Ten-year incidence of age-related macular degeneration according to diabetic retinopathy classification among Medicare beneficiaries

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Abstract

Purpose—To compare the longitudinal incidence over 10 years of dry and wet age-related macular degeneration (AMD) in a U.S. sample of Medicare beneficiaries with: no diabetes mellitus (no DM); diabetes mellitus without retinopathy (DM); non-proliferative diabetic retinopathy (NPDR); and proliferative diabetic retinopathy (PDR).

Design—Retrospective, longitudinal cohort analysis

Methods—Using Medicare claims data, the 10-year incidence of dry and wet AMD was followed from 1995–2005 in beneficiaries aged >69 years with newly diagnosed DM (n=6,621), NPDR (n=1,307), and PDR (n=327) compared with each other and matched controls without diabetes for each group.

Results—After controlling for covariates, newly diagnosed NPDR was associated with significantly increased risk of incident diagnosis of dry AMD (hazard ratio (HR) 1.24; 95% confidence interval (CI) 1.08–1.43) and wet AMD (HR 1.68; 95% CI: 1.23–2.31). Newly diagnosed PDR was associated with significantly increased risk of wet AMD only (HR 2.15; 95% CI: 1.07–4.33). Diabetes without retinopathy did not affect risk of dry or wet AMD. There was no difference in risk of wet AMD in PDR compared to NPDR.

Conclusion—Elderly individuals with non-proliferative or proliferative diabetic retinopathy may be at higher risk of AMD compared to those without diabetes mellitus or diabetic retinopathy.

Keywords

Age-related macular degeneration; AMD; incidence; diabetes; diabetic retinopathy; Medicare database

INTRODUCTION

Age-related macular degeneration (AMD) and diabetic retinopathy are major causes of irreversible blindness in higher income countries.[1–4] Surprisingly, the relationship between

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these two diseases is poorly understood with inconsistent conclusions from previous clinical and epidemiological studies. Some reports have suggested an increased risk in either geographic atrophy or neovascular AMD with diabetes mellitus (DM).[5–9] Anecdotal clinical observations suggest a lower risk of advanced AMD in diabetics,[10,11] which has been demonstrated in one report.[12] In other investigations, no association between these two diseases was noted.[13–17] Previous studies have generally been limited by small patient samples, lack of follow-up data inherent in cross-sectional study design, and/or absence of differentiation of diabetic and/or AMD subtypes.

We used the 5% sample of Medicare claims data to determine the rate of incident dry or wet AMD in beneficiaries aged 69+ with new onset DM, non-proliferative diabetic retinopathy (NPDR), and proliferative diabetic retinopathy (PDR) over a 10 year period (1995–2005) relative to a matched population of persons without DM during the same period. We provide evidence suggesting that diabetic retinopathy, both non-proliferative and proliferative, may be associated with increased risk of AMD.

METHODS

Data

Under a Duke University Institutional Review Board-approved protocol, Medicare 5% inpatient, outpatient, and Part B claims files were used to identify a nationally representative sample of Medicare beneficiaries aged 65 or older who were diagnosed with DM, NPDR, and PDR or dry AMD and wet AMD from 1991–2005. The Medicare 5% claims file is a random sample of beneficiaries taken from the 100% file by selecting beneficiaries with a 05, 20, 45, 70, or 95 in positions 8 and 9 of the Medicare-generated beneficiary identification number located on its enrollment file. Once a beneficiary is selected for the 5% file s/he remains in the sample until death. Medicare risk plans (HMOs) do not generate claims, and residents living outside the United States (U.S.) are generally not covered by Medicare while away from the U.S. We considered transition from fee-for-service to a risk plan or moving outside the U.S. to be an exit from our analysis sample even if the beneficiary later returned to fee-for-service or to the U.S., since we had no knowledge of the care or diagnoses the beneficiary received during the gap periods.

The claims data contained information on diagnosis (International Classification of Diseases, 9th Revision, Clinical Modification; ICD-9-CM) and procedure codes (Current Procedural Terminology, CPT-4; Healthcare Common Procedure Coding System, HCPCS) submitted with each claim and were merged with Medicare denominator files for information on enrollment dates in fee-for-service Medicare, death, and beneficiary demographic characteristics. Diagnosis was based on ICD-9-CM codes for the appropriate disease state (Table 1). Individuals with no DM were identified by exclusion of all diabetes mellitus codes; individuals with no AMD were identified by exclusion of all AMD codes.

Sample Selection

We constructed a sample of individuals first diagnosed with DM, NPDR, or PDR in 1995. To ensure these were incident cases of diabetes mellitus or diabetic retinopathy and to identify other comorbidities, we employed a 4-year look-back period, which necessitated all individuals to be age 69+ in 1995 in order to have a full look-back. Individuals with a new diagnosis of PDR required exclusion of any previous PDR code in the look-back; individuals with a new diagnosis of NPDR required exclusion of any previous NPDR or PDR diagnosis in the look-back; individuals with a new diagnosis of DM required exclusion of any previous DM, NPDR, or PDR diagnosis in the look-back period. We also excluded individuals age 95+ in 1995 and persons who entered a Medicare risk plan (HMO) or lived

outside of the U.S for 12 months or more during the look-back period. To ensure that AMD diagnosis occurred after the diagnosis of all diabetes mellitus, we excluded any individual initially diagnosed with AMD prior to a diabetes mellitus or diabetic retinopathy diagnosis in 1995. To minimize bias from differences in visits to an eye care provider, we excluded any individual who had not seen an eye care provider at least once during the look-back and at least once during both the first and the last five years of the follow-up period.

Sample individuals were followed for the incident diagnosis of dry or wet AMD for 10 years or until censored. Individuals were censored as of their date of death, the date they joined an HMO, or the date they moved outside of the U.S. Individuals who enrolled in an HMO or moved out of the U.S. were censored as of January 1st of the year in which they reported enrollment or extended travel outside of the U.S.

Propensity Score Matching

A control group was created consisting of persons never diagnosed with any DM, with the same exclusion restriction described above. Using propensity score matching, we created a control sample of equal number to each of the diabetic diagnoses (DM, NPDR, PDR) based on observable covariates. The matched sample consisted of 16,510 individuals.

Eligible persons with a new diagnosis in 1995 of DM (n = 6,621), of NPDR (n = 1,307), and of PDR (n = 327) were compared to an equivalent number of controls without DM. For each group, we performed logit analysis to predict the probability of an individual having DM, NPDR, or PDR, respectively, considering the control pool in all 3 analyses being persons never diagnosed with diabetes mellitus. Covariates for the logit analysis were variables for age, male, black and other non-white race, hypertension (401.xx–405.xx), atherosclerosis (440.xx), stroke (430.xx–438.xx), coronary heart disease (410.xx–414.xx), hyperlipidemia (272.0–272.4) and the Charlson index of general health.[18]

Using the predicted probabilities from the logit analysis, we paired an individual in the DM, NPDR, or PDR group with the individual's nearest match in the control group. Matching on propensity score reduces selection bias between individuals with a diagnosis, in this case DM, NPDR, and PDR, and those without. We matched treatment to each of the control groups with nearest neighbor matching. The program, SAS Greedy 5 to 1 digit match macro (http://www2.sas.com/proceedings/sugi29/165-29.pdf: Parsons LS. Performing a 1:N Case-Control Match on Propensity Score (accessed April 9, 2012)[19]) uses SAS PROC LOGISTIC and made the best match first by pairing individuals in the treatment and control group on exact 5 digit matches of their predicted probability of receipt of DM, NPDR, and PDR. Considering all persons not previously matched, the macro then attempted to match individuals based on 4 digits of their propensity score, then 3, then 2, and 1. Individuals unable to be matched on 1 digit were excluded. Standardized differences were calculated for the matched samples. A standardized difference is the difference in mean values in treated and control group (probabilities in dichotomous variables) divided by the square root of half of the sum of the variances in the treated and control groups.[20] Cox proportional hazard analysis controlled for other differences in covariates not captured by the matching process.

RESULTS

Individuals with DM, NPDR, and PDR were matched at baseline to an equivalent number of 'no DM' controls by age, gender, race, history of hypertension, atherosclerosis, stroke, coronary heart disease, hyperlipidemia, and Charlson index (Table 2). All variables were matched between diabetic/diabetic retinopathy subtypes and controls except for the Charlson index, which could not be matched to a standard difference <10% for individuals with NPDR or PDR.

Persons from all subtypes of diabetes/diabetic retinopathy had increased mean number of visits to an eye care provider over the 10-year period compared to matched controls (27.08 (DM) versus 26.38 (control), p=0.031; 35.87 (NPDR) versus 25.79 (control), p<0.0001; 42.43 (PDR) versus 27.01 (control), p<0.0001) (Table 3). Additionally, all subtypes of diabetes/diabetic retinopathy had greater rates of death over the 10-year follow-up compared to matched controls without DM (38% (DM) versus 30% (control), p<0.0001; 49% (NPDR) versus 30% (control), p<0.0001; 55% (PDR) versus 28% (control), p<0.0001).

Over 10 years, the risk of dry or wet AMD diagnosis was not significantly different between persons with a DM diagnosis compared to matched controls without DM (Table 3 and 4). Persons with NPDR were at significantly higher risk of both dry AMD (35% (NPDR) versus 30% (control), p=0.003; hazard ratio (HR) 1.24 (95% confidence interval (CI): 1.08–1.43)) and wet AMD (9% (NPDR) versus 6% (control), p=0.001; HR 1.68 (95% CI: 1.23–2.31)) compared to persons without diabetes mellitus. Persons with PDR had an equivalent risk of dry AMD compared to persons without diabetes mellitus. Before controlling for other variables, individuals with PDR had increased risk of being diagnosed with wet AMD; however, the difference was not statistically significant (7% (PDR) versus 4% (controls), p=0.14)(Table 3). After controlling for other variables, including various systemic comorbidities and the Charlson index, the risk of being diagnosed with wet AMD was statistically significant (p=0.03), with over 2 times higher risk for persons with a PDR diagnosis compared to controls without diabetes mellitus (HR 2.15 (95% CI: 1.07–4.33)) (Table 4). The risk of wet AMD diagnosis was not different in NPDR compared to PDR persons (p=0.24).

DISCUSSION

Age-related macular degeneration and diabetic retinopathy are among the leading causes of vision loss in the world.[1–4] Our analysis of 5% Medicare claims data suggests that diabetic retinopathy, both nonproliferative and proliferative, may predispose individuals to an increased risk of AMD, which was not evident among those with diabetes mellitus without retinal manifestations. Interestingly, NPDR increased risk of both dry and wet AMD diagnoses while PDR increased risk of a diagnosis of wet AMD only.

Previous studies examining the relationship between DM and AMD have been contradictory (Table 5). Examination of these studies demonstrates that large population-based cross-sectional and longitudinal studies, including the Beaver Dam Eye Study, [5] the Blue Mountains Eye Study,[6] the EUREYE Study,[9] the Age-Related Eye Disease Study,[7] and the Barbados Eye Disease Study,[8] suggest an increased risk of AMD with diabetes mellitus. While these studies did not differentiate between diabetes and diabetic eye disease, our results, which demonstrate increased risk of AMD with diabetic retinopathy, are in line with these investigations.

These studies are in contrast to anecdotal clinical observations [10,11] and smaller case-control-type studies [12,21] that indicate a lower prevalence of AMD among persons with diabetes mellitus. Still other reports have not demonstrated an association between AMD and diabetes mellitus. Some of these investigations were small case-control studies [14–16] or small prospective cohort studies [17] that may not have been sufficiently powered to detect any difference. The Framingham Eye Study also did not reveal an association between AMD and diabetes mellitus, but this study was likely limited by different criteria and/or less sensitive methods for the detection of AMD than in current practice.[13]

Our study utilized a large, nationally representative, longitudinal sample of U.S. elderly individuals to further investigate the relationship between AMD and diabetes/diabetic

retinopathy. An important strength of our study is the large, nationally representative sample size, which yielded ample statistical power and allowed us to distinguish between diabetes mellitus and types of retinopathy, in contrast to previous larger studies which examined patients broadly classified with diabetes mellitus.[5–9] Our results indicate that diabetic persons without retinopathy are not at significantly higher risk of developing an AMD diagnosis. It is possible that patients diagnosed with diabetes mellitus who were examined in these previous ophthalmologic studies, which did not distinguish between patients with and without retinopathy, were biased towards having retinopathy.

Another strength of this study is the longitudinal tracking of incident AMD over a 10-year period. Cross-sectional studies examining prevalence of these conditions may be biased by selective mortality increased in patients with diabetes mellitus and diabetic retinopathy, which may result in a selectively diminished prevalence of diabetes mellitus and diabetic retinopathy in the elderly population most affected by AMD. Anecdotal clinical observations on the low prevalence of neovascular AMD and diabetes mellitus may be similarly influenced by this phenomenon and by presentation bias given the racial predilection of diabetes mellitus in African-Americans and of AMD in Caucasians.[1]

We acknowledge several study limitations. The Medicare database represents information collected for billing purposes and not for the analysis of clinical investigations. Relevant conditions may sometimes have been incorrectly coded. The database includes clinically ambiguous codes, including 362.81 (retinal hemorrhage: preretinal, retinal (deep) (superficial), subretinal), which may arise secondary to either non-proliferative or proliferative/neovascular etiologies, and 362.57 (drusen), which is often used to code for peripheral drusen not diagnostic for macular degeneration. While we did not include these ambiguous codes in our final analysis, a parallel analysis was performed with inclusion of these codes (data not shown), resulting in similar results with significantly increased risk of wet AMD (but not dry AMD) in patients with NPDR and PDR only. The Medicare database is also limited in its inability to identify which eye has disease. Diabetic retinopathy and age-related macular degeneration are generally considered to be bilateral conditions, but it is possible, although unlikely, that the associations observed in this study apply to the same individual but in different eyes. Alternatively, diagnostic coding does not accurately assess dietary intake, anti-oxidant supplementation, smoking history, or family history of AMD, and analysis of the Medicare claims data is therefore unable to match these factors that may modulate AMD pathogenesis. Moreover, we cannot rule out the possibility that the associations observed in this study may be a result of differences in follow-up. We attempted to control for this ascertainment bias by excluding individuals who did not have at least 1 visit to an eyecare provider in the look-back period, in the first 5 years, and in the last 5 years. While persons with worsening diabetic retinopathy demonstrated increased numbers of visits to the eyecare provider, the lowest mean number of visits, observed in the control group, was nearly 26 visits over the study period, which should be sufficient to detect incident AMD if present. Although there is a single Medicare code for the specialty of ophthalmology, which cannot distinguish between ophthalmology subspecialists, optical coherence tomography (OCT) may be considered a surrogate marker for a retinal exam. OCT was not first coded until 1999 and not standard of clinical practice until well after, but comparison of number of OCT exams among all groups including the control group (data not shown) did not reveal any statistically significant differences.

In matching beneficiaries for our longitudinal analysis, the declining general health in the PDR and NPDR groups made it difficult to find suitable matches in the control group. We were unable to match Charlson index to a standardized difference < 10% for the NPDR or PDR groups, which is likely a reflection of the systemically poorer health of persons with NPDR or PDR. Systemic health is well-associated with AMD, and while it may be possible

that differences in Charlson index contributed to differences in AMD risk, we were successful in matching specific variables associated with increased risk for AMD, specifically age, gender, black and other non-white race, hypertension, atherosclerosis, stroke, coronary heart disease, and hyperlipidemia. In addition, to further account for these differences in health in our hazard analysis, we controlled for the Charlson index and, as an extra caution, all other matched variables in the hazard analysis to better isolate the effect of diabetes/diabetic retinopathy on the incidence of AMD independent of the Charlson index and the other matched variables.

The Medicare database is inherently restricted to individuals aged 65+. As a result of our 4-year look-back period, our study was limited to persons aged 69+ with new onset diabetes mellitus or diabetic retinopathy at 1995. In the Wisconsin Epidemiologic Study of Diabetic Retinopathy, the mean age of diagnosis of adult-onset diabetes mellitus was 54.8 years of age.[22] In another study, persons with type 2 diabetes mellitus who were diagnosed before age 45 were found to have higher prevalence and increased severity of diabetic retinopathy than those diagnosed at an older age.[23] Our study design, necessary to obtain a pure cohort, analyzes a study population composed of persons who had diabetes mellitus or diabetic retinopathy later in life. Elderly persons with diabetes mellitus represent a sizeable and rapidly growing population with high rates of ophthalmic and systemic complications,[24,25] and AMD is a disease by definition of older individuals, making the Medicare population in many ways the most relevant one for this type of inquiry. Nonetheless, it is possible that these persons may not be representative of the general population of persons with diabetes mellitus.

Diabetic retinopathy is generally considered to be a disease of the inner retina, in contrast to the outer retinal involvement in age-related macular degeneration, but there may be features common to both diseases. Macular retinal pigment epithelium abnormalities and increased area of drusen have been correlated with increased blood sugar levels and impaired glucose tolerance.[26–28] Carbohydrate-related mechanisms have been implicated in the pathogenesis of both diseases, including the formation of advanced glycation end products.[29,30] Additionally, a higher dietary glycemic index was found to be associated with increased risk of early and late AMD in non-diabetic subjects[31] and with increased risk of AMD progression in early stages of disease.[32] Moreover, both wet AMD and diabetic retinopathy appear to be vascular endothelial growth factor (VEGF) mediated, and the use of anti-VEGF pharmaceutical agents has proven useful in the treatment of both diseases. While analysis of claims data is not designed towards biologic conclusions, these results raise the possibility that diabetic retinopathy and AMD may share pathogenic features and that improved control of diabetes may reduce development of AMD. It is interesting that NPDR increased risk of both dry and wet AMD while PDR increased risk of wet AMD only; this discrepancy may represent a difference in the biology within the spectrum of these diseases. Further studies would be needed to test these possibilities.

We designed our 10-year longitudinal analysis to terminate in 2005. While pegaptanib was FDA-approved for the treatment of AMD in December 2004, the use of anti-VEGF agents exploded after the initial report of the efficacy of bevacizumab for the treatment of neovascular AMD in 2005.[33,34] It is unclear if the use of anti-VEGF agents, which appear to be useful in the treatment of numerous retinal diseases, alters the incidence of retinal diseases, and we limited our study period to the pre-bevacizumab/pre-ranibizumab era to minimize these potentially confounding effects. As we obtain long-term information on patients treated with these agents, it will be interesting to determine if any shifts occur in the relationship observed in the pre-anti-VEGF era between wet AMD and diabetic retinopathy.

CONCLUSION

Our results indicate that non-proliferative diabetic retinopathy may increase the risk of both dry and wet age-related macular degeneration and that proliferative diabetic retinopathy may increase the risk of wet age-related macular degeneration. Further studies examining this relationship in patients and investigating common pathogenic mechanisms should be undertaken to gain a better understanding of these disease processes.

Acknowledgments

References

1. Munoz B, West SK, Rubin GS, et al. Causes of blindness and visual impairment in a population of older Americans: The Salisbury Eye Evaluation Study. Arch Ophthalmol. Jun; 2000 118(6):819–825. [PubMed: 10865321]

2. Weih LM, VanNewkirk MR, McCarty CA, Taylor HR. Age-specific causes of bilateralvisual impairment. Arch Ophthalmol. Feb; 2000 118(2):264–269. [PubMed: 10676793]

3. Fong DS, Aiello L, Gardner TW, et al. Retinopathy in diabetes. Diabetes Care. Jan; 2004 27 (Suppl 1):S84–87. [PubMed: 14693935]

4. Friedman DS, O'Colmain BJ, Munoz B, et al. Prevalence of age-related macular degeneration in the United States. Arch Ophthalmol. Apr; 2004 122(4):564–572. [PubMed: 15078675]

5. Klein R, Klein BE, Moss SE. Diabetes, hyperglycemia, and age-related maculopathy. The Beaver Dam Eye Study. Ophthalmology. Oct; 1992 99(10):1527–1534. [PubMed: 1454318]

6. Mitchell P, Wang JJ. Diabetes, fasting blood glucose and age-related maculopathy: The Blue Mountains Eye Study. Aust N Z J Ophthalmol. Jun-Aug;1999 27(3–4):197–199. [PubMed: 10484190]

7. Clemons TE, Milton RC, Klein R, Seddon JM, Ferris FL 3rd. Risk factors for the incidence of Advanced Age-Related Macular Degeneration in the Age-Related Eye Disease Study (AREDS) AREDS report no. 19. Ophthalmology. Apr; 2005 112(4):533–539. [PubMed: 15808240]

8. Leske MC, Wu SY, Hennis A, et al. Nine-year incidence of age-related macular degeneration in the Barbados Eye Studies. Ophthalmology. Jan; 2006 113(1):29–35. [PubMed: 16290049]

9. Topouzis F, Anastasopoulos E, Augood C, et al. Association of diabetes with age-related macular degeneration in the EUREYE study. Br J Ophthalmol. Aug; 2009 93(8):1037–1041. [PubMed: 19429584]

10. Gass JD. Drusen and disciform macular detachment and degeneration. Arch Ophthalmol. Sep; 1973 90(3):206–217. [PubMed: 4738143]

11. Benson, WE.; Brown, GC.; Tasman, W. Diabetes and its ocular complications. Philadelphia: Saunders; 1988.

12. Borrone R, Saravia M, Bar D. Age related maculopathy and diabetes. Eur J Ophthalmol. Nov-Dec; 2008 18(6):949–954. [PubMed: 18988167]

13. Kahn HA, Leibowitz HM, Ganley JP, et al. The Framingham Eye Study. II. Association of ophthalmic pathology with single variables previously measured in the Framingham Heart Study. Am J Epidemiol. Jul; 1977 106(1):33–41. [PubMed: 141882]

14. Maltzman BA, Mulvihill MN, Greenbaum A. Senile macular degeneration and risk factors: a case-control study. Ann Ophthalmol. Aug; 1979 11(8):1197–1201. [PubMed: 556147]

15. Hyman LG, Lilienfeld AM, Ferris FL 3rd, Fine SL. Senile macular degeneration: a case-control study. Am J Epidemiol. Aug; 1983 118(2):213–227. [PubMed: 6881127]

16. Blumenkranz MS, Russell SR, Robey MG, Kott-Blumenkranz R, Penneys N. Risk factors in age-related maculopathy complicated by choroidal neovascularization. Ophthalmology. May; 1986 93(5):552–558. [PubMed: 2425325]

17. Voutilainen-Kaunisto RM, Terasvirta ME, Uusitupa MI, Niskanen LK. Age-related macular degeneration in newly diagnosed type 2 diabetic patients and control subjects: a 10-year follow-up on evolution, risk factors, and prognostic significance. Diabetes Care. Nov; 2000 23(11):1672–1678. [PubMed: 11092291]

18. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987; 40(5):373–383. [PubMed: 3558716]

19. Parsons, LS. [accessed April 9, 2012] Performing a 1:N Case-Control Match on Propensity Score. http://www2.sas.com/proceedings/sugi29/165-29.pdf

20. Austin PC, Grootendorst P, Anderson GM. A comparison of the ability of different propensity score models to balance measured variables between treated and untreated subjects: a Monte Carlo study. Stat Med. Feb 20; 2007 26(4):734–753. [PubMed: 16708349]

21. Zylbermann R, Landau D, Rozenman Y, Abrahami S, Pollack A. Exudative age-related macular degeneration in patients with diabetic retinopathy and its relation to retinal laser photocoagulation. Eye (Lond). 1997; 11 (Pt 6):872–875. [PubMed: 9537150]

22. Klein R, Klein BE, Moss SE, Davis MD, DeMets DL. The Wisconsin epidemiologic study of diabetic retinopathy. III. Prevalence and risk of diabetic retinopathy when age at diagnosis is 30 or more years. Arch Ophthalmol. Apr; 1984 102(4):527–532. [PubMed: 6367725]

23. Wong J, Molyneaux L, Constantino M, Twigg SM, Yue DK. Timing is everything: age of onset influences long-term retinopathy risk in type 2 diabetes, independent of traditional risk factors. Diabetes Care. Oct; 2008 31(10):1985–1990. [PubMed: 18628565]

24. Bethel MA, Sloan FA, Belsky D, Feinglos MN. Longitudinal incidence and prevalence of adverse outcomes of diabetes mellitus in elderly patients. Arch Intern Med. May 14; 2007 167(9):921–927. [PubMed: 17502533]

25. Sloan FA, Bethel MA, Ruiz D Jr, Shea AM, Feinglos MN. The growing burden of diabetes mellitus in the US elderly population. Arch Intern Med. Jan 28; 2008 168(2):92–199. discussion 199.

26. Vidaurri JS, Pe'er J, Halfon ST, Halperin G, Zauberman H. Association between drusen and some of the risk factors for coronary artery disease. Ophthalmologica. 1984; 188(4):243–247. [PubMed: 6204260]

27. Algvere P, Efendic S, Luft R, Wajngot A. Retinal microangiopathy and pigment epithelial lesions in subjects with normal, borderline, and decreased oral glucose tolerance. Br J Ophthalmol. Jun; 1985 69(6):416–419. [PubMed: 4005209]

28. Jensen VA, Lundbaek K. Diabetic pigmentopathy of the mascula lutea; a new ophthalmological anomaly in long-term diabetes. Ophthalmologica. Feb; 1955 129(2):89–93. [PubMed: 14384209]

29. Howes KA, Liu Y, Dunaief JL, et al. Receptor for advanced glycation end products and age-related macular degeneration. Invest Ophthalmol Vis Sci. Oct; 2004 45(10):3713–3720. [PubMed: 15452081]

30. Stitt AW. AGEs and diabetic retinopathy. Invest Ophthalmol Vis Sci. Oct; 2010 51(10):4867–4874. [PubMed: 20876889]

31. Chiu CJ, Milton RC, Gensler G, Taylor A. Association between dietary glycemic index and age-related macular degeneration in nondiabetic participants in the Age-Related Eye Disease Study. Am J Clin Nutr. Jul; 2007 86(1):180–188. [PubMed: 17616779]

32. Zhang X, Gregg EW, Cheng YJ, et al. Diabetes mellitus and visual impairment: national health and nutrition examination survey, 1999–2004. Arch Ophthalmol. Oct; 2008 126(10):1421–1427. [PubMed: 18852421]

33. Rosenfeld PJ, Moshfeghi AA, Puliafito CA. Optical coherence tomography findings after an intravitreal injection of bevacizumab (avastin) for neovascular age-related macular degeneration. Ophthalmic Surg Lasers Imaging. Jul-Aug;2005 36(4):331–335. [PubMed: 16156152]

34. Curtis LH, Hammill BG, Schulman KA, Cousins SW. Risks of mortality, myocardial infarction, bleeding, and stroke associated with therapies for age-related macular degeneration. Arch Ophthalmol. Oct; 2010 128(10):1273–1279. [PubMed: 20937996]

Summary statement

Using the 5% sample of Medicare claims data, the 10-year incidence of dry and wet AMD was compared among elderly beneficiaries with newly diagnosed DM without retinopathy (n=6,621), NPDR (n=1,307), and PDR (n=327) compared with an equivalent number of matched controls without diabetes for each sample group. A significantly increased risk of dry and wet AMD was identified with newly diagnosed NPDR; a significantly increased risk of wet AMD only was identified with newly diagnosed PDR. Diabetes mellitus without retinopathy did not affect risk of dry or wet AMD.

Table 1

ICD-9-CM codes

Diabetes Mellitus (DM)
250.xx (diabetes mellitus)
Non-Proliferative Diabetic Retinopathy (NPDR)
362.01 (background diabetic retinopathy)
362.03 (nonproliferative diabetic retinopathy, NOS)
362.04 (mild)
362.05 (moderate)
362.06 (severe)
362.07 (diabetic macular edema)
250.5 + 362.53 (diabetes with ophthalmic manifestations + cystoid macular edema)
250.5 + 362.83 (diabetes with ophthalmic manifestations + retinal edema: cotton wool spots, edema (localized) (macular)(peripheral))
Proliferative Diabetic Retinopathy (PDR)
362.02 (proliferative diabetic retinopathy)
250.5 + 364.42 (diabetes with ophthalmic manifestations + rubeosis iridis)
250.5 + 379.23 (diabetes with ophthalmic manifestations + vitreous hemorrhage)
250.5 + 361.81 (diabetes with ophthalmic manifestations + traction detachment of retina)

Dry AMD
362.50 (macular degeneration (senile), unspecified)
362.51 (nonexudative senile macular degeneration)
Wet AMD
362.52 (exudative senile macular degeneration)
362.42 (serous detachment of retinal pigment epithelium)
362.43 (hemorrhagic detachment of retinal pigment epithelium)

Table 2

Baseline demographics of matched samples with standardized differences

Variable	DM (n=6621)	Controls (n=6621)	Std. Diff	NPDR (n=1307)	Controls (n=1307)	Std. Diff	PDR (n=327)	Controls (n=327)	Std. Diff
Age (years)	76.04	76.09	−1.01	75.25	75.67	−9.55	74.87	75.36	−11.70
Male gender	0.35	0.35	0.00	0.36	0.36	0.32	0.34	0.37	−5.11
Black race	0.07	0.07	0.24	0.13	0.20	−20.74	0.17	0.17	0.81
Other race	0.03	0.03	−0.36	0.04	0.04	0.00	0.05	0.06	−5.50
Hypertension	0.71	0.70	0.50	0.77	0.76	0.54	0.76	0.73	−6.33
Atherosclerosis	0.11	0.11	−0.05	0.14	0.14	0.22	0.15	0.18	−6.58
Stroke	0.19	0.19	0.66	0.21	0.24	−5.31	0.25	0.28	−7.62
Coronary heart disease	0.41	0.41	−0.06	0.44	0.46	−4.15	0.47	0.47	−0.61
Hyperlipidemia	0.45	0.45	0.12	0.41	0.39	4.06	0.38	0.41	−5.00
Charlson Index	1.88	1.73	6.66	3.53	2.05	54.03	3.79	2.75	34.65

Table 3

Univariate analysis of matched sample outcomes over 10 years

	DM (n=6621)	Controls (n=6621)	NPDR (n=1307)	Controls (n=1307)	PDR (n=327)	Controls (n=327)
Developed dry AMD (%/100)	0.33	0.33	0.35	0.30 **	0.30	0.29
Developed wet AMD (%/100)	0.07	0.06	0.09	0.06 **	0.07	0.04
Death (%/100)	0.38	0.30 **	0.49	0.30 **	0.55	0.28 **
# eye doctor visits	27.08	26.38 *	35.87	25.79 **	42.43	27.01 **

*
Significant at the 5% level

**
Significant at the 1% level

Table 4

Hazard analysis for the incidence of dry or wet AMD according to diabetic/diabetic retinopathy status from 1995–2005

	Dry AMD			Wet AMD		
	Hazard Ratio (95% CI) for Development of Dry AMD			Hazard Ratio (95% CI) for Development of Wet AMD		
	DM (n=6621)	NPDR (n=1307)	PDR (n=327)	DM (n=6621)	NPDR (n=1307)	PDR (n=327)
Diabetes Subtype	1.03 (0.97 1.09)	1.24 (1.08 1.43) **	1.10 (0.83 1.47)	1.11 (0.97 1.27)	1.68 (1.23 2.31) **	2.15 (1.07 4.33) *
Age (years)	1.07 (1.06 1.07) **	1.07 (1.06 1.09) **	1.06 (1.02 1.09) **	1.07 (1.05 1.08) **	1.08 (1.05 1.12) **	1.07 (0.99 1.16)
Male gender	0.96 (0.90 1.03)	0.75 (0.65 0.88) **	0.95 (0.70 1.30)	0.99 (0.86 1.15)	0.82 (0.59 1.13)	1.38 (0.68 2.77)
Black race	0.48 (0.41 0.56) **	0.37 (0.29 0.48) **	0.37 (0.22 0.63) **	0.35 (0.23 0.53) **	0.32 (0.17 0.59) **	---
Other race	0.87 (0.72 1.04)	0.73 (0.51 1.05)	0.78 (0.40 1.53)	0.51 (0.29 0.88) *	0.37 (0.12 1.17)	3.37 (1.26 9.01) **
Hypertension	1.01 (0.94 1.08)	1.17 (0.99 1.39)	0.92 (0.66 1.28)	1.00 (0.86 1.17)	1.05 (0.73 1.49)	0.71 (0.33 1.51)
Atherosclerosis	1.03 (0.94 1.14)	1.00 (0.81 1.23)	1.05 (0.71 1.55)	1.13 (0.92 1.40)	1.13 (0.73 1.75)	0.78 (0.26 2.33)
Stroke	1.11 (1.02 1.20) *	0.93 (0.77 1.11)	0.75 (0.53 1.06)	1.06 (0.88 1.27)	0.96 (0.65 1.42)	0.58 (0.23 1.48)
Coronary heart disease	1.04 (0.98 1.11)	0.96 (0.83 1.11)	1.04 (0.76 1.42)	0.84 (0.72 0.98) *	1.00 (0.73 1.37)	0.80 (0.39 1.67)
Hyperlipidemia	0.98 (0.92 1.04)	0.93 (0.81 1.07)	0.79 (0.58 1.07)	0.87 (0.76 1.00)	0.79 (0.58 1.08)	1.37 (0.70 2.70)
Charlson Index	1.01 (0.99 1.02)	1.02 (0.99 1.05)	1.06 (1.00 1.11) *	1.02 (0.99 1.05)	1.00 (0.94 1.07)	1.01 (0.89 1.15)

*
significant at the 5% level

**
significant at the 1% level

--- indicates sample size too small to register event