)	3 (4%)
SGLT-2 inhibitors	12 (1%)	1 (3%)	10 (1%)	1 (2%)	1 (0%)	0 (0%)
Bile acid sequestrants	5 (0%)	0 (0%)	2 (0%)	1 (2%)	2 (0%)	0 (0%)

AMD = age-related macular degeneration; DPP-4 = dipeptidyl peptidase IV; SGLT-2 = sodium-glucose transporter-2

*Some patients taking more than medication; does not sum to the total number of patients

Table 4:

Association between age-related macular degeneration and a variety of diabetes medications.

Odds ratios represent the results of propensity score-weighted logistic regression models conducted at the person level, with separate models for each medication. Models for the AMD outcome included both non-neovascular and neovascular AMD. No observations were excluded for any of the analyses (i.e., N=3120 persons per analysis).

	AMD		Non-neovascular AMD only	
Medication class	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
Metformin	0.70 (0.55-0.88)	0.003	0.59 (0.46-0.77)	<0.001
Insulins	0.90 (0.71-1.14)	0.38	0.95 (0.73-1.23)	0.70
Sulfonylureas	1.20 (0.95-1.51)	0.12	1.25 (0.97-1.61)	0.09
DPP-4 inhibitors	0.96 (0.76-1.21)	0.73	0.98 (0.76-1.27)	0.87
Thiazolidinediones	0.85 (0.66-1.08)	0.17	0.92 (0.71-1.19)	0.51
Meglitinides	1.44 (1.16-1.80)	0.001	1.54 (1.22-1.96)	<0.001

AMD, age-related macular degeneration; CI, confidence interval; DPP-4, dipeptidyl peptidase IV; OR, odds ratio