

Higher pulse pressure, systolic arterial hypertension, duration of diabetes and family history of diabetes in Central Africans

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Abstract

Objective: to assess the prevalence and the risk factors of diabetic retinopathy (DR) in urban diabetics from Kinshasa, DRC. **Methods:** this is a community-based cross-sectional survey and a case-control study on diabetic retinopathy in Kinshasa, the capital of DRC. The medical charts of all diabetics (n=3010) \geq 20 years were studied to estimate the prevalence of DR during November 2004. 10% (n=301) of these were randomly selected to reveal 95 diabetics with DR and 206 diabetics without DR (control). Both groups were matched for primary care centre, sex, age, body mass index, and waist circumference, attending the primary care centres between December 2004 and December 2005, and were screened for DR using stereo color photography and ophthalmoscopy. **Results:** the overall prevalence rate of DR in the population was 31.6% (n=950 95% confidence interval [CI]:26.3 – 36.9). Delayed diagnosis of diabetes (\geq 55 years) in the study sample in women, men with high socioeconomic status, and pregnancy onset after the diagnosis of DR among women, were identified as variables for Univariate analysis and for significant risk factors of DR. Logistic regression analysis showed that longer duration of diabetes (\geq 4years) (LDD), systolic arterial hypertension (SAH), higher pulse pressure (\geq 60 mmHg, clinical pre-atherosclerosis/arterial stiffness), and family history of diabetes (FHD), were the significant and independent determinants of DR in the sample study. The multivariate risk of DR conferred by these determinants is enhanced among female diabetics ($y=2.679 + 1.528$ SHT + 1.080 LDD + FHD; $p<0.01$) and patients with type 2 diabetes ($y=2.725 + 1.316$ SHT + LDD + 1.246 FHD; $p<0.05$). The adjusted odds-ratio for DR conferred by higher pulse pressure was 5 (95% CI 2 – 12.8; $p<0.05$). **Conclusion:** Longer duration of diabetes, arterial systolic hypertension, and higher pulse pressure (arterial stiffness) were the most significant independent risk factors of diabetic retinopathy. However, a population-based study is warranted to identify the risk factors, as well as the prevalence of diabetic retinopathy.

Keywords: Africans, diabetic retinopathy, prevalence, pulse pressure, risk factors, type-2 diabetes mellitus.

Introduction

Diabetes mellitus (DM) is a massive problem worldwide with 171 million with the condition today and projected to increase to 360 millions in 2030.¹ In Sub-Saharan Africa in general² and in Democratic Republic of the Congo (DRC) in particular³ the prevalence of DM varies from 1-2% in rural areas to 16% in urban areas. One of the diabetic microvascular complications is diabetic retinopathy (DR) which is defined as damage to microvascular system in the retina due to prolonged hyperglycaemia and is an important cause of blindness in the world.⁴ However, hospital-based data on DR in African settings are fragmented.⁵ Because of the large number of diabetic subjects, DR is likely to pose a heavy public health burden in Sub-Saharan Africa. Community-based data on the prevalence and risk factors of DR in Kinshasa, DRC (Central Africa), are lacking. The aim of this study was to determine the prevalence and the

risk factors of diabetic retinopathy in urban diabetics from Kinshasa, DRC.

Material and methods

Study of DR prevalence

The findings of two color fundus photographs and ophthalmoscopy performed on both eyes of all diabetic patients (n=3010) aged \geq 20 years and belonging to all (n=24) primary care centres for DM in Kinshasa, the largest city (7 millions inhabitants) and capital of DRC were retrospectively analysed in November 2004.

Univariate and multivariate risk factors of diabetic retinopathy

Ten percent (n=301 cases), inclusive of known diabetics with DR, were randomly selected using random digits. Those diabetics with DR (n=95) and 206 controls (diabetics without DR) matched for primary care centres, sex, age, body mass index (BMI), and waist circumference were requested to participate in the cross-sectional and analytic study carried out in the interval between December 2004 and December 2005. Verbal informed consent was obtained from all eligible patients at the examination site. After the study approval by the University of Kinshasa committee of

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Table 1: Univariate risk of diabetic retinopathy conferred by longer duration of diabetics mellitus (≥ 4 years)

Variables	or (ci 95%)	P
In study population	4 (2.7 to 7.1)	<0.000001
Among men	3.7 (1.5 to 2.7)	<0.01
Among women	4.4 (2.5 to 7.7)	<0.000001
In patients with type 2 DM	4.2 (2.2 to 8.4)	<0.000001

Table 2: Insulin treatment related univariate risk of diabetic retinopathy

Variables	or (ci 95%)	P
In study population	2 (1.2 to 3.5)	<0.01
In men	1.3 (0.5 to 3.1)	Ns
In women	2.7 (1.4 to 5.4)	<0.001
In patients with type 2 DM	2.4 (1.4 to 4.1)	<0.001

Ns: $p > 0.05$, not significant.

ethics, all participants were referred to the ophthalmologist (NK J) for diabetic retinopathy screening. The presence and absence of DR were confirmed in case and controls, respectively

Questionnaire

The questionnaire used to obtain information in this cross-sectional study was adapted from the study by Blessey.⁶ The questionnaire sought relevant information on age, sex, delayed diagnosis (age at diagnosis), DM duration, treatment compliance, family history of DM, ethnicity, DM treatment, socioeconomic status, weight, height, body mass index (BMI), waist circumference, systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse pressure, type of DM, pills use and pregnancy after DM onset. The questionnaire was tested in a pilot study with 20 patients prior to the main study. Based on their responses and the level of understanding of the questions in the standardized questionnaire administered during 30 minutes, some ambiguous or unclear questions were restructured or modified.

Procedure

Data were collected during working hours (10:00 am – 15:00 pm). The researchers interacted with each respondent and their physical (anthropometry), clinical (blood pressure components and ophthalmologic characteristics) were noted. Participants had two colour retinal photography ff 450 plus camera (Carl Zeiss Meditec, Jenna, Germany), of one randomly selected eye and ophthalmoscopy performed on both eyes at the examination. A detailed fundus examination was done at the best possible mydriasis, after dilating the pupils with tropicamide (1%) and phenylephrine (10%), using 90 d lens and slit lamp biomicroscope.

Definitions

The diagnosis of DM at age ≥ 55 years was considered delayed. The DM duration was defined by the time interval in years between the DM diagnosis date and the date of the present study. Ethnicity was defined by the cultural

background according to the language (Kongo, Ngala, Luba, Swahili). Longer duration of DM was set at a level of ≥ 4 years (median). The intake of ≥ 4 drinks/day was considered excessive alcohol intake.

DM was defined by a fasting glycaemia ≥ 126 mg/dl (7 mmol/l) (7). Hypertension was defined as systolic blood pressure (SBP) of 140 mmHg or greater or diastolic blood pressure (DBP) of 90 mmHg or greater or under antihypertensive drug treatment as recommended by the 1999 WHO guideline committee.⁸ Higher pulse pressure (SBP-DBP ≥ 60 mmHg) defined pre-clinical atherosclerosis or arterial stiffness.⁹

The minimum criterion for diagnosis of DR was the presence of at least one definite microaneurysm in any field photographed. Photographs were assessed and assigned a retinopathy level, and the final diagnosis for each patient was determined from the grading of the worse eye according to the ETDRS criteria for severity of disease in the individual eye,¹⁰ and from photographs against a light board using Donaldson's stereo viewer.

Statistical analysis

SPSS for windows version 10.0 (SPSS Inc, Chicago, Illinois, USA) was used for statistical analysis. Data are reported as proportions (%) sometimes with 95% confidence interval (95%CI) and mean \pm SD values. The chi-square test was used to compare proportions. Comparisons between groups for continuous variables were made using the student t-test.

The univariate risk of DR was assessed in calculating odds ratios (OR) and its 95% confidence intervals (95% CI) with Mantel Haenszel chi-squared test for comparisons. For multivariate analysis, logistic regression models were used to identify independent predictors (determinants) of DR. Two logistic regression models were used because of the colinearity between pulse pressure ≥ 60 mmHg and arterial systolic hypertension. Statistical significance was set at a level of < 0.05 .

Results

Study of DR prevalence

The prevalence of overt diabetic retinopathy (DR) was 31.6% (n=950/3010 diabetics) (95% CI; 26.3-36.9).

Risk factors of DR

In pooled data of cases and controls, 7(2.3%) were suffering from type 1DM and 294 (97.7%) from type 2 DM.

Univariate analysis

There was no significant association ($p > 0.05$) between age (56.9 \pm 12.1 years vs 58.1 \pm 11.8 years), sex, ethnicity, profession, smoking, excessive alcohol intake, education attainment, residence, and the presence of diabetic retinopathy (results not presented).

Compared to men with low socioeconomic status (12.8% n=6), men with high socioeconomic status presented higher univariate risk of diabetic retinopathy (40.9% n=27, or=5 ci95% 1.7 to 14.3; $p < 0.001$).

Table 3: Anthropometry, components of blood pressure, and hypertension duration according to the presence of diabetic retinopathy in the population

Variables	Presence of diabetic retinopathy	Absence of Diabetic retinopathy	P
Weight (kg)	58.1 ± 11.6	60.3 ± 12.9	ns
Height (m)	1.580 ± 0.1	1.590 ± 0.1	ns
BMI(kg/m ²)	23.1 ± 3.8	23.8 ± 5	ns
Waist girth (cm)	86.1 ± 10.3	88.8 ± 12.7	ns
SBP(mmHg)	131.4 ± 25.6	125.4 ± 22.4	<0.05
DBP(mmHg)	74.4 ± 12.6	75.7 ± 13.6	ns
Pulse pressure (mmHg)	56.9 ± 18.3	49.7 ± 15.2	<0.001
Hypertension duration (years)	4.4 ± 5	4 ± 6	ns

Ns: p>0.05, not significant

Table 4: Pulse pressure (≥60 mmHg) associated risk of diabetic retinopathy

Variables	OR (CI 95%)	P
In study population	2.3 (1.4 to 3.9)	<0.001
In men	3.4 (1.4 to 8.1)	<0.01
In women	1.9 (1.01 to 3.5)	<0.05
In patients with type 2 DM	2.3 (1.4 to 3.8)	<0.001

Table 5: Predictors of diabetic retinopathy in the study population with logistic regression not including pulse pressure ≥60 mmHg

Independent variables	Beta	ES	Wald	Adjusted OR (CI 95%)	p
Systolic hypertension (SBP ≥ 140 mmHg)	1.423	0.469	9.190	4.2 (1.7 to 10.4)	<0.01
DM duration (≥4 years)	1.315	0.455	8.377	3.7 (1.5 to 9.1)	<0.01
Family history of DM	1.159	0.513	5.105	3.2 (1.7 to 8.7)	0.05
Constant	-2.613				<0.0001

Adjusted or for sex, age, socioeconomic status, smoking, alcohol intake, profession, education attainment, type of DM, and DM treatment.

There was a significant association between the presence of diabetic retinopathy and the diagnosis of DM at the age ≥ 55 years in the study population (36.6% n=56 vs 25.5% n=37, or=1.7 CI 95%=1.02 to 2.8; p<0.05), in women (38.5% n=40 vs 24.7% n=20, OR=2 CI95%=1.01 to 3.7; p<0.05), but not in men (37.7% n=16 vs 26.6% n=17; p>0.05).

There was a very significant association between the presence of diabetic retinopathy and longer duration of DM (≥4 years) in general, and in both women and type 2-diabetes in particular (Table 1).

Table 6: Higher pulse pressure, family history of DM and longer DM duration identified significant predictors of diabetic retinopathy in the study population

Independent variables	Beta	ES	Wald	Adjusted OR (CI 95%)	p
Family history of DM	1.155	0.520	4.936	3.2 (1.2 to 8.8)	<0.05
DM duration (≥4 years)	1.233	0.460	7.198	3.4 (1.4 to 8.5)	<0.01
Pulse pressure (≥ 60)	1.615	0.477	11.483	5 (2 to 12.8)	<0.001
Constant	-2.626				<0.05

Adjusted or for sex, age, socioeconomic status, smoking, alcohol intake, profession, education attainment, type of DM, and DM treatment

The association between diabetic retinopathy and insulin treatment was significant in the study population, women and type-2 diabetes, but not in men (Table 2).

The anthropometric parameters, DBP, and hypertension duration were not related to the diabetic retinopathy while higher levels of SBP and pulse pressure were significantly associated with the presence of diabetic retinopathy in the study population (Table 3).

In the study population, arterial hypertension (p>0.05) and diastolic arterial hypertension (p>0.05) were not associated with diabetic retinopathy, whereas systolic arterial hypertension was significantly associated with diabetic retinopathy (OR=2.3 CI 95% 1.4 to 3.8; p<0.01).

The significant association between pulse pressure ≥ 60 mmHg (pre-clinical atherosclerosis/ arterial stiffness) and diabetic retinopathy was shown in the study population, men, women, and type-2 DM (Table 4).

Family history of DM was significantly associated with diabetic retinopathy among women (55.6% vs 25.9%, OR=2.9 CI 95%= 1.0 to 3.7; p>0.05), but not in the study population (41.6% vs 26.3%; p>0.05) or in men (30 % vs 27.3%; p>0.05), in type-1 DM (50% vs 33.3%), and in type-2 DM (41.3% vs 25.7%).

The use of contraceptive pills was not associated with diabetic retinopathy (31.6% vs 33.5%; p>0.05), whereas the onset of pregnancy after the diagnosis of diabetic retinopathy was significantly associated with diabetic retinopathy (65% vs 28%, or=3.2 CI95%= 1.2 to 13.2; p<0.05) among women.

In the type-1 DM, diabetic retinopathy was not associated with SBP and pulse pressure, respectively (results not shown).

Multivariate analysis

In the first multivariate analysis (without higher pulse pressure), systolic arterial hypertension, longer duration of

DM, and family history of DM were identified as significant and independent determinants (predictors) of diabetic retinopathy in the study population (Table 5).

However systolic arterial hypertension was not a significant predictor of diabetic retinopathy in men ($y = -1.946 + 1.812$ DM duration; $p < 0.05$) while diabetic retinopathy was predicted by systolic arterial hypertension, longer DM duration, and family history of DM in women ($y = -2.679 + 1.528$ systolic hypertension + 1.080 longer DM duration ± 1.574 family history of DM; adjusted or conferred by systolic hypertension = 4.3 CI95% = 1.5 to 14.2 ; $p < 0.01$); adjusted or conferred by DM duration ≥ 4 years = 2.9 CI95% 1.5 to 8.4 ; $p < 0.05$); and adjusted or conferred by family history of DM = 4.8 CI95% = 1.4 to 16.9 ; $p < 0.01$) and in type-2 DM ($y = -2.725 + 1.316$ systolic hypertension + 1.418 DM duration ≥ 4 years + 1.246 family history of DM; adjusted or conferred by systolic hypertension = 3.7 CI95% = 1.5 to 9.5 ; $p < 0.01$; adjusted or conferred by DM duration ≥ 4 years = 4.1 CI95% = 1.7 to 10.4 ; $p < 0.01$); and adjusted or conferred by family history of DM = 3.5 CI95% = 1.2 to 10 ; $p < 0.05$).

When the last logistic regression analysis had not included systolic arterial hypertension, pulse pressure ≥ 60 mmHg (pre-clinical atherosclerosis) conferred higher adjusted or and statistical power for diabetic retinopathy in the study population (Table 6).

Discussion

Prevalence of diabetic retinopathy (DR)

This study reports the prevalence of DR (31.6%) in diabetic urban Africans with exclusive type-2 DM (97.7%). The current increase of DM in general and that of DR in particular may be attributed to the past rapid economic, demographic, epidemiologic and nutritional changes experienced in Sub-Saharan Africa.^{2,3} These changes life style has resulted in an increased prevalence of obesity and DM.

This study suggests that the prevalence of DR in Congolese diabetics is lower than 75% reported among Caucasians from USA.^{12,13} However, this confirms the findings shown in developing countries of Sub-Saharan Africa (prevalence of DR between 15 and 52%)^{14,15}, India¹⁶ and Pakistan.¹⁷ Genetic and environmental factors, geographic sites, methodology, and hospital-related biases might explain the different prevalence rates of DR from the literature.¹⁶ In Indian sub-continent, the onset of type-2 DM is at a younger age,¹⁸ obesity is less common,¹⁹ and genetic factors appear to be stronger.²⁰

To exclude the limitations that underscore DR prevalence data, the present community-based study involved selecting a representative sample of diabetics by the analysis of medical charts and inclusion of newly diagnosed DR by using international standard/ETDRS.¹⁰ In Sub-Saharan Africa with the epidemic size increase in DM in general and in type-2 DM in particular,¹⁻³ diabetic retinopathy is fast becoming an important cause of visual disability. As visual disability in DM is largely preventable and treatable, this study aimed also at identifying modifiable (environment)

and non modifiable (genetics) risk factors of DR. Indeed, many epidemiologic surveys have reported valuable information on the prevalence of DR in western societies that is useful for identifying individuals at high risk and for the planning of public health policies.¹³

Risk factors and determinants of diabetic retinopathy

The present univariate and multivariate analyses suggest that the onset and progression of DR result from the interaction of genetic and environmental factors. This is logical as DM is a multifactorial disease. Multivariate analysis has identified the determinants of DR excluding confounding factors.

In univariate analysis, age, gender, ethnicity, profession, smoking, excessive alcohol intake, education attainment, residence, and contraceptive pill use for women were not identified as significant risk factors for DR. However, several studies²¹ have reported age ≥ 50 years, cigarette smoking, alcohol and contraceptive pills use as risk factors for DR. The significant univariate risk factors for DR in these African diabetics were delayed diagnosis of DM in the study population, men with high socioeconomic status, women with delayed diagnosis of DM, and pregnancy after DR onset among women.

Gender as a systemic risk factor of DR

Studies from literature²² has shown varying results when predicting sex as a risk factor for developing DR. Male preponderance in DR has been shown in India,¹⁶ the UKPDS,²³ the Hyderabad Study,²⁴ and a study of Pima Indians.²⁵ Farhan et al.²⁶ reported similar prevalence of DR in male and female type-2 diabetics from Kuwait.

Pregnancy

It is well established that DR can progress rapidly during pregnancy due to hormonal changes and poor glycaemic control in the 1st trimester.²²

Smoking and alcohol intake

There are studies which did not show a significant impact of smoking and alcohol²⁸ on the genesis of DR as reported in the present study. However, increased monoxide (CO) and platelet anomalies explain the deleterious role of tobacco in the pathogenesis of DR.²⁹

Insulin treatment

The present higher prevalence of DR among these diabetic Africans, women, and patients with type-2 DM on insulin treatment, may be explained by the fact that patients with DR may have been preferentially treated with insulin. Insulin therapy –related immune vascularitis is perhaps responsible for the presence of DR.²⁵

Delayed diagnosis of DM

Delayed diagnosis of DM is characteristic for Africans with DR.¹⁴ This factor of DR justifies improvement of diabetes care in Africans using a multidisciplinary approach.

Systemic arterial hypertension and diastolic arterial hypertension

Contrary to this study, African studies have shown a significant association between DR and arterial

hypertension.^{14,30,31} Control of arterial hypertension in these diabetics may justify the absence of a significant correlation, as the impact of hypertension duration was also not different. However, the entry of the anomalies of the BP components (SBP, DBP, and pulse pressure) within separate multivariate analyses confirmed the effects of increased shear stress of blood flow to damage the retinal capillary endothelial cells in the eyes of diabetics during aging.²²

Multivariate analysis

The major and independent risk factors (determinants) for DR in this study population were DM duration ≥ 4 years, family history of DM, systolic arterial hypertension (sbp ≥ 140 mmHg), and higher pulse pressure ≥ 60 mmHg (pre-clinical atherosclerosis or arterial stiffness), consistent with findings of the world literature.^{16,22,30-35} Logistic regression analyses revealed that the effect of these major risk factors for DR was stronger in diabetic women and type-2 diabetics than in diabetic men. This raises the possibility that there are differences in susceptibility to DR in certain ethnic groups.

Family history of DR

Several studies have outlined the role of genetic factors in susceptibility to DR as some patients develop DR in spite of good control and others escape DR despite poor control.^{36,37}

Duration of diabetic disease

Longer duration of diabetes mellitus is probably the strongest predictor for development of DR. Ignorance, poverty, and delayed diagnosis of DM may explain the shorter mean duration of DM in this study (6 years) in comparison with good control of DM and longer duration of DM (20 years) in western countries before the onset of DR.⁴

Atherosclerosis and arterial stiffness

This study confirms the deleterious action of higher pulse pressure ≥ 60 mmHg (pre-clinical atherosclerosis and arterial stiffness) which predicts diabetic cardiomyopathy,⁹ overt atherosclerosis and congestive heart failure³⁸ among central African diabetics from Kinshasa, DRC. It is also consistent with Indian studies which showed a significant association between pre-clinical atherosclerosis / arterial stiffness (Intima-Media thickness) with DR, even after adjusting for age, duration of DM, HBA1C, serum cholesterol, serum triglycerides, and microalbuminuria.³⁹ In addition to BP components, recent studies in western subjects have reported that DR is associated with atherosclerotic end points.⁴⁰⁻⁴² Our recent study has also concluded that diabetic retinopathy predicts incident ischemic stroke in Africans with diabetes, independent of other risk factors. Those associations suggest that common pathogenic mechanisms (impaired auto-regulation, hyperperfusion, vascular endothelial growth factor, oxidant stress) might predispose to diabetic micro and macroangiopathy.²²

Limitations and strengths

Because of low resources, other risk factors of DR such as HBA1C, renal disease, elevated serum lipids, and

hypoglutathionemia²² were not assessed by this study. Furthermore, a limitation of the study is that, because it was a cross-sectional study, no information on causality was obtained.

However, the strengths of this study are that it was based on retinal photography, ophthalmoscopy, and international standards of DR definition, and it was also the first study from Central Africa to report on prevalence and risk factors of DR using stereo retinal color photography. Moreover, the study included a representative population with DM, and results could be extrapolated to the all diabetics from Kinshasa city.

Conclusion

The present study suggests that among urban diabetics from Kinshasa with epidemic rate of type 2 diabetes, the prevalence of diabetic retinopathy is high and similar to that reported in other African cities. Diabetic retinopathy will pose a double burden for DRC. This emphasizes the need for routine retinal screening of diabetic individuals to detect diabetic retinopathy in the early stages.

A strong positive association was observed between longer duration of diabetes, systolic arterial hypertension, higher pulse pressure, family history of diabetes, and the presence of diabetic retinopathy. The risk of diabetic retinopathy conferred by these determinants is enhanced among female diabetics and type 2 diabetics.

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