NIH Public Access
Author Manuscript
Ophthalmology. Author manuscript; available in PMC 2012 May 1.

Published in final edited form as:
Ophthalmology. 2011 May ; 118(5): 860–865. doi:10.1016/j.ophtha.2010.08.040.

Is Diabetic Retinopathy Related to Subclinical Cardiovascular Disease?

Ryo Kawasaki[1,2], **Ning Cheung**[1], **FM Amirul Islam**[1], **Ronald Klein**[3], **Barbara EK Klein**[3], **Mary Frances Cotch**[4], **A Richey Sharrett**[5], **Daniel O'Leary**[6], and **Tien Y. Wong**[1,7] **for the Multi-Ethnic Study of Atherosclerosis (MESA)***

[1] Centre for Eye Research Australia, Royal Victorian Eye and Ear Hospital, University of Melbourne, Australia

[2] Centre for Clinical Research Excellence in Diabetes, St. Vincent Hospital, Australia

[3] Department of Ophthalmology and Visual Sciences, University of Wisconsin School of Medicine and Public Health, Wisconsin, USA

[4] Division of Epidemiology and Clinical Applications, National Eye Institute, National Institutes of Health, Maryland, USA

[5] Department of Epidemiology, Johns Hopkins University Bloomberg School of Public Health, Maryland, USA

[6] Caritas Carney Hospital, Dorchester, Massachusetts

[7] Singapore Eye Research Institute, National University of Singapore, Singapore

Abstract

OBJECTIVE—Persons with diabetic retinopathy (DR) have an increased risk of clinical cardiovascular events. Our study aimed to determine whether DR is associated with a range of measures of subclinical cardiovascular disease (CVD) in persons without clinical CVD.

DESIGN—Population-based, cross-sectional epidemiologic study

PARTICIPANTS—Nine hundred and twenty seven persons with diabetes without clinical CVD in the Multi-Ethnic Study of Atherosclerosis.

METHODS—DR was ascertained from retinal photographs according to modification of the Airlie House Classification system. Vision threatening DR (VTDR) was defined as severe non-proliferative DR, proliferative DR or clinically significant macular edema. Subclinical CVD measures were assessed and defined as follows: high coronary artery calcium (CAC) score, defined as CAC score≥400; low ankle-brachial index (ABI), defined as ABI<0.9; high ABI, defined as ABI≥1.4; high carotid intima-media thickness (IMT), defined as highest 25% of IMT; and carotid stenosis, defined as >25% stenosis or presence of carotid plaque.

MAIN OUTCOME MEASURES—Associations between DR and subclinical CVD measures.

Correspondence to: Tien Yin Wong, MD, MPH, PhD, Centre for Eye Research Australia, University of Melbourne, 32 Gisborne Street, Victoria 3002 Australia, Tel: +61 3 9929 8352, Fax: +61 3 9662 3859, twong@unimelb.edu.au.

*A full list of participating MESA investigators can be found at http://www.mesa-nhlbi.org.

Conflict of Interest/Disclosure: None

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

RESULTS—The prevalence of DR and VTDR in this sample was 30.0% and 7.2%, respectively. VTDR was associated with a high CAC score (odds ratio [OR] 2.33, 95% condifence interval [CI] 1.15–4.73), low ABI (OR 2.54; 95%CI, 1.08–5.99) and high ABI (OR 12.6, 95% CI, 1.14, 140.6), after adjusting for risk factors including hemoglobin A1c level and duration of diabetes. The association between VTDR and high CAC score remained significant after further adjustment for hypoglycemic, anti-hypertensive and cholesterol-lowering medications. DR was not significantly associated with measures of carotid artery disease.

CONCLUSIONS—In persons with diabetes without a history of clinical CVD, the presence of advanced stage of DR is associated with subclinical coronary artery disease. These findings emphasize the need to be careful about the use of anti-vascular endothelial growth factor for the treatment of DR.

It is well known that in persons with diabetes, the presence of diabetic retinopathy (DR) is a marker for an increased risk of clinical cardiovascular disease (CVD) events, such as stroke, coronary heart disease and heart failure[1–3]. One possible hypothesis explaining these associations is that retinal microvascular abnormalities may reflect early subclinical disease in the coronary or cerebral microvasculature, predisposing people to develop clinical cardiovascular events [2, 4].

However, to date, relatively little is known about the relationship between DR and subclinical CVD. A few studies have explored the association between DR and subclinical measures of CVD. In the Cardiovascular Health Study (CHS) [5], there was a three-fold increased risk of having DR in persons with thicker carotid intima-media thickness (IMT). In the Atherosclerosis Risk in Communities Study (ARIC) [6] study, low ankle-brachial index (ABI) of <0.9, a measure of peripheral artery disease and thicker carotid IMT, were associated with DR. In the general population, mild retinopathy signs have been shown to be associated with coronary artery calcification [7], reduced arterial compliance [8], and increased aortic stiffness[9]. Findings from these studies are clinically relevant, particularly with the emerging interest and use of anti-vascular endothelial growth factor (anti-VEGF) therapy for treating advanced stages of DR, because such treatments might increase a person's risk of CVD.[10–12]

In this study, we investigate the relationships between DR and measures of subclinical vascular disease in the coronary, carotid and peripheral circulations in the Multi-Ethnic Study of Atherosclerosis (MESA).

RESEARCH DESIGN AND METHODS

Study Population

The MESA is a population-based cohort study of white, African American, Hispanic, and Chinese American men and women aged 45–84 years without a history of clinical cardiovascular disease enrolled from six communities in the United States, and detailed study procedures have been described elsewhere [13, 14]. Markers of atherosclerosis were available from 6,814 individuals from the first examination (July 2000 to August 2002) [15]. Fundus photography was performed at the second examination using a standardized protocol; both eyes of each participant were photographed using a 45-degree digital non-mydriatic camera. Two photographic fields, centered on the optic disc and macula, were sent from the six field centers to the Fundus Reading Center at the University of Wisconsin (Madison, WI) for assessment of DR and other retinal pathologies. 6,176 had completed retinal photography [13, 14]. Amongst these 6,176 persons, we included 927 persons with diabetes, defined as fasting glucose ≥7.0 mmol/l (126 mg/dl) or use of insulin or oral medication for diabetes; no distinction was made between type 1 and type 2 diabetes;

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

however, because >95% of people were diagnosed to have diabetes after the age of 30 years, the majority were type 2 diabetes.[14] The tenets of the Declaration of Helsinki were followed, and institutional review board approval was granted at each study site. Written informed consent was obtained from each participant.

Assessment for Diabetes and Diabetic retinopathy

The detailed assessment process for DR in the MESA has been described elsewhere [14]. In brief, a retinopathy severity score was determined based on masked grading of retinal images with a modification of the Airlie House Classification system [14]. Levels 14–20 were defined as 'minimal non-proliferative DR (NPDR),' levels 31 and 41 as 'early to moderate NPDR,' and levels 51–80 as 'severe NPDR or PDR.' Presence of clinically significant macular edema (CSME) was also assessed. Vision threatening DR (VTDR) was defined as having either 'severe NPDR or PDR' or CSME.

Markers of Subclinical CVD

Coronary Artery Calcium (CAC) score—Computed tomography of coronary arteries was performed with cardiac-gated electron beam scanners at three centers (Imatron C-150; Imatron, Inc., San Francisco, California) or with a prospectively electrocardiogram-triggered scan acquisition at 50 percent of the R-R interval with multidetector scanners [16] at the remaining three centers. CAC scores among scanning centers and between participants were adjusted with a phantoms of known physical calcium concentrations. Scans were read centrally at Harbor-University of California Medical Center (Los Angeles, California) for quantification of CAC score, with high agreement for presence of coronary calcification (κ-statistic 0.90–0.93 inter- and intra-grader intraclass correlation coefficient [ICC]) and for CAC score (ICC = 0.99). "High CAC score" was defined as having the Agatston CAC score of ≥400.

Ankle-Brachial Index (ABI)—Measurements for calculation of ABI were obtained using a hand-held Doppler instrument with a 5-mHz probe (Nicolet Vascular, Golden, Colorado). Systolic blood pressure measurements were obtained from bilateral brachial, dorsalis pedis, and posterior tibial arteries[17]. The ABI was computed separately for each leg, with the numerator of the highest of the dorsalis pedis or posterior tibial artery and with the denominator of the highest of the right and left brachial systolic pressure; the ABI for the subject was the lower of the right or left ABI [18]. ABI <0.9 was used as a cut-off value to define "low ABI." High ABI was defined as >1.4, because high ABI is considered as reflecting a medial calcification of muscular arteries commonly found in elderly and diabetic patients [19].

Intima-Media Thickness (IMT) and Stenosis of carotid artery with plaque—Images of bilateral common carotid and internal carotid arteries were obtained using high-resolution B-mode ultrasonography [20]. A Logiq 700 ultrasound machine (GE Medical Systems, Waukesha, Wisconsin) was used at all study centers. Mean maximum wall thickness across all scans for the left and right sides and across the near and far walls for the common and internal carotid were averaged to obtain maximum internal and maximum common carotid IMT value. "High IMT" was defined as having IMT of the highest 25 percentile in persons with diabetes included in this analysis. "Carotid stenosis" was defined as ≥25% stenosis in the common or internal artery with carotid plaque.

Assessment of other cardiovascular risk factors

Participants underwent detailed interview and assessment of cardiovascular risk factors at the first and second examination. Variables for this analysis were based on data collected at

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

the second examination when fundus photography was performed, unless data were not available, in which case data from the first examination were used. Details of assessment have been described elsewhere. In brief, blood pressure was measured three times with the participant in the seated position, and the average of the last two measurements was adopted; mean arterial blood pressure calculated as "1/3 systolic blood pressure + 2/3 diastolic blood pressure" of the first and second examination were used for further analysis. Height and weight were measured with the participant wearing light clothing and no shoes, and body mass index (BMI) was calculated as weight divided by the square of height (kg/m^2). A detailed questionnaire was used to obtain information about medical history, cigarette smoking, and medication use. Fasting blood samples were drawn from participants and analyzed for plasma total and high density lipoprotein (HDL) cholesterol, plasma triglycerides, serum glucose, glycosylated hemoglobin, and C-reactive protein (CRP). Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥ 90 mmHg, or current use of antihypertensive medication.

Statistical analysis

Presence of any DR, presence of CSME, or presence of VTDR was analyzed as the exposures variables. We used multiple logistic regression models to estimate the odds ratio of having each of the five subclinical CVD measures: high CAC, low and high ABI, high carotid IMT, and carotid stenosis. We used three statistical models adjusting for age, gender, race/ethnicity, and study centers (**Model 1**), adjusting for variables in model 1 plus BMI, mean arterial blood pressure of the first and second examinations, serum total cholesterol, triglyceride, HDL, cigarette smoking and C-reactive protein (**Model 2**), adjusting for variables in model 2 plus hemoglobin A1c, duration of diabetes and presence of diabetic nephropathy (**Model 3**), and adjusting for variables in model 3 plus anti-hypertensive medication, cholesterol lowering medication, and type of diabetes medication (insulin or oral medication) (**Model 4**). Interaction between race/ethnicity and presence of any DR, CSME, or VTDR were examined by adding interaction-terms in each models.

RESULTS

DR was present in 30% of persons with diabetes, and VTDR and CSME was present in 7.2% and 5.5%, respectively. Table 1 shows that those with DR have higher serum glucose, higher systolic blood pressure, higher hemoglobin A1c, and longer duration of diabetes compared to diabetic participants without DR, and more were using medications for diabetes.

The presence of any DR, CSME and VTDR was associated with a high CAC score (odds ratio [OR] 1.80, 3.11, and 3.23, respectively) after adjusting for variables in Model 2 (**Model 2,** Table 2). VTDR was associated with higher CAC (OR 2.34), after further adjusting for hemoglobin A1c, duration of diabetes, diabetic nephropathy and medication for diabetes, hypertension and high cholesterol (**Model 4**, Table 2).

Presence of any DR, CSME, and VTDR was associated with low ABI (OR 1.87, 4.35, and 4.93, respectively) after adjustment for age, gender, race/ethnicity, and study center (**Model 1,** Table 2). The association for VTDR and low ABI remained significant after adjusting for other cardiovascular risk factors in Model 3 (OR 2.54). Presence of CSME and VTDR were associated with higher risk of high ABI after multivariate adjusting (OR 13.4 and 11.8, respectively) (**Model 3,** Table 2), but not after adjusted for medication for diabetes, high cholesterol and hypertension (**Model 4,** Table 2).

The presence of any DR was associated with high IMT after adjustment for age, gender, race/ethnicity, and study center (**Model 1,** Table 2). However, this association was

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

substantially attenuated and became non-significant after further adjustment for duration of diabetes and diabetic nephropathy. Presences of any DR, CSME or VTDR were not significantly associated with carotid stenosis in any of the models (Table 2).

In a supplementary analysis, there were no significant interaction between race/ethnicity and presence of any DR, CSME, or VTDR (data not shown).

DISCUSSION

The MESA allowed a unique opportunity to determine the relationship of DR with a range of subclinical measures of CVD (e.g., CAC, carotid IMT and ABI). CAC is commonly used to provide more accurate prediction of CVD that is independent of standard risk factors or inflammatory markers.[21, 22] Low ABI is a well known marker of peripheral artery disease, and is also predictive of clinical CVD [23].

In this multi-ethnic cohort of persons with diabetes without a history of clinical CVD, we found that the presence of severe DR (i.e., severe NPDR, PDR or CSME) was associated with 2-fold higher odds of having a high CAC score (OR 2.33) and low ABI of <0.9 (adjusted OR 2.69) after adjusting for traditional cardiovascular risk factors plus hemoglobin A1c, duration of diabetes and diabetic nephropathy (**Model 3,** Table 2). After further adjusting for medications for diabetes, hypertension, and high cholesterol, the association between VTDR and CAC remained significant, while associations between VTDR and low or high ABI were diminished (**Model 4,** Table 2). This findings support the hypothesis that there is a pathophysiologic link between DR and subclinical CVD, especially for increased CAC.

Contrary to our expectations, the presence of DR was not associated with high IMT or carotid stenosis in this study. Although the ARIC [6] reported 0.1 mm increase in IMT was associated with 10% higher risk of having DR, the CHS did not find any significant association between DR and carotid IMT or plaque,[5] after adjusting for blood pressure and glucose level [5]. Higher IMT and carotid plaque are manifestations of atherosclerosis in the carotid arteries, and they are also reported to be associated with CVD [20]. Some studies have reported that predictive power of high IMT on myocardial infarction was less than that of CAC score [24]. The presence of retinopathy lesions was associated with high IMT in persons without diabetes in the MESA after adjusting traditional cardiovascular risk factors (adjusted OR 1.35, 95%CI 1.03, 1.77; data not shown), suggesting non-diabetic retinopathy and DR may have different associations with higher IMT. This needs to be investigated in future studies.

We also found that the presence of CSME or VTDR was marginally associated with high ABI of≥1.4 independent of cardiovascular risk factors (Table 2, **Model 3**), although it was not significant after further adjusting for hypoglycemic, anti-hypertensive and cholesterol-lowering medications (Table 2, **Model 4**). The reasons for this finding are not apparent but could be related to the small number of participants in high ABI group.

Our findings have clinical relevance to both general physicians and ophthalmologists. Our data show that persons with severe DR are more likely to have subclinical vascular disease, especially in the coronary circulation, than those without DR. Thus, patients with severe DR are not only at risk of losing sight from DR but also are at risk of life-threatening systemic vascular complications of diabetes, even in the absence of clinically apparent CVD.[2, 3] A detailed cardiovascular examination might be warranted for these patients identified by ophthalmologists. Furthermore, there is growing interest and use of anti-VEGF therapy for treating severe DR. Although this form of treatment is administered intravitreally, a significant proportion of anti-VEGF agents could pass into the systemic circulation.[10] Thus,

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

systemic inhibition of angiogenesis is a potential risk, which could compromise critical vascular responses to ischemic events in patients with diabetes. Long-term systemic exposure to anti-VEGF agents and the need for repeated administration might be associated with increased risks of systemic vascular complications,[10–12] such as stroke and non-ocular hemorrhages (eg, gastric and renal).[25, 26] Although clinical trials on the use of intravitreal anti-VEGF therapy for treatment of age-related macular degeneration generally show low rates of vascular complications, this risk could be magnified in patients with DR because of pre-existing diabetes-related subclinical vascular disease. Thus, both clinicians and patients should recognize and weigh the risks and benefits of these agents when they are used to treat diabetic retinopathy.[1]

The strength of this study is as a large, multi-ethnic sample with standardized assessment of atherosclerotic markers, retinal photographs and cardiovascular disease risk factors. Limitations of this study should be noted. First, as this is a cross-sectional study, the nature of the study design does not provide whether retinopathy antecedent to atherosclerotic markers or vice versa. Secondly, subclinical CVD were assessed at the first examination while DR was assessed in the second examinations. Although the time distance between first and second examination was relatively short (up to 2 years), this is not strictly a cross-sectional analysis. Third, we may be relatively underpowered to examine some of the relations involving VTDR and CSME which have a relatively low frequency in the cohort.

In summary, our data show that people with severe DR are more likely to have subclinical systemic vascular disease, especially in the coronary circulation, than those without DR. Therefore, people with severe DR are not only at risk of losing sight but may be at risk of life-threatening systemic vascular complications of diabetes even in the absence of a history of clinical CVD. These findings have implications for the management of diabetes patients, including the use of anti-VEGF agents for advanced DR, for both general physicians and ophthalmologists.

Acknowledgments

Source of Funding: Supported by Contracts N01-HC-95159 through N01-HC-95165 and N01-HC-95169 and Grant R01HL69979 (Klein R and Wong TY) from the National Heart, Lung and Blood Institute and a NIH Intramural Research Award Z01EY00403 (MFC) from the National Eye Institute, USA. Additional support was provided by National Institutes of Health grants HL69979-03 (Klein R and Wong TY).

References

1. Cheung N, Mitchell P, Wong TY. Diabetic Retinopathy. Lancet. 2010; 376(9735):124–36. [PubMed: 20580421]
2. Cheung N, Wang JJ, Klein R, et al. Diabetic retinopathy and the risk of coronary heart disease: the Atherosclerosis Risk in Communities Study. Diabetes Care. 2007; 30(7):1742–6. [PubMed: 17389333]
3. Cheung N, Rogers S, Couper DJ, et al. Is diabetic retinopathy an independent risk factor for ischemic stroke? Stroke. 2007; 38(2):398–401. [PubMed: 17194880]
4. Krentz AJ, Clough G, Byrne CD. Interactions between microvascular and macrovascular disease in diabetes: pathophysiology and therapeutic implications. Diabetes Obes Metab. 2007; 9(6):781–91. [PubMed: 17924862]
5. Klein R, Marino EK, Kuller LH, et al. The relation of atherosclerotic cardiovascular disease to retinopathy in people with diabetes in the Cardiovascular Health Study. Br J Ophthalmol. 2002; 86(1):84–90. [PubMed: 11801510]
6. Klein R, Sharrett AR, Klein BE, et al. The association of atherosclerosis, vascular risk factors, and retinopathy in adults with diabetes: the atherosclerosis risk in communities study. Ophthalmology. 2002; 109(7):1225–34. [PubMed: 12093643]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

7. Wong TY, Cheung N, Islam FM, et al. Relation of retinopathy to coronary artery calcification: the multi-ethnic study of atherosclerosis. Am J Epidemiol. 2008; 167(1):51–8. [PubMed: 17893402]
8. Cheung N, Islam AFM, Jacobs DR, et al. Arterial compliance and retinal vascular caliber in cerebrovascular disease. Annals of Neurology. 2007; 62(6):618–24. [PubMed: 17918248]
9. Cheung N, Sharrett AR, Klein R, et al. Aortic distensibility and retinal arteriolar narrowing: the multi-ethnic study of atherosclerosis. Hypertension. 2007; 50(4):617–22. [PubMed: 17698721]
10. Wirostko B, Wong TY, Simo R. Vascular endothelial growth factor and diabetic complications. Prog Retin Eye Res. 2008; 27(6):608–21. [PubMed: 18929676]
11. Ueta T, Yanagi Y, Tamaki Y, Yamaguchi T. Cerebrovascular accidents in ranibizumab. Ophthalmology. 2009; 116(2):362. [PubMed: 19187826]
12. Nicholson BP, Schachat AP. A review of clinical trials of anti-VEGF agents for diabetic retinopathy. Graefes Arch Clin Exp Ophthalmol. 2010; 248(7):915–30. [PubMed: 20174816]
13. Wong TY, Islam FM, Klein R, et al. Retinal vascular caliber, cardiovascular risk factors, and inflammation: the multi-ethnic study of atherosclerosis (MESA). Invest Ophthalmol Vis Sci. 2006; 47(6):2341–50. [PubMed: 16723443]
14. Wong TY, Klein R, Islam FM, et al. Diabetic retinopathy in a multi-ethnic cohort in the United States. Am J Ophthalmol. 2006; 141(3):446–55. [PubMed: 16490489]
15. Katz R, Wong ND, Kronmal R, et al. Features of the metabolic syndrome and diabetes mellitus as predictors of aortic valve calcification in the Multi-Ethnic Study of Atherosclerosis. Circulation. 2006; 113(17):2113–9. [PubMed: 16636166]
16. Carr JJ, Crouse JR, Goff D. Evaluation of sub-second gated helical CT for quantification of coronary artery calcium and comparison with electron beam CT. Am J Radiol. 2000; 174:915–21.
17. McDermott MM, Criqui MH, Liu K. Lower ankle/brachial index, as calculated by averaging the dorsalis pedis and posterior tibial arterial pressures, is associated with leg functioning in peripheral arterial disease. J Vasc Surg. 2000; 32:1164–71. [PubMed: 11107089]
18. Aboyans V, Criqui MH, McClelland RL, et al. Intrinsic contribution of gender and ethnicity to normal ankle-brachial index values: the Multi-Ethnic Study of Atherosclerosis (MESA). J Vasc Surg. 2007; 45(2):319–27. [PubMed: 17264011]
19. Micheletti RG, Fishbein GA, Currier JS, Fishbein MC. Monckeberg sclerosis revisited: a clarification of the histologic definition of Monckeberg sclerosis. Arch Pathol Lab Med. 2008; 132(1):43–7. [PubMed: 18181672]
20. O'Leary DH, Polak JF, Kronmal RA, et al. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. Cardiovascular Health Study Collaborative Research Group. N Engl J Med. 1999; 340(1):14–22. [PubMed: 9878640]
21. Arad Y, Goodman KJ, Roth M, et al. Coronary calcification, coronary disease risk factors, C-reactive protein, and atherosclerotic cardiovascular disease events: the St. Francis Heart Study J Am Coll Cardiol. 2005; 46(1):158–65.
22. Detrano R, Guerci AD, Carr JJ, et al. Coronary Calcium as a Predictor of Coronary Events in Four Racial or Ethnic Groups. N Engl J Med. 2008; 358(13):1336–45. [PubMed: 18367736]
23. Fowkes FG, Murray GD, Butcher I, et al. Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality: a meta-analysis. Jama. 2008; 300(2):197–208. [PubMed: 18612117]
24. Vliegenthart R, Oudkerk M, Song B, et al. Coronary calcification detected by electron-beam computed tomography and myocardial infarction. The Rotterdam Coronary Calcification Study. Eur Heart J. 2002; 23(20):1596–603. [PubMed: 12323159]
25. Wong TY. Age-Related Macular Degeneration. Why Should Stroke Physicians Care? Stroke. 2010; 41(4):575–6. Erratum in Stroke; 41(7) e12. [PubMed: 20150541]
26. Wong TY. Age-related macular degeneration and cardiovascular disease in the era of anti-vascular endothelial growth factor therapies. Am J Ophthalmol. 2009; 148(3):327–9. [PubMed: 19703607]

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

Table 1

Characteristics of 927 Participants with Diabetes in the Multi-Ethnic Study of Atherosclerosis

	Diabetic Retinopathy		
	Absent n=649	**Present n=278**	
	Mean (SD) or %	***Mean (SD) or %***	***p-value****
Age, years	65.7 (9.3)	65.0 (9.2)	0.29
Gender, Male	51.9 %	52.1 %	0.96
Serum glucose, mg/dL	148.5 (49.0)	166.1 (63.4)	<0.001
Haemoglobin A1c, %	7.0 (1.4)	7.8 (1.9)	<0.001
Diabetic medication			
Oral diabetic medication	47.2%	55.5%	<0.001
Insulin	5.9%	21.5%	<0.001
Diabetes duration			
<3 year	75.3 %	39.9 %	
3–10 years	15.6 %	24.8 %	<0.001
≥10 year	9.1%	35.3 %	
Median (inter quartile range), years	0 (0 – 5.0)	7.0 (0 – 16.0)	<0.001
Systolic blood pressure, mmHg	129.3 (20.0)	133.9 (24.9)	0.003
Diastolic blood pressure, mmHg	70.7(10.1)	70.3 (11.3)	0.47
Hypertension	71.7 %	76.8 %	0.09
Lipid-Lowering Medication	25.7 %	25.8 %	0.99
Alcohol consumption	38.4 %	34.7 %	0.26
Current cigarette smoker	11.4 %	10.1 %	0.56

SD: standard deviation

*P-value based on chi-square or Mann-Whitney U test, comparing diabetes participants with and without diabetic retinopathy.

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

Table 2

Associations of Diabetic Retinopathy and Subclinical Markers of Cardiovascular Disease.

	¶ n (%)	† Model 1 OR (95% CI)*	‡ Model 2 OR (95% CI)*	‡‡ Model 3 OR (95% CI)*	# Model 4 OR (95% CI)*
Coronary Artery Calcium >400					
§ DR Absent	*94/649 (14.5)*	1.00	1.00	1.00	1.00
§ DR Present	*55/278 (19.8)*	**1.68 (1.13, 2.47)**	**1.72 (1.16, 2.56)**	1.51 (0.98, 2.35)	1.53 (0.99, 2.38)
CSME	*16/47 (34.0)*	**2.75 (1.40, 5.38)**	**2.86 (1.44, 5.66)**	2.03 (0.93, 4.42)	2.06 (0.93, 4.54)
VTDR	*21/65 (32.3)*	**2.83 (1.56, 5.10)**	**2.97 (1.62, 5.42)**	**2.33 (1.15, 4.73)**	**2.34 (1.13, 4.84)**
Low Ankle Brachial Index <0.9					
§ DR Absent	*39/639 (6.1)*	1.00	1.00	1.00	1.00
§ DR Present	*25/271 (9.2)*	**1.87 (1.06, 3.28)**	1.67 (0.94, 2.97)	1.10 (0.58, 2.09)	1.21 (0.62, 2.34)
CSME	*10/45 (22.2)*	**4.35 (1.88, 10.0)**	**4.08 (1.73, 9.59)**	1.88 (0.70, 5.02)	1.63 (0.58, 4.55)
VTDR	*15/62 (24.2)*	**4.93 (2.38, 10.2)**	**4.56 (2.17, 9.59)**	**2.54 (1.08, 5.99)**	2.12 (0.87, 5.19)
High Ankle Brachial Index ≥1.4					
§ DR Absent	*4/639 (0.6)*	1.00	1.00	1.00	1.00
§ DR Present	*6/271 (2.2)*	**4.05 (1.11, 14.8)**	**4.58 (1.17, 17.9)**	3.56 (0.77, 16.5)	4.69 (0.87, 25.3)
CSME	*3/45 (5.4)*	**10.9 (2.56, 46.3)**	**16.6 (3.26, 84.3)**	**14.4 (1.39, 150.2)**	**21.4 (1.14, 401.8)**
VTDR	*3/62 (7.2)*	**9.29 (2.18, 39.6)**	**14.5 (2.89, 72.4)**	**12.6 (1.14, 140.6)**	14.6 (0.71, 300.5)
Carotid IMT in the highest 25%					
§ DR Absent	*218/620 (35.2)*	1.00	1.00	1.00	1.00
§ DR Present	*112/265 (42.3)*	**1.46 (1.07, 1.99)**	**1.48 (1.08, 2.02)**	1.22 (0.86, 1.72)	1.23 (0.87, 1.74)
CSME	*26/60 (43.3)*	1.13 (0.59, 2.19)	1.09 (0.56, 2.11)	0.72 (0.35, 1.47)	0.76 (0.37, 1.57)
VTDR	*18/43 (41.9)*	1.26 (0.72, 2.21)	1.20 (0.68, 2.11)	0.74 (0.39, 1.40)	0.77 (0.40, 1.48)
Carotid stenosis (≥25%) by plaque					
§ DR Absent	*103/639 (16.1)*	1.00	1.00	1.00	1.00
§ DR Present	*55/275 (20.0)*	1.39 (0.96, 2.03)	1.40 (0.95, 2.05)	1.29 (0.85, 1.97)	1.32 (0.87, 2.00)
CSME	*8/44 (18.2)*	0.91 (0.40, 2.07)	0.93 (0.41, 2.13)	0.74 (0.30, 1.81)	0.73 (0.30, 1.80)
VTDR	*10/62 (16.1)*	0.80 (0.39, 1.65)	0.78 (0.37, 1.62)	0.57 (0.25, 1.29)	0.56 (0.25, 1.28)

Ophthalmology. Author manuscript; available in PMC 2012 May 1.

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

[*] OR: odds ratio; CI: confidence interval

[¶] n (%), number (percentage) of endpoint in persons with diabetic retinopathy lesions.

[§] DR=Diabetic Retinopathy with grade>14. VTDR: vision-threatening diabetic retinopathy defined as proliferative diabetic retinopathy or clinically significant macular edema (CSME).

[†] Model 1: Adjusted for age, gender, race/ethnicity, and study center;

[‡] Model 2: Adjusted for variables in model 1 plus body mass index, mean arterial blood pressure (average of the first and second examination), total cholesterol, triglyceride, high-density lipoprotein cholesterol, cigarette smoking and C-reactive protein.

[‡‡] Model 3: Adjusted for variables in model 2 plus hemoglobin A1c, duration of diabetes and presence of diabetic nephropathy.

[#] Model 4: Adjusted for variables in model 3 plus anti-hypertensive medication, cholesterol lowering medication, and type of diabetes medication (insulin or oral medication).