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ORIGINAL ARTICLE

Effectiveness of remote screening for diabetic retinopathy among patients referred to Mozambican Diabetes Association (AMODIA): a retrospective observational study

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Abstract

Aims Diabetes represents a growing public health problem in sub-Saharan Africa, where diabetic retinopathy (DR) is a major cause of permanent visual loss. We reported the results of a remote screening of DR among urbanized Mozambican people with diabetes.

Methods We retrospectively collected retinal images and clinical characteristics from 536 patients screened for DR in Maputo (Mozambique), over a period of 2 years (2018–2019). Retinal photographs were captured, digitally stored, and scored locally and by an expert ophthalmologist in Italy remotely.

Results The overall prevalence of DR was 29% with sight-threatening forms accounting for 8.1% of that number. Inter-reader agreement between the local and the Italian ophthalmologists was poor ($k < 0.2$). Patients with DR were older, had a longer duration of disease, worse glycaemic control, and a higher prevalence of comorbidities. In the multivariate logistic regression analysis, HbA1c, diabetes duration, and coronary heart disease (CHD) were associated with DR.

Conclusion Prevalence of DR among urbanized Mozambican patients was similar to that observed in Western countries. Telediagnosis might partially overcome the paucity of local ophthalmologists with experience in DR.

Keywords Diabetes · Retinopathy · Remote screening · Mozambique

Introduction

The prevalence of diabetes is rapidly growing worldwide, in both developed and developing countries. The International Diabetes Federation (IDF) has estimated that the number of patients with type 2 diabetes in Sub-Saharan Africa (SSA) is expected to increase from 19 million in 2019 to 47 million by 2045 [1]. Despite this dramatic scenario, the needs for diabetes diagnosis and management remain mostly unmet [2]. IDF has estimated that 60% of people with diabetes remain undiagnosed and will be referred to healthcare facilities only when chronic complications have already arisen.

DR represents a common and disabling complication of chronic hyperglycaemia. DR can be divided into two main categories: non-proliferative diabetic retinopathy (NPDR)

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and proliferative diabetic retinopathy (PDR). NPDR is characterized by abnormal permeability of retinal capillaries leading to retinal oedema, vascular occlusion, and ischaemia. PDR occurs when retinal ischaemia leads to neovascularization. In this stage, visual loss occurs when the new abnormal vessels bleed into the vitreous or when tractional retinal detachment is present. It has been estimated that approximately 30% of patients with diabetes experience some degree of DR during their lives [3]. A recent meta-analysis reported that the global prevalence of DR and STDR was 22.3% and 6.2%, respectively. Sub-Saharan Africa had the highest prevalence of DR (36%) and STDR (14.3%) [4]. The Global Burden of Disease Study found that in adults aged 50 years and older, DR was the fifth leading cause of blindness and severe vision impairment [5]. In the period between 1990 and 2020, the prevalence of blindness due to DR arises by 140% in SSA compared to a 35% reduction in Western Europe. These data highlight the need to improve the screening for DR to identify patients that need timely treatment to avoid permanent vision loss.

In 2018, a program focused on the implementation management of diabetes was launched in Mozambique. It was financed by the Italian Agency for Cooperation and Development and implemented by a partnership between Doctors with Africa CUAMM, Mozambican Diabetes Association (AMODIA), and the Mozambican Ministry of Health. Within this project, AMODIA was equipped with a fully automated ophthalmoscope that permits the remote scoring of locally acquired retinal images. The present study was carried out to investigate the prevalence of DR and the clinical characteristics associated with DR in diabetic patients referred to AMODIA for the retinal examination over a period of two years. Furthermore, the agreement between a local and an Italian ophthalmologist was assessed.

Methods

Study design

This is an observational retrospective study. We collected data of urbanized patients with diabetes screened for DR at the headquarters of AMODIA (Hospital Central de Maputo) during the period of January 2018 to December 2019. Retinal images and clinical data were captured, encrypted, and stored in a telemedicine platform for remote consultation. As data were anonymized at the time of extraction, making patient re-identification impossible, no informed consent was required according to national regulations concerning retrospective studies.

Clinical data collection

We recorded the following data: age, sex, weight, body mass index (BMI), type of diabetes, diabetes duration, glycated haemoglobin (HbA1c), serum creatinine, lipid profile, concomitant risk factors, micro- and macrovascular complications of diabetes, and anti-diabetic medications. Concerning the type of diabetes, given the lack of pancreatic autoantibodies determination, we considered type 1 those who required intensive insulin treatment before 30 years with a BMI lower than 25 kg/mq. Hypertension was defined as systolic blood pressure (BP) of 140 mm Hg or greater or diastolic blood pressure of 90 mm Hg or greater or the use of antihypertensive medications. Dyslipidaemia was defined as an LDL cholesterol level $\geq$ 3.4 mmol/L or a triglycerides level $\geq$ 1.7 mmol/L or use of lipid-lowering drugs. Smoke was defined as being habitually smoking one or more cigarettes per day. Metabolic syndrome (MS) was defined using International Diabetes Federation (IDF) criteria [6]. Among patients with diabetes, MS was diagnosed in the presence of BMI $\geq$ 30 kg/mq and at least one of the following criteria: systolic or diastolic BP $\geq$ 130/85 mmHg; HDL cholesterol < 1.16 mmol/L in men or < 1.29 mmol/L in women; triglycerides $\geq$ 1.7 mmol/L. The estimated glomerular filtration rate (eGFR) was calculated according to the Chronic Kidney Disease (CKD) Epidemiology Collaboration formula. CKD was defined as an eGFR less than 60 mL/min per 1.73 m^2. Coronary artery disease was defined as a past history of acute coronary syndrome or coronary revascularization; cerebrovascular disease was defined as a past history of cerebral ischaemia or evidence of carotid artery atherosclerosis. According to the International Working Group on the Diabetic Foot (IWGDF), a diabetic foot was defined by the presence of an ulcer or previous minor or major amputation [7].

Grading of DR

DR was defined based on 45-degree non-mydriatic retinal fundus images (Nexy, Next Sight), according to the Early Treatment Diabetic Retinopathy (ETDR) classification [8]. Sight-threatening forms referred to proliferative retinopathy and/or macular oedema. Proliferative DR was defined by the presence of neovascularization or preretinal haemorrhage. Macular oedema was defined as retinal thickening at or around the fovea with or without hard exudates. Digital retinal images were both examined by a local ophthalmologist and scored remotely by an experienced ophthalmologist in Italy to evaluate inter-rater reliability. The scoring by Italian ophthalmologist was

considered the gold standard to divide patients with and without DR.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD) or median and interquartile range (IQR), where appropriate. Categorical variables were reported as a percentage. The normality of the variables was tested by a Kolmogorov–Smirnov test. Non-normal variables were log-transformed before the analysis. Comparison between two groups was performed using unpaired, two-tail Student's t test for continuous variables and Chi-square test for categorical variables. A multiple logistic regression analysis was used to find variables associated with retinopathy among those emerging from univariate analysis with p values of < 0.05. Cohen's kappa coefficient (k) was used to measure inter-rater reliability between retinal fundus images scored locally and remotely by an experienced ophthalmologist. A k value ≥ 0.7 indicated good agreement. The number need to screen (NNS) was calculated to define the number of people with diabetes who needed to be screened by telemedicine to detect one case of visual-threatening DR. It was calculated as the reciprocal of the difference between the prevalence of severe DR scored

Table 1 Characteristics of patients

	Total	NS	S	p value	NDR	DR	p value
N	536	102	434		307	127	
Age, y	56 ± 13	61 ± 13	55 ± 13	**< 0.001**	54 ± 14	57 ± 11	**0.011**
Male sex, %	37	34	38	0.5	37	39	0.7
Weight, Kg	72 ± 14	71 ± 15	72 ± 14	0.4	72 ± 14	73 ± 12	0.4
BMI, Kg/mq	26	25 ± 5.4	26 ± 5.3	0.5	26 ± 5.5	26 ± 4.9	0.7
Obesity, %	22	23	22	0.8	20	27	0.2
T2DM, %	94	93	95	0.6	92	98	**0.026**
DM duration, y	4 (1–9)	5 (2–11)	4 (1–9)	**0.050**	3 (1–7)	6 (2–12)	**< 0.001**
HbA1c, % (mmol/mol)	9.9 ± 3.9 (85 ± 19)	9.9 ± 3.2 (85 ± 11)	9.8 ± 4 (84 ± 20)	0.9	9.4 ± 3 (79 ± 9)	10 ± 5.8 (96 ± 40)	**0.006**
Total-C, mmol/L	4.8 ± 1.1	4.7 ± 1	4.8 ± 1.1	0.6	4.8 ± 1.1	4.8 ± 1.2	0.6
HDL-C, mmol/L	1.2 ± 0.6	1.3 ± 1	1.2 ± 0.3	0.3	1.2 ± 0.4	1.2 ± 0.3	0.8
LDL-C, mmol/L	3.3 ± 1.1	3.1 ± 1.3	3.3 ± 1	0.1	3.3 ± 1	3.3 ± 1.2	0.9
TGL, mmol/L	1.2 ± 0.8	1.2 ± 0.7	1.2 ± .8	0.8	1.2 ± 0.8	1.2 ± 0.8	0.9
Dyslipidemia, %	52	61	50	0.1	49	52	0.5
Hypertension, %	61	72	58	**0.008**	55	67	**0.019**
Smoke, %	0.9	0	1.2	0.3	1.3	0.8	0.6
MS, %	19	20	20	0.8	17	25	0.1
Microangiopathy							
eGFR, ml/min	90 ± 25	83 ± 26	91 ± 24	**0.002**	93 ± 24	87 ± 24	**0.014**
CKD, %	12	22	10	**0.001**	7.8	16	**0.007**
Neuropathy, %	50	52	50	0.6	51	50	0.5
Macroangiopathy							
CHD, %	2.8	2.9	2.8	0.9	1.3	6.3	**0.004**
Stroke, %	0.7	1	0.7	0.7	0.8	0.7	0.9
PAD, %	2.6	2.9	2.5	0.8	2.3	3.1	0.6
Diabetic foot, %	4.7	2.9	5.1	0.4	3.9	7.9	0.9
Diabetes therapy							
Diet only, %	9.9	9.8	9.9	0.9	12	3.9	**0.007**
Metformin, %	72	68	73	0.3	72	77	0.2
Sulphonilureas, %	20	23	19	0.4	19	20	0.8
Insulin, %	27	30	26	0.4	21	37	**0.001**

Significant p-values are bold

NS not suitable for medical reporting; *S* suitable for medical reporting; *NDR* non-diabetic retinopathy; *DR* diabetic retinopathy; *BMI* body mass index; *T2DM* type 2 diabetes mellitus; *MS* metabolic syndrome; *eGFR* estimated glomerular filtration rate; *CKD* chronic kidney disease; *CHD* coronary heart disease; *PAD* peripheral artery disease

locally and remotely. Statistical significance was accepted at $p < 0.05$, and SPSS version 21.0 was used.

Results

Overall Patient characteristics

We recorded data on a total of 536 patients. Baseline characteristics of patients are shown in Table 1. Among them, 102 patients (19%) had poor quality fundus images that were unsuitable for medical reporting. The patients with ungradable retinal images were significantly older ($p = 0.05$) with a higher rate of hypertension and chronic kidney disease. The patients suitable for screening of DR ($n = 434$) were 55 ± 13 years old, and 38% were males. The median diabetes duration was 4 years (IQR 1–9) and glycaemic control was poor. Individuals with type 1 diabetes (6.1%) had significantly worse glycaemic control than those with type 2 diabetes (Hb1Ac 12% vs 9.7%, $p = 0.001$). Approximately, 20% of patients were obese and a half had dyslipidaemia or arterial hypertension. The prevalence of MS was 20% according to the IDF criteria. Six per cent of patients had macroangiopathy and 60% had at least one microangiopathic complication. Metformin was the most common anti-hyperglycaemic drug, whilst one-third of patients were on insulin.

Prevalence of DR

The overall prevalence of DR scored by the Italian ophthalmologist was 29%, significantly higher than 12% reported locally ($p < 0.0001$). STDR accounted for 8.1%. The value of Cohen's kappa coefficients was lower than 0.2 suggesting a poor inter-rater agreement between Italian and local physicians (Table 2). The NNS was 13 for STDR over two years. Therefore, remote scoring of 100 patients potentially identifies 13 individuals that need timely treatment to avoid permanent vision loss. In Mozambique, where an estimated 337,500 people have diabetes, an extensive two-year remote scoring campaign might preserve more than 40,000 patients from blindness if only a proper treatment were available.

Characteristics of patients with DR

Patients with DR were older, had a longer duration of disease, a worse glycaemic control, and a higher prevalence of comorbidities than those without DR. Insulin therapy was more common among patients with retinal damage compared to those without (Table 1). Clinical characteristics of patients with STDR were similar to those with NPDR, except for lower levels of HDL cholesterol and a higher rate of metformin users (Supp. Table 1).

Clinical variables associated with DR

Variables emerging from univariate analysis with $p < 0.05$ (age, type and duration of diabetes, HbA1c, hypertension, eGFR, CKD and CHD) were included in the multivariate logistic regression analysis (Table 3). In the multivariable analysis, HbA1c, duration of diabetes, and CHD were associated with DR. Notably, the presence of DR led to a fourfold higher odd of CHD (Supp. Table 2).

Table 2 Prevalence of DR and agreement between Italian (ITA) and Mozambican (MZB) readers. DR: diabetic retinopathy; NPRD: non-proliferative diabetic retinopathy; STDR: sight-threatening diabetic retinopathy, including proliferative retinopathy and/or macular oedema. K Cohen < 0.2 indicated poor inter-rater concordance

	ITA	MZB	Person Chi-square	k Cohen
Total DR, %	29	12	< 0.0001	0.18
NPDR, %	21	12	0.031	0.10
STDR, %	8.1	0.5	0.029	0.05

Table 3 Univariate and multivariable logistic regression analysis for factors associated with the presence of overall DR. The OR refers to 1-unit increase in independent variables

	Univariate analysis				Multivariate analysis			
Variables	p value	OR	LL	UL	p value	OR	LL	UL
T2DM, %	0.036	3.7	1.08	12	0.2	2.72	0.64	11
DM Duration, y	< 0.001	1.08	1.04	1.12	**0.018**	1.05	1.01	1.09
HbA1c, %	0.001	1.12	1.05	1.19	**0.001**	1.13	1.05	1.21
eGFR, ml/min	0.015	0.98	0.98	0.99	0.9	0.99	0.98	1.01
CKD, %	0.008	2.33	1.24	4.37	0.2	1.77	0.76	4.12
Neuropathy, %	0.5	0.85	0.56	1.29	Not included			
Hypertension, %	0.020	1.67	1.08	2.58	0.5	1.21	0.74	1.96
CHD, %	0.009	5.10	1.50	17	**0.044**	3.71	1.04	13

Significant p-values are bold

Discussion

To our knowledge, this is the first study reporting the prevalence of DR in a cohort of urbanized Mozambican outpatients. The overall (29%) and vision-threatening (8.1%) prevalence of DR was similar to that observed in different African countries by Burgess [9], and comparable to that reported in Western countries [10, 11]. A previous meta-analysis by our group found an analogous prevalence of retinopathy (26%) in a wide cohort of African patients with diabetes having foot ulcers [12]. However, the high rate of ungradable retinal images might underestimate the prevalence of DR. Previous reports using ultrawide field imaging indicated that the prevalence of STDR is likely to be at least 10% in patients with ungradable retinal images [13]. Therefore, reducing the rate of unassessable images is pivotal for telemedicine programs. Although we did not evaluate the proportion of any visual impairment due to DR, a population-based study from South Africa identified DR as the cause of 8% of blindness and 11% of severe visual loss in persons ≥ 50 years [14]. Moreover, a recent global meta-analysis showed that, in the last twenty years, the prevalence of blindness due to DR increased by 140% in SSA compared to a 35% reduction in Western Europe [5]. Systemic screening for DR is cost-effective in terms of sight years preserved compared with no screening [15]. African countries face a chronic lack of equipment, trained healthcare workers and ophthalmologists. In particular, SSA has one of the lowest numbers of ophthalmologists per million population worldwide, with fewer than three ophthalmologists per million population, compared with the approximately 80 ophthalmologists per million population in high-income countries [16]. Hence, the identification of appropriate and cost-effective strategies to detect and manage DR with less strain on human sources is a compelling need.

Tele-ophthalmology might represent an opportunity to improve screening for DR in resource and specialist limited-countries. The Zimbabwe Retinopathy Telemedicine Project is a positive example of such types of approach [17]. In our study, non-mydriatic retinal images were captured by a trained nurse, evaluated by a local ophthalmologist, and finally graded by an experienced reader in Italy. Approximately, 20% of stored images were of low quality and did not permit fundus oculi exploration. The project funded by the Italian Agency for Cooperation and Development intended to improve the training of the healthcare personnel involved in the acquisition and scoring of retinal images. In particular, the project aims to fund remote teaching and local meetings with Italian experts, but the COVID-19 pandemic had significantly delayed the educational schedule. Furthermore, remote reporting was not real-time, meaning patients had to be recalled at a later date to receive their results. We realized this "stored and forward mode" was difficult to pursue in the Mozambican context, where patients often travel long distances to the hospital and do not have a telephone to be contacted again. Therefore, providing patients with instant feedback is preferred. A strength of our study was the evaluation of inter-rater diagnostic agreement between local and Italian ophthalmologists. The prevalence of overall DR assessed by the Italian reader was three times higher than that reported by the Mozambican ophthalmologist. The disagreement was even higher for the sight-threatening disease. This worrying discrepancy emphasizes the insufficiency of trained specialists for the management of DR that need to be tackled immediately to prevent blindness.

In this context, the emerging technologies based on artificial intelligence (AI), with the use of automated grading software, will provide a beneficial effect on the cost-effectiveness of the screening. This allows non-clinicians to be trained on retinal imaging, obtaining interpretation of the images within minutes and thus giving patients instant feedback. Recently, the accuracy of an AI model using deep learning has been evaluated in a population-based diabetic retinopathy screening program in Zambia [18]. The AI showed a good performance in detecting DR, STDR, and macular oedema, with a sensitivity and specificity similar to human graders. Analogous results were reported by the only other study involving AI and DR in Africa which was done in Nakuru, Kenya [19]. The use of a smartphone's in-built camera for retinal imaging could be another valuable approach to detecting DR due to its portability and ease of use. Images obtained can be graded remotely by trained graders or using smartphone-based automated analysis software [20]. Recent evidence from cost-effectiveness analysis shows that AI, either standalone or used with humans, might be more cost-effective than manual DR screening [21]. Unfortunately, efforts to improve screening programs faced with the lack of treatments such as photocoagulation and intravitreal injections of vascular endothelial growth factor (VEGF) that are unavailable in many parts of Africa.

Few studies evaluated the clinical features of patients with diabetes in Mozambique. In 2005, the cross-sectional study by Silva-Matos et al. reported an average age of 40 years and a body mass index of 23 kg/mq in a cohort of patients with diabetes mainly from rural areas [22]. Over 15 years, we observed a significant increase in life expectations and body mass index as a result of lifestyle changes and urbanization. Notably, the prevalence of MS was around 20%. This demographic transition leads to widespread of detrimental comorbidities such as hypertension, coronary heart disease, and kidney failure. In our study, 70% of patients aged over 50 years had hypertension. Approximately, 3% of subjects had CHD and 12% had CKD. However, the prevalence of coronary and renal disease might be underscored due to the lack of appropriate diagnostics. The metabolic control was

extremely poor and more than 70% of patients had HbA1c higher than 7.5% (58 mmol/mol). Similar findings have been reported from other sub-Saharan countries and might reflect both limited access to drugs and poor awareness of long-term diabetes complications [23, 24]. Notably, the duration of diabetes was very short for a predominantly type 2 population. This might be explained by the delay between onset and clinical diagnosis. Because of the gradual and asymptomatic onset, type 2 diabetes may remain undiagnosed for 4–6 years before a clinical diagnosis. Therefore, the real duration of type 2 diabetes might be longer than 10 years.

Several limitations of this study have to be acknowledged. First, we used a single non-mydriatic 45-degree central-field photograph to facilitate the local staff training. However, we are aware that such a method is burdened by a low sensibility (54–78%) and specificity (88–89%) and is not recommended for community-based screening in high-income countries, where two to four-field imaging is preferred [25]. Furthermore, this approach did not permit the grading of non-proliferative forms of DR. Second, outpatients referred to the AMODIA office in Maputo might not be sufficiently representative of rural areas. Third, we considered type 1, patients who required intensive insulin therapy before 30 years. This is a conservative estimate that might not include late-onset autoimmune diabetes. Finally, data on albuminuria were not available, leading to a potential underestimate of diabetic renal impairment.

In conclusion, the prevalence of DR among urbanized Mozambican patients with diabetes was similar to Western countries. Screening programs play a crucial role in the detection of sight-threatening diseases but are uncommon in Africa due to insufficient ophthalmologists and expensive equipment. In such a context, telediagnosis might be cost-effective, providing time and human sparing solutions. However, any diagnostic effort is likely to be useless if a treatment opportunity is not made available. In logistic regression analysis, HbA1c levels, duration of diabetes, and CHD were associated with DR. The improvement of glycaemic control is still an unmet need that requires immediate action to prevent the future development of detrimental healthcare burden complications.

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Author contributions MR study designed, data analysis and manuscript writing. LN, LS and LMCS data collection. GPF, AA, GP and AT manuscript revision. All authors read and approved the final version of the manuscript. MR is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Declarations

Conflict of interest MR received lecture and advisory board fees from AstraZeneca, Boehringer, Lilly, Mundipharma, Novo Nordisk, Sanofi. AA received research grants, lecture or advisory board fees from Merck Sharp-Dome, AstraZeneca, Novartis, Boeringher-Ingelheim, Sanofi, Mediolanum, Janssen, Novo Nordisk. GPF received lecture fees or grant support from Abbott, AstraZeneca, Boehringer, Lilly, Merck-Sharp-Dome, Mundipharma, Novartis, Novo Nordisk, Sanofi, Servier. The other authors declare no conflict of interest.

Human and animal rights The study was conducted in accordance with the Declaration of Helsinki.

Ethical standard The protocol was approved by the local Ethics Committee.

Informed consent In agreement with National regulations retrospective studies and on data protection and privacy, no informed consent was collected because the database was anonymous.

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