AMERICAN ACADEMY™ OF OPHTHALMOLOGY

First Prospective Cohort Study of Diabetic Retinopathy from Sub-Saharan Africa

High Incidence and Progression of Retinopathy and Relationship to Human Immunodeficiency Virus Infection

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Purpose: To describe the prevalence, incidence, and progression of retinopathy and to report associations with demographic, clinical, and biochemical variables in people with diabetes in Southern Malawi.

Design: Prospective cohort study.

Participants: Subjects were systematically sampled from 2 primary care diabetes clinics.

Methods: We performed the first prospective cohort study of diabetic retinopathy from Sub-Saharan Africa over 24 months. Visual acuity, glycemic control, blood pressure, human immunodeficiency virus (HIV) status, urine albumin-to-creatinine ratio, hemoglobin, and lipids were assessed. Retinopathy was graded at an accredited reading center using modified Wisconsin grading of 4-field mydriatic photographs.

Main Outcome Measures: Incidence of sight-threatening retinopathy and progression of retinopathy by 2 steps on the Liverpool Diabetic Eye Study Scale.

Results: A total of 357 subjects were recruited to the 24-month cohort study. At baseline, 13.4% of subjects were HIV positive and 15.1% were anemic. The 2-year incidence of sight-threatening diabetic retinopathy (STDR) for subjects with level 10 (no retinopathy), level 20 (background), and level 30 (preproliferative) retinopathy at baseline was 2.7% (95% confidence interval [CI], 0.1−5.3), 27.3% (95% CI, 16.4−38.2), and 25.0% (95% CI, 0−67.4), respectively. In a multivariate logistic analysis, 2-step progression of diabetic retinopathy was associated with glycosylated hemoglobin (odds ratio [OR], 1.27; 95% CI, 1.12−1.45), baseline grade of retinopathy (OR, 1.39; 95% CI, 1.02−1.91), and HIV infection (OR, 0.16; 95% CI, 0.03−0.78). At 2 years, 17 subjects (5.8%) lost ≥15 letters.

Conclusions: Incidence of STDR was approximately 3 times that reported in recent European studies. The negative association of HIV infection with retinopathy progression is a new finding. *Ophthalmology 2016;123:1919-1925 © 2016 The Authors. Published by Elsevier Inc. on behalf of the American Academy of Ophthalmology. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).*

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The International Diabetes Federation has estimated that the number of adults diagnosed with diabetes in Africa will increase from 12.1 million in 2010 to 23.9 million in 2030.[1] The prevalence and incidence of sight-threatening diabetic retinopathy (STDR) in developed countries[2−4] and the association with systemic factors, including glycemic control,[5,6] blood pressure,[7] and blood lipid levels,[8] are well documented. No cohort studies have investigated the determinants of severity and progression of diabetic retinopathy (DR) in Sub-Saharan Africa.[9] In this resource-poor setting, population-specific variables, such as a high burden of infectious disease (including human immunodeficiency virus [HIV] and malaria) and anemia, may affect the spectrum of pathology encountered.

Malawi (population 15.9 million) is one of the poorest countries in the world, with an annual per capita health care expenditure of US$77.[10] The World Health Organization (WHO) Malawi national STEPwise survey estimated a prevalence of diabetes of 5.6% in adults aged 25 to 64 years, with a similar prevalence in rural and urban areas.[11] In 2007, our group performed a cross-sectional study using clinical ocular examination to assess grades of retinopathy in patients attending the diabetes clinic at Queen Elizabeth Central Hospital (QECH), Blantyre.[12,13] We reported a high prevalence of sight-threatening and proliferative retinopathy: 19.6% and 5.7%, respectively. Because of these important findings, we performed the Malawi Diabetic Retinopathy Study (MDRS), a prospective, observational cohort study of patients attending 2 hospital diabetes clinics over 24 months. The study aimed to describe the prevalence, incidence, and progression of DR in Southern Malawi and to investigate the determinants of retinopathy severity and

http://dx.doi.org/10.1016/j.ophtha.2016.05.042
ISSN 0161-6420/16

progression in this population. Baseline data from the cohort have been published.[14]

Methods

Setting

The QECH in Blantyre is the main teaching hospital in Malawi. It provides primary and secondary care to the urban and semi-urban population of greater Blantyre (~1.0 million people, 50% adult) and tertiary care to the southern region. Zomba Central Hospital (ZCH) provides primary and secondary care to the Zomba district. The diabetes clinics at QECH and ZCH are the only public sector diabetes clinics in Blantyre and Zomba, with approximately 2000 and 250 registered patients, respectively. The clinics provide free consultation and monitoring (measurement of height and weight, blood pressure, and fasting blood glucose). Medications regularly available free of charge are metformin, glibenclamide, and insulin (lente and soluble), as well as a limited range of antihypertensives.

Participants

Patient selection has been described.[14] Briefly, systematic random sampling was used to select subjects from the diabetes clinics at QECH and ZCH between December 2011 and May 2012. Patients attend these clinics for medical management of diabetes; no eye care is provided. The inclusion criterion was a diagnosis of diabetes according to American Diabetes Association criteria.[15] Exclusion criteria were age <18 years and diagnosis of gestational diabetes according to American Diabetes Association criteria. The diabetes clinics at QECH and ZCH provide predominantly primary diabetes care (primary care for diabetes is nonexistent at the health center level). Central hospitals are tertiary centers that receive referral cases. To effectively exclude referral cases, patients living more than 60 km from the clinic in question and those visiting the clinic for the first time were excluded from the study.

Procedures

After assessment at baseline, subjects were recalled (by telephone or home visit) at 12 and 24 months. Clinical assessment of subjects in the MDRS has been described.[14] Briefly, visual acuity (VA) (uncorrected and using pinhole) was measured as the number of letters read on a standard Early Treatment of Diabetic Retinopathy Study (ETDRS) chart. Moderate visual impairment (50−59 letters; equivalent to 6/24 Snellen) and severe visual impairment or blindness (<50 letters; equivalent to 6/36 or worse) were defined according to the WHO.[16] For each patient with corrected VA <80 letters in the better eye, the primary cause of visual impairment was recorded by the examining clinician (P.I.B.). Subjects were classified as having hypertension according to the WHO definition[11]: taking antihypertensive medication, systolic blood pressure ≥140 mmHg, or diastolic blood pressure ≥90 mmHg. All subjects were offered point-of-care testing for HIV (Malawian national protocol[17]) and hemoglobin level. Thresholds for anemia were set according to WHO guidelines: 130 g/l for men and 120 g/l for women.[18] Blood samples were assayed for putative biochemical risk factors: fasting glucose, triglycerides, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, serum creatinine, urine albumin-to-creatinine ratio (uACR), and glycosylated hemoglobin (HbA1c).

Retinopathy and maculopathy were classified by feature-specific grading using definitions established in the Liverpool Diabetic Eye Study (LDES)[19] (Appendix Fig 1, available at www.aaojournal.org). Dual grading of digital photographic images of four 45° standard fields[19] was performed by accredited graders at the Liverpool Reading Centre. Sight-threatening diabetic retinopathy was defined as any of the following: moderate preproliferative retinopathy or worse (level 40 to ≥71); macular exudates in a circinate pattern or within 1 disc diameter of the foveal center or clinically significant macular edema (ETDRS definition[20]) (level 3−4: sight-threatening maculopathy); or other diabetes-related retinal vascular disease: central or branch retinal artery occlusion, central or branch retinal vein occlusion. Subjects who met thresholds for scatter or macular laser treatment were treated by 1 ophthalmologist (P.I.B.). Threshold for scatter laser treatment was the ETDRS 4-2-1 rule (4 quadrants of hemorrhages/microaneurysms standard 2A or greater, *or* 2 quadrants of venous beading standard 6A or greater, or 1 quadrant of intraretinal microvascular abnormalities standard 8A or greater). Threshold for macular laser was clinically significant macular edema as defined in the ETDRS[20] and VA less than 85 ETDRS letters. The majority of deaths in Malawi are not registered. The relatives of deceased subjects were visited at home by a study nurse to confirm the death. Death was recorded if confirmed by a first-degree relative or "traditional authority" (village leader in rural districts).

Statistical Analysis

Grades of retinopathy were calculated by patient according to the worse or only gradable eye. Visual acuity data were investigated by patient according to the better eye. The primary outcome was progression of DR by 2 or more steps on the LDES severity scale (equates to 1-step progression in both eyes *or* 2-step progression in 1 eye). We constructed a multiple logistic regression model (backward stepwise with probability of removal of 0.2) to determine the odds ratio (OR) and 95% confidence intervals (CIs) for 2-step progression in association with an initial 12 variables: time since diagnosis of diabetes, type of diabetes, baseline grade of DR, mean HbA1c (mean of measurement at baseline and 12 and 24 months), systolic blood pressure, uACR, hemoglobin, high-density lipoprotein cholesterol, triglycerides, HIV status, age, and scatter laser treatment any time between baseline and 24 months. Descriptive analysis showed that uACR did not demonstrate a linear association with probability of a 2-step progression; a logarithmic transformation (base 10) was more suitable. All tests were 2 sided, and a P value <0.05 was taken to indicate statistical significance. All calculations were performed using STATA version 12 (StataCorp LP, College Station, TX). The study was approved by the University of Liverpool Research Ethics Committee and the University of Malawi College of Medicine Research Ethics Committee. All participants gave written informed consent.

Results

Of 357 subjects recruited, 322 were seen for at least 1 further study visit and are included in the progression analysis. A total of 313 subjects (88%) and 295 subjects (83%) were assessed at 12 and 24 months, respectively (Appendix Fig 2, available at www.aaojournal.org). Median time to follow-up was 2.0 years (interquartile range, 1.9−2.1 years). Baseline characteristics of subjects seen at 24 months and those who were not seen are shown in Table 1. A total of 50 subjects (14.0%) were HIV positive (48 at baseline and 2 new diagnoses during the study). Incidence of death in the MDRS cohort at 24 months was 8.0% (95% CI, 5.1−10.9; n = 357; Life Table method). Incidence of death among HIV-positive subjects was 18.1% (95% CI, 7.4−28.8; n = 50). Death during the MDRS was associated with STDR (OR, 2.51; 95% CI,