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Research Article

Association of Normal Weight Status, Early-Onset Type 2 Diabetes, Vitamins Deficiency, Migration, Low Urbanization, and Visual Disability with Diabetic Macular Edema in Type 2 Diabetes Central Africans

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Abstract

Aim: To determine the prevalence of visual consequences, and risk factors for diabetic macular edema (DME) in all type 2 diabetes mellitus (T2DM) Central Africans and in all diabetic retinopathy (DR) T2DM patients by age at T2DM diagnosis and DR stages.

Methods: Community-Based cross-sectional study carried out Ethnic Bantu blacks with T2DM living in Kinshasa region, Democratic Republic of the Congo, Central Africa. Between July and September, 200 participants underwent standardized interview, physical examination, laboratory measurements, and an extensive ophthalmic examination, including current visual acuity and retinal photographs after pupil dilatation. Any DR and DME graded according to Early treatment of diabetic Retinopathy Study Scale and the American Academy of Ophthalmology, visual disability (VD), independent risk factors and interpretation for DME using logistic regression analysis and comparisons of risk factors by DR stages and age at T2DM diagnosis.

Results: Prevalence rates of DME were 15.5% and 42.3% among all T2DM patients and T2DM patients with DR. All cases of DME were living in low urbanization (rural, semi-rural, slums) areas. Out of DME cases, 90% and 10% were diffuse and focal. In multivariate analysis in all, independent risk factors for DME were early-onset T2DM < 40 years vs. ≥ 40 years (OR = 2.8 95% CI 1.2-6.7; P = 0.017), and normal body mass 18.5-24.9 kg/m2 vs. malnutrition and obesity (OR = 2.8 95% CI 1.2-6.7; P = 0.021). In T2DM patients with DR, independent risk factors for DME were high socioeconomic status (SES) vs. low SES (OR = 3.8 95% CI 1.1-12.8; P = 0.033) and serum magnesium deficiency vs. normal serum magnesium (OR = 5.7 95% CI 1.8-18.4; P = 0.004). Early-onset T2DM was associated with higher levels of HDL-C, LDL-C, diabetes duration, but lower levels of BMI, current age, and serum vitamin D. Severe DR was associated with late-onset T2DM, highest levels of apolipoprotein B (ApoB), HOMA-IR, 8-OHdG, but lowest vitamin C, and vitamin D. In mild NPDR, migration was the risk factor for DME. In moderate NPDR, diabetes duration < 5 years, diabetes duration ≥11 years, serum vitamin C deficiency, and serum vitamin D deficiency were the risk factors for DME. In combined severe NPDR + PDR, serum magnesium deficiency, serum vitamin E deficiency, normal weight, and elevated ApoB were the risk factors for DME.

Conclusions: DME is a public problem health in T2DM black Central Africans. Severe DR, normal weight, high socioeconomic status, early-onset T2DM, deficiency serum magnesium, visual disability is significantly associated with DME.

Keywords: *Diabetic Macular Edema, Antioxidants, Environmental Factors, Central Africans*

Introduction

The chronic hyperglycemia resulting from defects in insulin secretion, insulin action or both, characterizes diabetes mellitus (DM) which is projected to be estimated at 552 million by year 2030 [1]. The rising burden of DM and its long-term complications such as macrovascular and microvascular lesions is well established [2-4]. The microvascular complications include diabetic retinopathy (DR), diabetic macular edema (DME), diabetic neuropathy, and diabetic nephropathy [3, 5-12].

It is well known that DR and DME may damage visual acuity and lead to visual disability (VD = visual impairment and blindness) [13] and impaired Health Related Quality of life [9]. DME can occur at any stages of DR and after 20 years of life in developed countries and DME may affect central visual acuity [14,15].

Despite the significance of this problem, and the rising prevalence's of DM, incidence of type 2 diabetes mellitus (T2DM), and DR notably in Central Africa with emerging Health transition, cardiometabolic risk, DM shorter duration and lifestyle changes [3,4,14-18], there are lack of information of the DME prevalence and contributory factors in T2DM Central Africans.

As shown in developed and other developing countries, ethnic differences in the clinical, monitoring and laboratory associations with epidemic rates of prevalence, macrovascular and microvascular complications of DM are characterized by early-onset DM [5,19], genetic anticipation in T2DM [20], tropical Central African environment [21], lean/metabolically obese normal-weight phenotype [22], current epidemiology and ecology [12,23-26], intake of vegetables [24], serum lipids [6,7,11], and emerging therapies [8].

Then, T2DM is a heterogeneous disease, characterized by genetic and non-genetic factors. DME is the consequences of the breakdown of the blood retinal barrier because of leakage of dilated hyperpermeable capillaries and microaneurysms. Generating a broader and more precise estimate of the prevalence of DME and its relationship with major modifiable risk factors is crucial for guiding patient's education and optimal clinical management of DME.

For the main objective, we therefore carried out this study at aiming to determine the prevalence of DME and its ocular disorders as well as its relationship to key risk factors in all T2DM patients and in T2DM patients with DR. The secondary objective of this study was to determine the characteristics of patients with T2DM by DR severity and diagnosed before the age of 40 years (early-onset DM) and after the age of 40 years (late-onset DM) for explaining their effects on DME presence.

Materials and Methods

Study design, setting and population

This study was a cross-sectional study conducted among T2DM patients who were randomly selected from the 4 administrative disctricts (urban Funa, urban Mont-Amba, rural Lukunga, and rural Tshangu) of Kinshasa city, Democratic Republic of Congo (DRC), from July to September 2010.

The survey protocol was approved by LOMO Medical Clinic Ethics Committee, Kinshasa Limited, DRC. Individual patients provided written informed consent at each examination for their anonymized data before to be used in evaluation, validation and statistical analysis.

The methods were carried out at the Division of Ophthalmology for Saint Joseph Hospital, Kinshasa, DRC. All participants were T2DM patients, black Bantu Africans with Kongo, Ngala, Luba, and Swahili ethnic groups. They were given a structured and standardized interview that included information on participant's current age, gender, early DM onset, smoking status, education level, socioeconomic status (SES), insulin use, rural-urban migration, residence (districts), intake of vegetables (Fumbwa), alcohol intake, and DM duration.

The physical examination included anthropometry (height, weight, waist circumference), systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse pressure (SBP-DBP).

Laboratory data included fasting plasma glucose (FPG), serum total cholesterol (TC), triglycerides (TG), high density lipoprotein-cholesterol (HDL-C), low density lipoprotein (LDL-C), non-HDL, TC/HDL-C ratio, TG/HDL-C ratio, LDL/HDL-C ratio, VLDL, selenium, zinc, vitamin E, insulin, apolipoprotein B (ApoB), uric acid, vitamin C, vitamin D, glycosylated hemoglobin (HbA1c), Thiobarbituric acid reacting substances (TBARS), oxidized-LDL (oxLDL), glutathione peroxidase (GPx), and reduced glutathione (GSH).

An ophthalmologist specialized on retina and Laser (MMv) as per the norms of the International Clinical Diabetic retinopathy guidelines, performed a comprehensive eye examination. He assessed patients' current visual acuity in both eyes (achieved with or without pinhole reading) with an illuminated 3m Snellen charts. Fundus photographs (non-mydriatic Canon DGi camera with 40D camera back) were performed after pupillary dilatation by 1% tropicamide eye drops.

The participants did not have previous intervention for DR, corneal opacities or lenticular opacities, type 1 DM, lipid lowering, neither pregnancy for women.

The details of the clinical, laboratory and comprehensive eye examination methods were previously published [27,28].

Assessment of DME

The findings from stereoscopic fundus photographs were used to grade DME. No DME = 10/20 and presence of DME (mild = 30, moderate = 40, and severe = 50) were defined by the American Academy of Ophthalmology classification [29].

Definitions

The operational definitions were obtained using the following cut-off points: advanced age (current age ≥ 60 years vs. young adults < 60 years), abdominal obesity according to IDF (waist circumference ≥ 94 cm for men and waist circumference ≥ 80 cm for women) [30], nutritional status (body mass index = BMI = weight in kg/height squared in m < 18.5 kg/m^2 for underweight, 18.5-24.9 kg/m^2 for normal weight, 25 - 29.9 kg/m^2 for overweight, and ≥ 30 kg/m^2 for obesity)[31], and 10-year Framingham risk [32].

DM duration was defined as the time period between the age at diagnosis of DM and the time of examination.

We referred early- and later-onset T2DM to those whose DM was diagnosed below and above the age of 40 years, respectively, according to the criteria of the NICE guidelines for T2DM [33] and Joint British Societies-2 guidelines [34].

As nonclinical classifications for DME (laser treatment and fluorescein leakage modifying the beneficial effect of photocoagulation for DME), we classified DME as focal or diffuse using extent and location of thickening, involvement or not of the center of the macula, quantity and features of lipid exudates [35-42].

DR was ascertained with microaneurysms, hemorrhage and hard exudates and based on the modified Klein classification of the Early Treatment Diabetic Retinopathy Study scale [32]. T2DM patients were divided then as having no DR, non-proliferative DR (NPDR) and proliferative DR (PDR). Two independent observers (M. Mv., B.MT) performed images in a masked fashion with high agreement for grading (kappa statistic = 0.845) similar with those from other studies [43,44]. No concordance between the two researchers was resolved by adjunction with two additional investigators (L.L, M.E).

Low urbanization included rural, semi-rural and slums areas without electricity in comparison with high urbanization in Westernized inner areas.

Statistical analysis

For univariate descriptive purposes, categorical variables were presented as frequency (number = n) and proportions (%), while quantitative variables were reported as mean ± standard deviation. The Chi-square test was used at comparing proportions between presence and absence of DME, DR severity and DM onset groups. The comparisons of means between these groups were done using the Student t-test.

We used One-Way variance (ANOVA with Bonferroni Post-Hoc test) or Fisher's Stepwise Discriminant function analysis to describe which variables discriminate between T2DM patients without DR, with NPDR, and with PDR, as well as without DR, with mild NPDR, with moderate NPDR, and with combined severe NPDR and PDR.

With respect to canonical analyses, the maximum number of functions equal to number of DR severity groups minus one. The larger standardized beta coefficient, the greater was the contribution of the respective variables to the discrimination between groups.

The multivariate analysis such as logistic regression model was computed to evaluate the simultaneous effect of significant and independent determinants associated with DME prevalence after adjusting for confounding factors.

A P-value < 0.05 was considered significant. Data analysis was performed using the IBM® Statistical Package for Social Sciences (SPSS) for Windows version 20 (SPSS Inc, Chicago, IL, USA).

Results

DME was diagnosed in 31 (15.5%) of the 200 T2DM patients (90 males, 110 females, and median duration = 5 years). There was not individual association (P > 0.05) between sex, education level, SES, ethnic groups, insulin therapy, intake of vegetables, smoking status, abdominal obesity, SBP, DBP, pulse pressure, DM duration, alcohol intake, 10-year Framingham risk, FPG, HbA1c, TC, HDL-C, LDL-C, TG, non-HDL, TC/HDL ratio, TG/HDL ratio, LDL-C/HDL-C ratio, VLDL, selenium, zinc, vitamin E, TBARS, oxLDL, albumin, GGT, uric acid, Apo B, insulinemia, GPx, and GSH (results not shown).

However, there were significant univariate associations of migration, rural Lukunga residence and DME, VD, blindness, visual impairment, and early-onset DM with DME prevalence (Table 1).

Variables of interest	Macula edema		P-value
	Presence n (%)	Absence n (%)	
Migration	16(51.6)	37(31.1)	0.033
Residence			0.022
Lukunga	4(57.1)	3(42.9)	
Tshangu	6(21.4)	22(78.6)	
Funa	6(35.3)	11(64.7)	
Mont-Amba	15(15.3)	83(84.7)	
VD	15(48.4)	38(31.9)	0.069
Blindness	7(22.6)	9(7.6)	0.015
Visual impairment	10(32.3)	27(22.7)	0.004
Early DM onset	16(51.6)	32(26.9)	0.009

Table 1: *Significant sociobiographical factors associated with DME presence.*

The levels of BMI, age at DM diagnosis, serum vitamin C, and vitamin D were significantly lower in DME presence than those in DME absence (Table 2).

Variables	Macula edema		P- value
of interest	Presence mean ± SD	Absence mean ± SD	
BMI	24.2 ± 4.3	26.2 ± 5.1	0.040
Vitamin C	1.3 ± 0.7	1.7 ± 0.7	0.008
Vitamin D	26.1 ± 14.8	34 ± 13.9	0.007
Age at DM diagnosis	42.1 ± 12.7	47.4 ± 12.9	0.045

Table 2: *Distribution of mean of BMI, vitamin C, vitamin D, and age at DM diagnosis by DME status.*

After adjusting for DM duration, migration, vitamin C, and vitamin D, only early DM-onset and normal weight (BMI = 18.5-24.9 kg/m^2) were identified as the significant and independent determinants of DME presence: Hosmer and Lemeshow test, P = 0.020 (Table 3).

	B Coefficient	Standard error	Wald Chi-square	OR (95% CI)	P-value
Independent					
variables					
Early DM onset					
vs. later DM onset	1.043	0.437	5.713	2.8 (1.2-6.7)	0.017
Nutritional status		7.087			0.029
Undernutrition	- 0.792	1.130	0.487	0.5 (0.1-4.2)	0.485
Normal weight	1.029	0.446	5.333	2.8 (1.2-6.7)	0.021
Overweight/obesity		REFERENCE		1	
Constant	- 2.218	0.378	34.371		<0.0001

Table 3: *Independent determinants of macula Edema presence.*

Table 4 summarizes the proportions of some semibiographical factors by early-onset T2DM and late-onset T2DM groups. There was no significant association between gender, low intake of Fumbwa leaves, VD, and early-onset T2DM. However, migration, insulin use, and DR were significantly associated with early-onset T2DM. Low SES, low education level, urban residence, abdominal obesity, metabolic syndrome, and high 10-year Framingham risk were significantly associated with late-onset T2DM.

Variables of interest	Early-onset T2DM n (%)	Late-onset T2DM n (%)	P-value
Gender			0.138
Men	25(52.1)	40(39.2)	
Women	23(47.9)	62(60.8)	
Low SES	28(58.3)	74(72.5)	0.06
Low education level	28(70.0)	79(84.0)	0.055
Urban residence	33(68.8)	82(80.4)	0.087
Migration	25(52.1)	28(27.5)	0.003
Abdominal obesity	17(35.4)	71(68.6)	<0.0001
Metabolic syndrome	26(54.2)	84(82.4)	<0.0001
Insulin use	34(70.8)	54(52.9)	0.038
High 10-year Framingham risk	10(20.8)	43(42.2)	0.011
Low intake of Fumbwa leaves	8(16.7)	27(26.5)	0.131
Visual disability	17(35.4)	36(35.3)	0.988
DR	31(64.6)	35(34.3)	<0.0001
DME	16(33.3)	15(14.7)	0.009

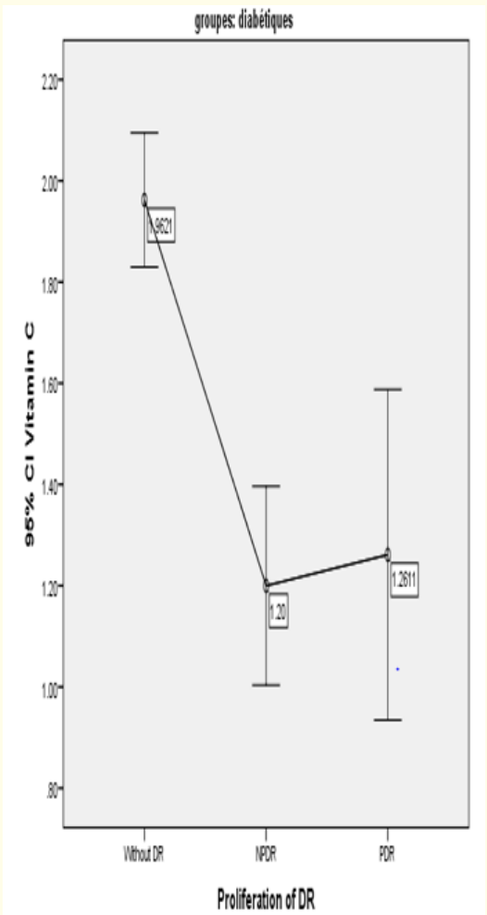
Table 4: *Distribution of sociobiographical factors by early-onset T2DM and late-onset T2DM groups.*

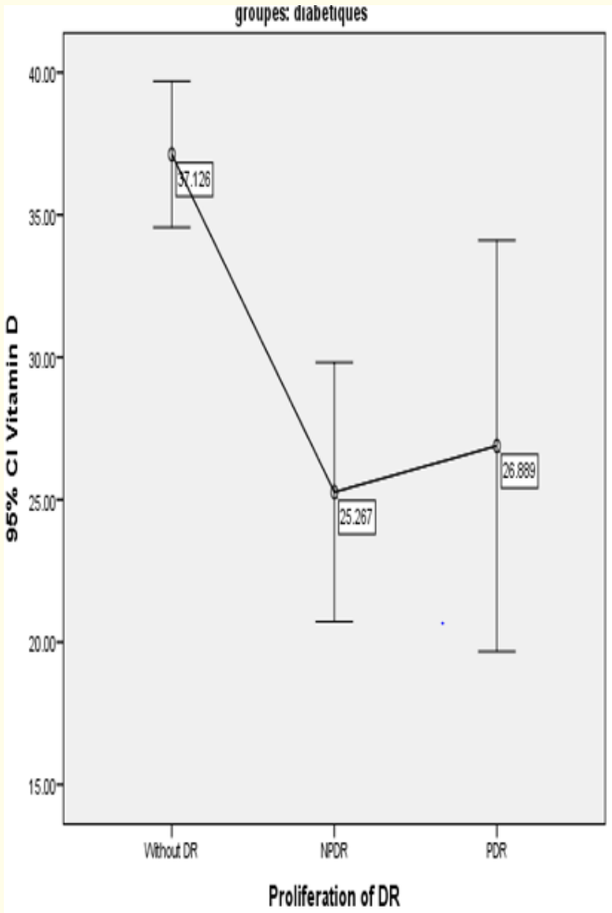
The participants had different levels of HDL-C, LDL-C, TG, WC, SBP, current age, BMI, 10-year Framingham score, DM duration, post migration time in town, serum vitamin C, vitamin D, and standardized vitamin E for total cholesterol according to the age at diagnosis of T2DM (Table 5). The patients with early-onset T2DM had significant higher levels of DM duration, HDL-C and LDL-C, but lower levels of TG, WC, current age, BMI, 10-year Framingham score, post migration time in town, SBP, serum vitamins C, D, and standardized vitamin E for total cholesterol than those in their counterparts with late-onset T2DM. The rest of variables of interest were similar (P > 0.05) between early-onset and late-onset T2DM groups (results not shown).

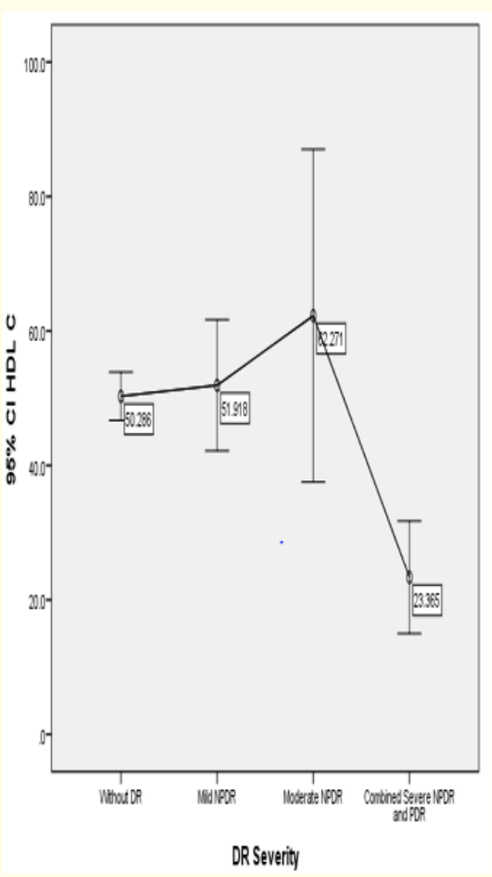
Variables of interest	Early-onset T2DM mean ± SD	Late-onset T2DM mean ± SD	P-value
HDL-C (mg/dL)	75.6 ± 13.5	50.9 ± 15.8	<0.0001
LDL-C (mg/dL)	95.7 ± 53.3	78.1 ± 42.9	0.032
TG (mg/dL)	121.4 ± 44.8	136.7 ± 45.3	0.054
WC (cm)	89.8 ± 18.6	97.0 ± 10.9	0.003
SBP (mmHg)	124.2 ± 24.2	131.2 ± 19.6	0.06
Current age (years)	43.4 ± 13.6	60.7 ± 8.2	<0.0001
BMI (kg/m^2)	24 ± 4.6	26.7 ± 5	0.002
10-year Framingham (%)	8.4 ± 9.6	11.2 ± 11.5	<0.01
Vitamin C	1.5 ± 0.8	1.7 ± 0.7	0.06
Vitamin D	28.7 ± 13.9	34.1 ± 14.4	0.031
Diabetes duration (years)	12.1 ± 10.1	7.4 ± 5.9	<0.0001
Post migration time	31.7 ± 13.9	42.9 ± 17.4	<0.0001
Standardized vitamin E for			
total cholesterol	3.1 ± 1.1	3.6 ± 1.5	0.048

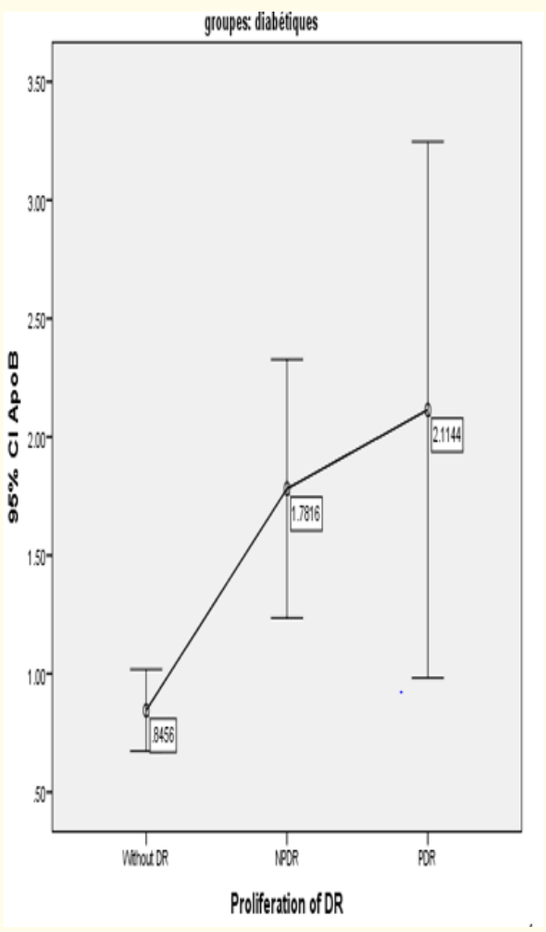
Table 5: *Distribution of lipid profile, anthropometry, current age, DM duration, blood pressure, post igration time in town, Framingham risk, vitamins C, D, and standardized vitamin E for total cholesterol by early-onset DM.*

Figure 1 shows significant (ANOVA P < 0.0001) variations of serum mean levels of vitamin C, vitamin D, ApoB, HOMA-IR, HDL-C, and 8-OHdG across T2DM groups without DR, NPDR, and PDR. The lowest levels of vitamin C and vitamin D (antioxidants deficiency), but the highest levels of 8-OHdG (increased and exaggerated oxidant activity) did not vary (Bonferroni Post-Hoc test > 0.05) between NPDR and PDR groups.


groupes: diabétiques
95% CI Vitamin C
2.20
2.00
1.80
1.60
1.40
1.20
1.00
.80
1.9621
1.20
1.2611
Without DR
NPDR
PDR
Proliferation of DR


groupes: diabétiques
95% CI Vitamin D
40.00
35.00
30.00
25.00
20.00
15.00
37.126
25.267
26.889
Without DR
NPDR
PDR
Proliferation of DR


95% CI HDL C
100.0
80.0
60.0
40.0
20.0
0
50.396
51.918
62.271
23.365
Without DR
Mild NPDR
Moderate NPDR
Combined Severe NPDR and PDR
DR Severity


groupes: diabétiques
95% CI ApoB
3.50
3.00
2.50
2.00
1.50
1.00
.50
.8456
1.7816
2.1144
Without DR
NPDR
PDR
Proliferation of DR

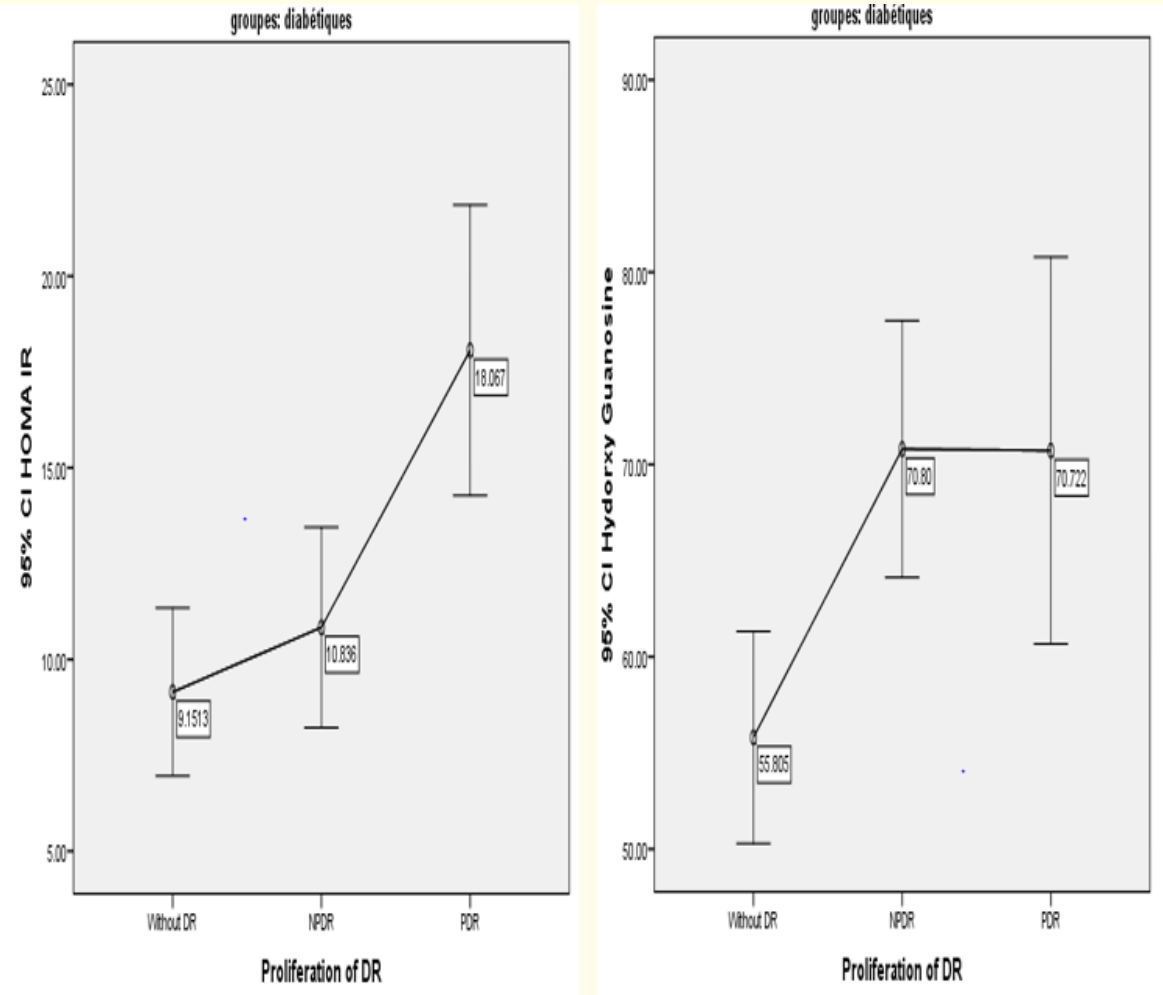


Figure 1: *Variations of the mean levels of vitamin C, vitamin D, ApoB, HDL-C, HOMA-IR, and 8-OHdG across the groups of progression to proliferation of DR severity in all T2DM patients.*

There was a significant and progressive increase in serum means of ApoB and HOMA-IR with DR severity: the highest levels of serum ApoB with larger variability and serum HOMA-IR being concomitant with PDR group, respectively. The lowest levels of HDL-C were in PDR group. However, after adjusting for creatinine, SOD, 8-OHdG, DM duration, HOMA-IR, and age, only serum vitamin C, vitamin D, ApoB, and HDL-C were the best discriminants of T2DM patients between without DR, mild NPDR, moderate NPDR, and combined severe NPDR + PDR groups (coefficients not shown).

Figure 2 describes significant ($P < 0.001$) variations of rates of without DR, mild NPDR, moderate NPDR, combined severe NPDR + PDR, and DME patients across the age at DM diagnosis groups. The rates of DME, mild NPDR, without DR, and moderate NPDR were decreasing with increased age at DM diagnosis, whereas the rates of combined severe NPDR + PDR were increasing with rising age at DM diagnosis.

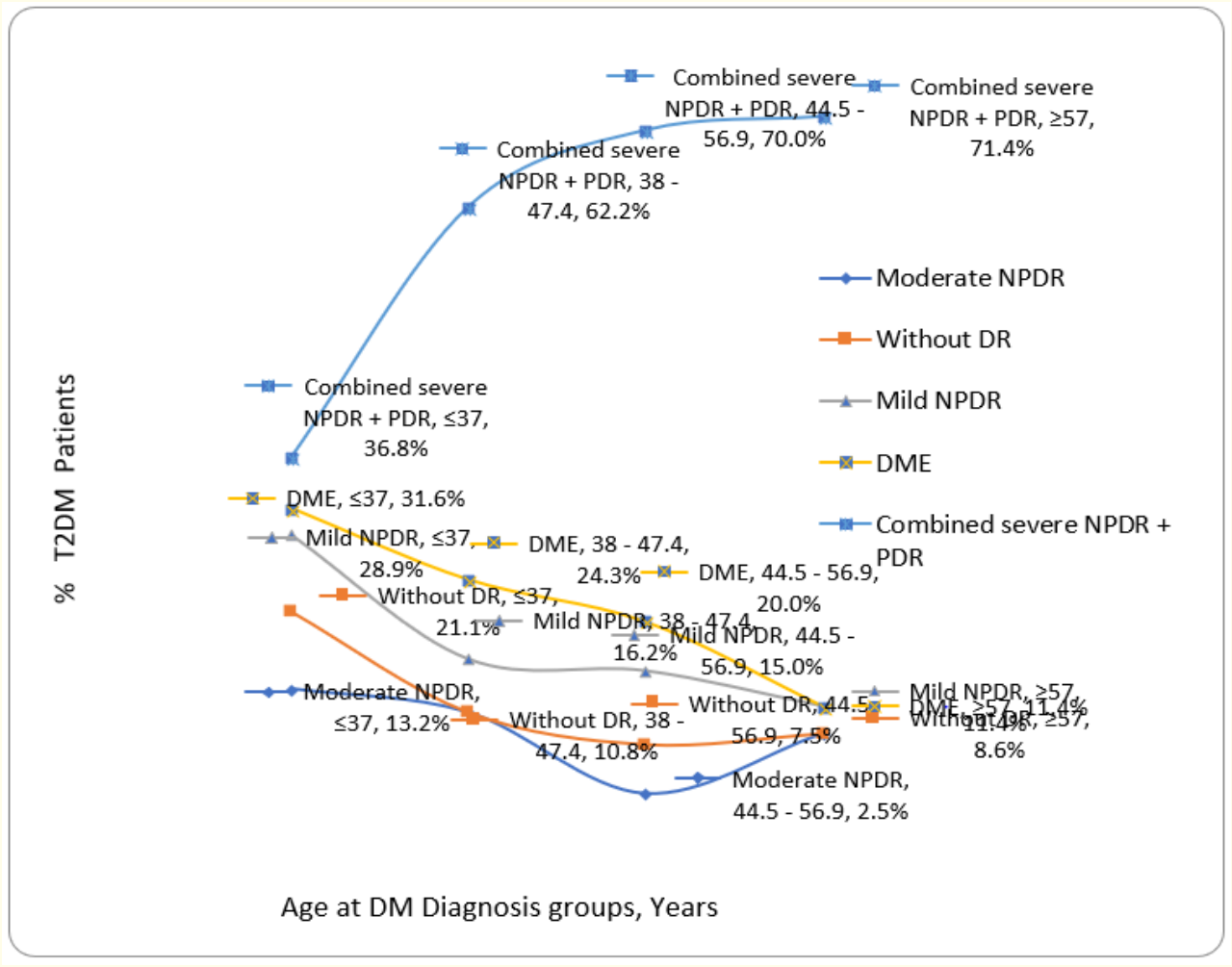


Figure 2: *Distribution of the rates of without DR, mild NPDR, moderate NPDR, combined severe NPDR+PDR, and DME by increasing age at DM diagnosis.*

Findings in T2DM patients with DR

Out of 71 T2DM patients with DR, 42.3% (n = 30) and 1.4% (n = 1) had classified DME (CSME) and non- classified DME, respectively. Out 30 classified DME cases, 90% (n = 27) and 10% (n = 3) had diffuse and focal DME cases, respectively.

All patients with DR and DME, the patient with non-classified DME and all patients classified DME, had low urbanization residence, respectively.

Compared with DR patients without DME (n = 40), patients with classified DME had similar (P > 0.05) rates of sex, abdominal obesity, overall overweight/obesity, smoking status, metabolic syndrome, pulse pressure ≥ 60 mmHg, insulin resistance, ethnicity, hypertension,

insulin therapy, alcohol intake, visual disability, education level, advanced age, glaucoma, consumption of vegetables, no glycemic control, no HbA1c control, lower levels of deficiencies of serum albumin, SOD, vitamin C, vitamin E, and vitamin D, but higher rates of elevated DU duration, 10-year Framingham risk ≥ 10%, serum uric acid, TC, TG, LDL-C, creatinine, GGT, oxLDL, TBARS, 8-Isoprostane, and 8-OHdG, non HDL, TC/HDL-C ratio, TG/HDL-C ratio, and LDL-C/HDL-C ratio (results not shown).

There was a significant linear positive association (biologic gradient, P for trend < 0.01) between classified DME and DR severity (Figure 3). However, there was a significant but negative association (dose-effect response, P for trend = 0.049) between classified DME and serum zinc groups in T2DM patients with DR (Figure 4). In mild NPDR group, only migration (Yes = 50% n = 6/12 vs. 12.5% n = 2/16; P = 0.030) was significantly associated with DME. In moderate NPDR group, both DM shorter duration (75% n = 3/4; DM duration = 2-5 years) and DM longer duration (80% n = 4/5) had higher (P = 0.020) cases of DME than intermediate DM duration (0% n = 0/5), while all DME cases (n = 7) had deficiency of vitamin C and vitamin D.

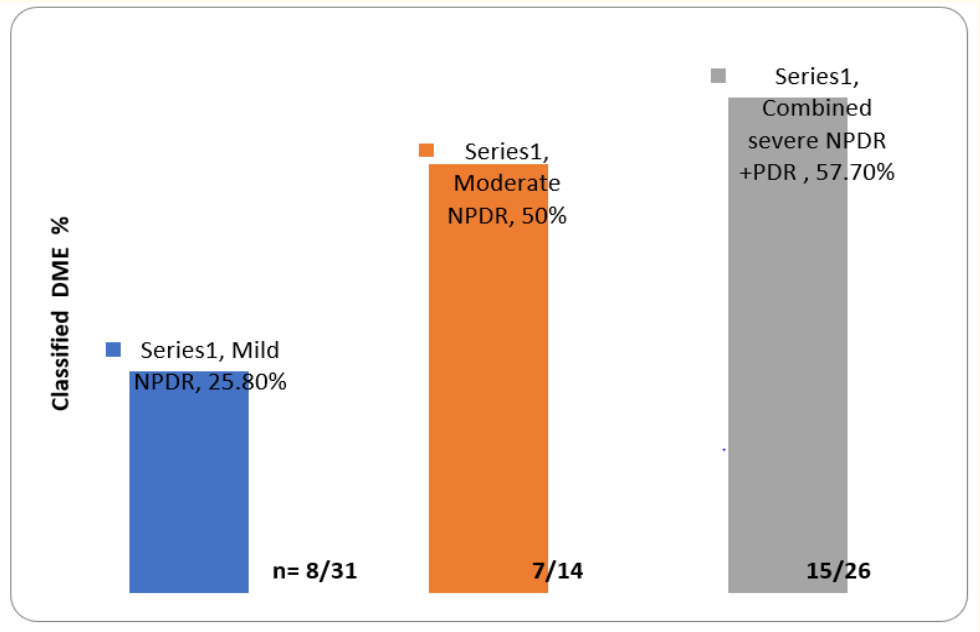


Figure 3: *Relationship between DR severity and classified DME prevalence in T2DM patients with DR.*

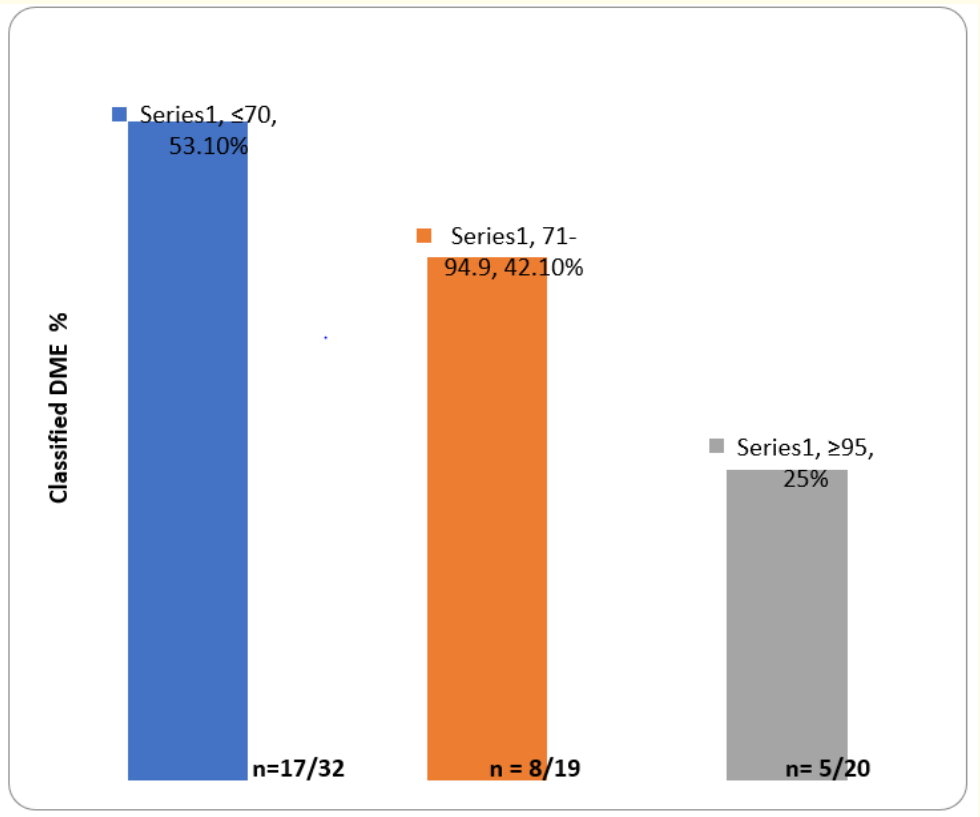


Figure 4: *Relationship between classified DME prevalence and serum Zinc (µg/L) groups among T2DM patients with DR.*

In combined severe NPDR and PDR, VD (Yes = 76.9% n = 10/13 vs. No = 38.5% n = 5/13; P = 0.047), magnesium deficiency (Yes = 81.8% n = 9/11 vs. No = 40% n = 6/15; P = 0.033) vitamin E deficiency (all DME cases), normal weight (normal BMI = 66.7% n = 10 vs. malnutrition = 6.7% n = 1, overweight = 13.3% n = 2, and obesity = 13.3% n = 2; P < 0.05), elevated ApoB (Yes = 68.4% n = 13/19 vs. No = 28.6% n = 2/7; P = 0.068) were associated with DME, respectively.

In patients with DR, migration, high SES, normal HDL-C group, serum selenium deficiency, serum magnesium deficiency, and serum zinc deficiency were the factors univariately and significantly associated with classified DME among T2DM patients with DR (Table 5).

After adjusting for migration, DR severity, serum HDL-C, selenium and zinc groups in logistic regression analysis, only high SES and magnesium deficiency were identified as the most important independent determinants for classified DME in T2DM patients with DR (Table 6).

Variables of interest	Presence of DME n (%)	OR (95% CI)	P- value
Migration			
Yes	16(55.2)	2.5(0.9-6.5)	0.056
No	14(33.3)		
SES			
Low	17(33.3)		
High	13(65.0)	3.3(1.3-10)	0.015
Selenium deficiency			
Yes	21(52.5)	2.7(1.001-7.3)	0.047
No	9(29)		
HDL-C groups			
Low	9(29)		
Normal/good	21(52.5)	2.5(1.1-7.1)	0.047
Magnesium deficiency			
Yes	16(72.7)	6.7(2.2-20.5)	<0.0001
No	14(28.6)		
Zinc deficiency			
Yes	24(50)	2.8(0.9-8.4)	0.056
No	6(26.1)		

Table 6: *Distribution of classified DME by migration, SES, serum selenium, HDL-C, serum magnesium, and serum zinc groups among T2DM patients with DR.*

The rest of variables of interest were similar (P > 0.05) between early-onset and late-onset T2DM groups (results not shown).

	B Coefficient	Standard error	Wald Chi-square	OR (95% CI)	P-value
Independent					
variables					
SES					
High	- 1.332	0.623	4.566	3.8	0.033
				(1.1-12.8)	
vs. low		Referent group		1	
Serum magnesium deficiency					
Yes	1.736	0.601	8.339	5.7	0.004
				(1.8-18.4)	
No		Referent group		1	

Table 7: *Independent determinants for classified DME presence among T2DM patients with DR*

Adjusted for migration, selenium, HDL-C, zinc, and DR severity.

Discussion

At our knowledge, this was the first study undertaken on valid prevalence rates, determinants and interpretations for DME in sub-Saharan Africa.

Prevalence rates of DME

DME was present in 15.5% and 42.3% of all T2DM patients and T2DM patients with DR, respectively. This study showed that DME prevalence in DR was higher (double) than 3%-28% of diabetics from developed countries [45-50]. The variations of DME prevalence may be explained by geography, races/ethnicity, types of diabetes and methods. The globalization of DM and the rising of DR in Central Africa may explain the present burden of DME [3,4,14-18].

Anatomopathology and DME disease Severity scale

The presence of DME among these central African T2DM patients was focal in 10% and diffuses in 90%. However, clinically significant DME, focal or diffuse was similar in 44% in US Latinos and 46% in African-Americans [51].

Despite the subjective and controversial detection of focal and diffuse DME [35-42], we might categorize 90% cases as mild DME with retinal thickening or exudates distant from the center of the macula and 10% cases as severe DME with retinal thickening or exudates involving the center of the macula [52]. We had one no classified DME as reported by other authors [14,15].

Current Epidemiology and New Pathophysiology Insights

The present study has focused on the current understanding of the natural history, the epidemiology, the pathophysiology, the diagnosis, and the prognosis of DR/ DME among central Africans with T2DM.

For the natural history, DME occurred faster and at any stage of DR despite the positive and significant dose-effect response relationship between DME rates and the stages of DR severity. This observation was consistent with the literature about DR severity and DME onset [14,15]. On contrary, DME was present among Central Africans T2DM patients with median DM duration equal to 5 years whereas DME occurs after longer DM duration (20 years of life) among diabetics from developed countries [14,15]. It meant that DME may be a

Bantu (black in West and Central Africa) Phenotype with a complex multifactorial pattern interpreted by the present univariate and multivariate analyses in all T2DM patients, by the stratification of DM onset, the presence and severity of DR. They demonstrated that Central African T2DM patients with DME had lower levels of age at DM diagnosis, BMI (normal weight/lean DM), serum vitamin C, but higher rates of migration, rural residence, early-onset T2DM, visual disability, blindness, and visual impairment than their T2DM counterparts without DME.

The pathophysiology of the DME was not fully despite shown evidence of the interaction of genetic factors (non-modifiable: race, ethnicity, age at DM diagnosis/anticipation, lean DM, heredity in T2DM) and environmental factors (systemic factors with retinal consequences, epidemiologic, demographic, and nutrition transitions, and lifestyle changes) in DME presence [3-12, 14-26].

In developed and emerging economics, there is a significant association between serum lipids and DME [6,7,11,46]. However, our results and those from the literature on lack of associations between lipid/lipoprotein profiles with DME were not consistent [46,53-58]. Paradoxically, central Africans with early-onset T2DM, independent determinant for DME, had higher levels of serum HDL-C and LDL-C, but lower levels of 10-year Framingham risk, total cholesterol, and triglycerides than those among their counterparts with late-onset T2DM. Furthermore, T2DM Central Africans with PDR had the lowest levels of ApoB and HDL-C in comparison with normal levels of ApoB and HDL-C observed among their counterparts without DR and with NPDR, respectively.

In these findings and our previous studies [3,4,59-62], Central Africans have a more favorable lipoprotein profile lower triglycerides and higher HDL-C in premature cardiometabolic diseases (metabolic syndrome, diabetic retinopathy, and cardiovascular diseases) compared with Caucasians because differential aspects of genetics and environmental factors [5,19,21].

Another ethnic pattern significantly and independently associated with DME in these T2DM patients, was lean/weight normal DM. genetically, Asian [64,64] and Central African [21] diabetics are lean. It is now established that lean/normal-weight T2DM is a representative distinct clinical entity of the medically obese normal-weight phenotype related significantly associated with higher risk of mortality [22], advanced age, latent autoimmunity diabetes of adults (LADA), poor beta-cell function, microvascular complications (diabetic nephropathy, diabetic retinopathy) much higher than macrovascular complications (coronary artery disease, stroke), and not significantly deranged lipid profile in T2DM patients [63-65].

Lack of DM care centered on normal weight DM may also explain higher risk of DME in these T2DM patients with normal weight, while the majority of obese T2DM patients receive early anti-diabetic treatment.

Accelerated DME burden in these T2DM Central Africans may be supported by Westernization/Acculturation, chaotic urbanization, and social inequalities. All patients with DME were living in rural areas after migration. Compared with late-onset T2DM Central Africans, those with early-onset T2DM and higher risk of DM, had higher proportions of migration, insulin use, and DR. In migrant Indian people living in newly urbanized and affluent areas, younger age and insulin treatment are significantly associated with DR [66].

Ion considering univariate risk of DME in T2DM Central Africans with DR, patients with DME had higher rates of migration, PDR, high SES, normal HDL-C, deficiencies of serum selenium, magnesium, and zinc than their counterparts without DME.

However, the univariate relationship between migration, HDL-C, PDR, and DME, was no longer significant in multivariate analysis which looked into consideration of the confounding influence multiple variables. Thus, only high SES and serum magnesium deficiency had significantly high odds ratio for DME.

In this study, it is postulated that persistent antioxidants deficiency (malnutrition for micronutrients and vitamins C and D) mediated disruption of the blood-retinal barrier, chronic hyperglycemia-related accumulation of free radicals, ischemia, inflammatory factors, and neurotoxicity (damage of ganglion cell and inner plexiform layer).

Thus T2DM-associated oxidant/antioxidant imbalance may explain the dysfunction of vascular autoregulation with loss of capillary pericyte, thickened capillary basement membrane, and delayed migration of leukocytes during the development of DME.

Magnesium is the most abundant intracellular cation which is important for insulin secretion and action.

We noticed that the stages of DR may affect each association of determinant with DME [66]. Logistic regression analysis was used to minimize the effects of DR severity, age at DM diagnosis, and confounding factors associated with DR stages and age at DM diagnosis. As expected, the severe stage (combined severe NPDR + PDR) was significantly associated with late-onset T2DM. However, DME, mild NPDR and moderate NPDR were significantly associated with early-onset T2DM, respectively.

Migration was the only risk factors for DME in mild NPDR. There were significant associations of deficiencies of vitamins C and D, and U-shaped relationship of DM duration with DME in moderate NPDR group. The distribution of the frequency of DME with moderate NPDR by DM duration had earlier two peaks (< 5 years and ≥14 years) in these Central Africans in comparison the first peak around 14 years and a second peak ≥30 years in Caucasians [47,67].

In all T2DM patients among DR patients with severe stage (combined severe NPDR and PDR), DME was the cause of high risk of VD (central vision loss) [68]. In DR patients with severe stage (combined NPDR + PDR), normal weight/lean, vitamin E deficiency, and elevated ApoB were mostly associated with DME. These interactions between genetics (ethnic phenotype of normal weight and elevated ApoB), deficiencies in antioxidants (vitamin E, micronutrient magnesium) and severe stage of DR may be additional components of DME pathophysiology such as US blacks and Hispanics [69], blood-retinal barrier concept, advanced glycemic end-products (AGE) proteins and protein kinase C formation and the subsequent activation of vascular growth factors (especially VEGF-A), vasoactive factors, and inflammatory factors, and the vitreo-retinal interface [70].

Clinical implication and Public Health perspectives.

These findings will impact on the prevention and prognosis of DME. Visual disability was significantly associated with DME in this study. We recommend effective laser photocoagulation treatment, supplementation of antioxidants, and adequate diet to reduce visual disability, DR, and DM. Intravitreal Corticosteroids and anti-VEGF drugs are now combined with laser photocoagulation.

Study strengths and limitations

The present study might be limited because of cross-sectional design and relatively small size of participants.

The strength of the study was recognized by potential causal association between early-onset DM (temporality, analogy, statistical difference), migration (temporality, analogy), and DME.

Conclusion

The present findings suggest that DME appears a public health problem in these T2DM Central Africans. Early-onset T2DM, normal weight, high SES, and serum magnesium are independently associated with.

The data reflect possible interactions between genetic factors and environmental stressors in the pathogenesis of DME in T2DM Central Africans facing Health transitions and Westernization.

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