Diabetes Epidemiology and Management 11 (2023) 100139

Contents lists available at ScienceDirect

Diabetes Epidemiology and Management

journal homepage: www.elsevier.com

Original article

Association between albuminuria and retinal microvascular dysfunction in type 2 diabetes with and without hypertension

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ARTICLE INFO

Article History:
Received 21 February 2023
Revised 8 March 2023
Accepted 10 March 2023
Available online 11 March 2023

Keywords:
Diabetes
Microvascular disease
Albuminuria
Nephropathy
Retinopathy
West Africans

ABSTRACT

Background: Studies assessing the concordance of albuminuria and retinal microvascular dysfunction (RMD) in type 2 diabetes (T2D) have yielded inconsistent results. Similar to ethnicity, hypertension may be a potential explanatory variable. We compared the association between albuminuria and RMD in West Africans with T2D with and without hypertension.

Materials and methods: This was a cross-sectional study among 177 systematically sampled Ghanaians with T2D aged ≥ 35 years. Albuminuria was based on urinary albumin-creatinine ratio≥30 mg/g. Retinal images were analyzed and graded according to the Early Treatment Diabetic Retinopathy Study criteria. Logistic regression was used to examine the associations of albuminuria and RMD with adjustments for age, sex, socioeconomic status, diabetes duration, HbA1c, smoking, systolic blood pressure (BP), BMI, and total cholesterol.

Results: RMD was more prevalent in individuals with albuminuria than in those without albuminuria (41.7% vs. 24.0%, p = 0.026). In the fully adjusted model, albuminuria remained significantly associated with RMD (odds ratio 2.41[95% CI:1.00−5.80], p = 0.049); the association between albuminuria and RMD was more pronounced in individuals with hypertension (3.10 [1.01−9.50], 0.048) than without hypertension (1.70[0.33 −8.77],0.523). In analyses stratified by BP control, albuminuria was significantly associated with RMD in individuals with suboptimal BP (2.76[1.07−7.14], 0.037) but not in individuals with optimal BP (0.24[0.00 −17.04],0.512)

Conclusion: Our study shows positive associations between albuminuria and RMD among West Africans with T2D, with the strength of association, accentuated in individuals with hypertension/suboptimal BP. Future studies could further characterize the role of hypertension in the associations between albuminuria and RMD.

Introduction

In 2021, 10.5% of the world's adult population, representing over half a billion people had diabetes, with this prevalence projected to rise to 12.2% by 2045 [1]. A characteristic complication of diabetes is a microvascular disease that may affect retinal and renal microcirculation. Diabetes-related retinal microvascular dysfunction (RMD) results in diabetic retinopathy, which is the most common cause of new cases of blindness among adults aged 20−74 years in high-

Abbreviations: ACR, Urine albumin-creatinine ratio; BMI, body mass index; BP, blood pressure; CI, confidence interval; DR, Diabetic retinopathy; HC, Hip circumference; NPDR, non-proliferative diabetic retinopathy; OR, odds ratio; PDR, proliferative diabetic retinopathy; RMD, retinal microvascular dysfunction; SSA, sub-Saharan Africa; T2D, type 2 diabetes; WC, Waist circumference; WHR, waist-to-hip ratio

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https://doi.org/10.1016/j.deman.2023.100139

income countries [2]. Renal microvascular dysfunction in diabetes results in diabetic nephropathy, which is the main cause of end-stage renal disease [3].

With diabetic microvascular dysfunction having some shared pathogenic bases[4], the presence of dysfunction in one microcirculation may be suggestive of dysfunction in another microcirculation. Such concordance, if present, may be clinically useful in diagnosis, screening plans, and prognostication[5,6]. Regardless of the mechanistic model linking dysfunction in one microcirculation to another [4], evidence from the available studies assessing the concordance of albuminuria and RMD in type 2 diabetes (T2D) has yielded inconsistent results [7,8]. Potential explanatory variables for these inconsistent results are the roles of ethnicity and systemic hypertension or sub-optimum blood pressure (BP) control. Previous studies by our team and other researchers have shown that the risk of vascular dysfunction varies by ethnicity [9–11]. For example, the vasculature of individuals of different ethnic backgrounds is known to exhibit different sensitivities to exposure to a given level of vascular injurious agent[11,12]. To date, studies assessing the associations between dysfunctions in different microcirculation (such as albuminuria and RMD) in many populations including sub-Saharan Africans are lacking. Besides ethnicity, the relationship between microvascular dysfunction in different circulations may be dependent on hypertension status or BP control, as the diagnosis of hypertension and/or poor BP control are independently associated with albuminuria[13] and RMD [14]. Interestingly, studies assessing the role of hypertension and/or BP control in the associations between microvascular dysfunctions in different circulations in individuals with T2D are lacking. Using a sample of Ghanaians managed at a National Diabetes Management and Research center, we evaluated the association between albuminuria and RMD in West Africans with T2D. Further, we evaluated the potential role of hypertension and sub-optimal BP control in this association.

Material and methods

Study design

This was a cross-sectional study among adult Ghanaians with T2D managed at a National Diabetes Management and Research center in Accra, Ghana. Between 2019 and 2022, a total of 500 eligible participants were recruited for pulmonary, cardiac, and vascular functional assessment. The participants were systematically sampled from patients who reported clinic visits during the study period. Eligible participants were patients with an established diagnosis of T2D (fasting plasma glucose ≥7.0 mmol/l and/or 2−h plasma glucose ≥ 11.1 mmol/l and/or on hypoglycaemic agents (oral hypoglycemic agents and/or insulin); who reported the start of their diabetes after the age of 30 years, and whose diabetes initially did not require insulin for management). Individuals with primary heart disease and/or previous/current heart failure were excluded. The current analyses included 177 participants aged ≥35 years with complete data on urinary albumin to creatinine ratio (ACR) results, hemodynamic measurements including blood pressure, and technically acceptable retinal photography. Before the start of data collection, ethical approval was obtained from the Ethics Committees of the University of Ghana College of Health Sciences (CHS-Et/M6-P20.14/2017−2018) and the KBTH (KBTH-IRB/000,124/2019). All participants provided written informed consent before enrolment in the study.

Measurements

A structured questionnaire was used to record the sociodemographic, lifestyle, and health-related behaviors of the study participants. Smoking status was classified into non-smokers, ex-smokers, and current smokers. Educational level was used as a proxy for socioeconomic status. Educational level was classified as lower (never or elementary and lower) and higher level. The duration of diabetes was obtained from the patient's medical records. Anthropometric and BP measurements were obtained by physical examination. Weight was measured in light clothing and without shoes with SECA-877 scales. Height was measured without shoes with a SECA-217 stadiometer. Obesity was defined as a body mass index (BMI)≥30 kg/m^2. Waist circumference (WC) was measured at the midpoint between the lower margin of the least palpable rib and the top of the iliac crest. Hip circumference (HC) was measured around the widest portion of the buttocks, at the level of the greater trochanters, with the tape parallel to the floor. Abdominal obesity was defined as a waist-to-hip ratio(WHR)≥0.90 for males and ≥0.85 for females. BP was measured thrice using the Omron BP Monitor HEM-907XL device, with appropriate-sized cuffs after at least 5 minutes of rest while seated. The mean of the last two BP measurements was used for the analyses. Hypertension was based on a clinical diagnosis code/documentation in the medical records, evidenced by documented elevated BP (≥140/90 mmHg) at the time of diagnosis, and the use of antihypertensive therapy. Suboptimal BP control was defined per the 2017 American College of Cardiology/American Heart Association guidelines criteria and European Society of Cardiology/European Society of Hypertension guidelines (for individuals with hypertension and diabetes) as systolic BP >/= 130 mmHg and/or diastolic BP >/= 80 mmHg [15]. These cutoff values are consistent with the American Diabetes Association's recommendation (2018 update) for individuals with diabetes with higher cardiovascular risk[16].

Biochemical analyses

Venous blood samples were drawn after an overnight fast of at least 10 h. Plasma samples were used to determine the concentration of glucose by spectrophotometry, using hexokinase as the primary enzyme (Roche Diagnostics, Japan). Total cholesterol, triglycerides, and HDL cholesterol were determined by colorimetric spectrophotometry (BS-800 Chemistry Analyzer, Mindray, UK). LDL cholesterol was calculated using the Friedewald formula [17]. Serum creatinine concentration was determined by a kinetic colorimetric spectrophotometric isotope dilution mass spectrometry calibration method (BS-800 Chemistry Analyzer, Mindray, UK). The estimated glomerular filtration rate (eGFR) was calculated using the 2009 CKD-EPI (CKD Epidemiology Collaboration) creatinine equation and the severity of kidney disease categorized according to the 2012 KDIGO guidelines [18]. Glycated hemoglobin (HbA1c) was measured with a National Glycohemoglobin Standardization Program (NGSP) certified Boronate Affinity on Tri-stat Analyzer with Tri-stat kits (Trinity Biotech, Bray, Ireland).

Microvascular functional assessment

The ZEISS 500 Fundus Camera (ZEISS Inc. JENA) was used for retinal photography after dilatation with tropicamide (1%) and phenylephrine (2.5%) ophthalmic solutions, according to the manufacturer's guidelines. Retinal images were analyzed and graded by a certified ophthalmologist according to the Early Treatment Diabetic Retinopathy Study (ETDRS) criteria [19]. Diabetic retinopathy when present was classified as either proliferative diabetic retinopathy (PDR) or non-proliferative diabetic retinopathy (NPDR). NPDR was graded as mild, moderate, severe, or very severe. Mild NPDR was based on the presence of at least one microaneurysm in the absence of any criteria for moderate, severe, or very severe NPDR. Moderate NPDR was based on the presence of hemorrhage/microaneurysm ≥ standard photograph #2A or soft exudates (cotton wool spots), venous beading, and intraretinal microvascular abnormalities present, in the absence of any criteria for severe or very severe NPDR or PDR. Severe NPDR was based on the presence of hemorrhage/microaneurysm ≥

standard photograph #2A in all 4 quadrants or venous beading in at least 2 quadrants or intraretinal microvascular abnormalities ≥ standard photograph #8A in at least 1 quadrant. Very severe NPDR was based on the presence of any two criteria for severe NPDR in the absence of PDR. PDR was graded as either early PDR, high-risk PDR, or severe PDR. Because of the smaller number of individuals in the moderate group (N = 1) for the NPDR group, we merged moderate and severe NPDR groups. Further, only two individuals were in the high-risk or severe PDR groups. Therefore, we graded diabetic retinopathy into either mild NPDR/early PDR or moderate or severe NPDR/high risk or severe PDR.

Direct analyses of urinary albumin and creatinine concentration were performed on an early morning urine sample. Urinary albumin concentration was measured by an immunochemical turbidimetric method (Roche Diagnostics). Urinary creatinine concentration was measured by a kinetic spectrophotometric method (Roche Diagnostics). Albuminuria was defined as ACR≥ 30 mg/g [category≥A2]) according to the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines [18]. Reduced eGFR was not used in the definition of renal microvascular dysfunction as it could also be due to macrovascular dysfunction (i.e. renal artery stenosis)[20].

Statistical analysis

Data with a normal distribution were presented as mean ± standard deviation whereas those not normally distributed were presented as median (interquartile range). Categorical data were presented as frequencies (percentages). Differences in sociodemographic, lifestyle and clinical measures were compared between participants with and without albuminuria. Multivariate logistic regression analyses were used to examine the associations between albuminuria (independent variable) and RMD (dependent variable), with adjustment for potential covariates. Four models were used to examine the data. Model 1 was unadjusted; Model 2 was adjusted for age and sex; Model 3 was additionally adjusted for socioeconomic status. Model 4 was adjusted for age, sex, socioeconomic status, diabetes duration, HbA1c, smoking, systolic BP, BMI, and total cholesterol concentration. Odds ratios (ORs) and their corresponding 95% CI were estimated. We verified whether the association between albuminuria and RMD differed by hypertension status and/or suboptimal BP. As significant interaction effects were found (p = 0.020 for hypertension status and p = 0.004 for suboptimal BP status), we further stratified the analyses by hypertension status and BP control status. A statistical test of significance was set at a p-value < 0.05. Data were analyzed using the IBM SPSS version 25 for Windows.

Results

General characteristics

The baseline characteristics of the study participants are summarized in Table 1. The proportion of males and females and mean age were similar in individuals with and without albuminuria. Although the differences were not statistically significant, individuals with albuminuria tended to be more frequently smokers or obese, less educated and had higher mean diabetes duration and HbA1c concentrations compared with individuals without albuminuria. Compared with individuals without albuminuria, individuals with albuminuria had statistically significantly higher mean systolic and diastolic BP levels and heart rates. Also, the mean total cholesterol concentration was significantly higher in individuals with albuminuria than in those without albuminuria; the difference in LDL-cholesterol and triglyceride concentrations were not statistically significant. Individuals with albuminuria had lower mean eGFR than those without albuminuria.

Prevalence of albuminuria and RMD

In the study population, the median ACR (interquartile range) was 17.0 (10.0 to 31.5) mg/g. The proportion of individuals in the albuminuria categories A1, A2, and A3 were 72.90%, 22.60%, and 4.5%, respectively. Overall, the prevalence of albuminuria [category A2 or A3] was 27.1%. The prevalence of RMD involving at least one eye was

Table 1
Baseline characteristics of the study participants.

Characteristics	All Participants (N = 177)	No Albuminuria (N = 129)	Albuminuria (N = 48)	P-value
Sex (%)				
Females	137 (77.4%)	96 (74.4%)	41 (85.4%)	0.157
Males	40 (22.6%)	33 (25.6%)	7 (14.6%)	0.157
Age (years)	55.93 (±9.35)	55.96 (±9.99)	55.85 (±7.45)	0.939
Secondary/higher education (%)	108 (61%)	54 (41.9%)	15 (31.3%)	0.227
Current/previous smoker (%)	4 (2.3%)	1 (0.8%)	3 (6.3%)	0.061
Duration of diabetes (years)	11.36 (±6.75)	11.05 (±6.52)	12.19 (±7.36)	0.307
Insulin use (%)	73 (41.2%)	51 (39.5%)	22 (45.8%)	0.494
Hypertension (%)	95 (53.7%)	65 (50.4%)	30 (62.5%)	0.176
Systolic BP, mmHg	137.32 (±16.55)	135.67 (±16.00)	141.77 (±17.34)	0.029
Diastolic BP, mmHg	78.57 (±8.85)	77.34 (±8.57)	81.85 (±8.86)	0.002
Systolic BP≥130 mmHg and/or Diastolic BP≥80 mmHg	134 (75.7%)	94 (72.9%)	40 (83.3%)	0.149
Heart rate beats per minute	78.97 (±12.38)	76.93 (±12.66)	84.46 (±9.74)	<0.001
Statin use	98 (55.4%)	68 (52.7%)	30 (62.5%)	0.308
Anthropometry				
BMI, kg/m^2	30.13 (±5.90)	29.75 (±5.81)	31.17 (±6.05)	0.155
Obesity (%)	77 (43.5%)	51 (39.5%)	26 (54.2%)	0.090
Waist circumference	96.36 (±11.95)	95.95(±11.57)	97.44 (±12.96)	0.464
Abdominal Obesity (%)	112 (63.3%)	79 (61.2%)	33 (68.8%)	0.386
Biochemical measures				
HbA1c,%	7.83 (±1.67)	7.81 (±1.66)	7.88 (±1.74)	0.801
Total cholesterol, mmol/l	5.03 (±1.30)	4.88 (±1.34)	5.39 (±1.12)	0.029
Triglyceride, mmol/l	1.28 (±0.49)	1.23 (±0.48)	1.39 (±0.51)	0.075
HDL- cholesterol, mmol/l	1.35 (±0.35)	1.34 (±0.36)	1.39 (±0.32)	0.466
LDL-cholesterol, mmol/l	3.09 (±1.20)	2.98 (±1.23)	3.38 (±1.08)	0.064
eGFR, ml/min/1.73m2	99.84 (±22.45)	103.43 (±21.44)	91.06 (±22.68)	0.002

Abbreviations: BMI = body mass index, BP = blood pressure, eGFR = estimated glomerular filtration rate, HBA1c = glycated hemoglobin; LDL = Low-Density Lipoprotein, WHR = waist-to-hip ratio. *Obesity:* BMI≥30 kg/m^2.
Abdominal obesity: waist to hip ratio ≥ 0.90 for males and ≥ 0.85 for females.

Table 2
Retinal microvascular characteristics in the study population.

Retinal microvascular characteristics	All Participants (*N* = 177)	No Albuminuria (*N* = 129)	Albuminuria (*N* = 48)	P-value
Diabetic Retinopathy				0.001
No Diabetic Retinopathy	126 (71.2%)	98 (76.0%)	28 (58.3%)	
PDR	4 (2.3%)	0 (0.0%)	4 (8.3%)	
NPDR	47 (26.6%)	31 (24.0%)	16 (33.3%)	
Grade of Diabetic Retinopathy				<0.001
No Diabetic Retinopathy	126 (71.2%)	98 (76.0%)	28 (58.3%)	
Mild NPDR / early PDR	45 (25.4%)	31 (24.0%)	14 (29.2%)	
Moderate to severe NPDR /high risk or severe PDR	6 (3.4%)	0 (0.0%)	6 (12.5%)	

Abbreviations: NPDR = non-proliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy.

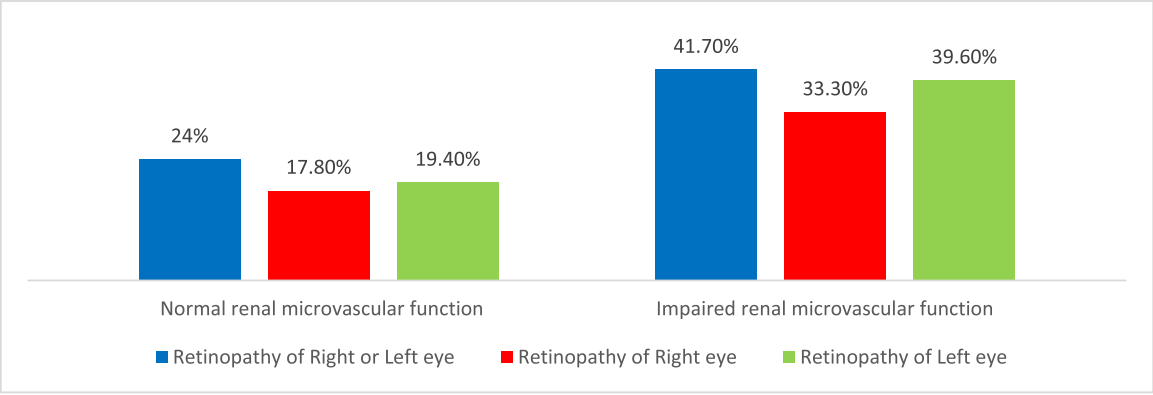

Fig. 1. Prevalence of RMD in individuals with and without albuminuria (*N* = 177).

Table 3
Associations between albuminuria and RMD in the study population and individuals with and without hypertension.

	Odds ratio (95% confidence interval), p-value				
	Whole Group (*N* = 177)	Individuals with Hypertension (*N* = 95)	Individuals without hypertension (*N* = 82)	Individuals with suboptimal BP* (*N* = 134)	Individuals with optimum BP control (*N* = 43)
Model 1	2.26 (1.12 – 4.56), 0.023	2.47 (1.00 – 6.11), 0.050	1.79 (0.57 – 5.61), 0.321	2.37 (1.10–5.10), 0.028	0.86 (0.09–8.54), 0.895
Model 2	2.16 (1.06 – 4.38), 0.033	2.36 (0.94 – 5.97), 0.069	1.78 (0.56 – 5.66), 0.325	2.27 (1.05–4.91), 0.038	0.82 (0.08–8.82), 0.872
Model 3	2.15 (1.06 – 4.37), 0.035	2.32 (0.92 – 5.88), 0.076	1.77 (0.56 – 5.63), 0.332	2.28 (1.05–4.94), 0.037	0.67 (0.06–7.77), 0.751
Model 4	2.41 (1.00–5.80), 0.049	3.10 (1.01–9.50), 0.048	1.70 (0.33–8.77), 0.523	2.76 (1.07–7.14), 0.037	0.24 (0.00–17.04), 0.512

Model 1 was unadjusted; model 2 was adjusted for age and sex; model 3 was adjusted for age, sex, and socioeconomic status; model 4 was adjusted for age, sex, socioeconomic status, diabetes duration, HbA1c, smoking, systolic blood pressure, BMI, and total cholesterol.
* Suboptimal BP control was defined per the 2017 American College of Cardiology/American Heart Association guidelines criteria and European Society of Cardiology/European Society of Hypertension guidelines (for individuals with hypertension and diabetes) as systolic BP >/= 130 mmHg and/or diastolic BP >/= 80 mmHg.
Abbreviation: RMD; Retinal microvascular dysfunction.

28.8% (left eye 22.6%; right eye 23.7%). The prevalence of both PDR and NPDR was higher in individuals with albuminuria compared with individuals without albuminuria (8.3% vs 0.0% for PDR and 33.3% vs 24.0% for NPDR, $p = 0.001$) (Table 2). Overall, the prevalence of diabetic retinopathy (PDR or NPDR) was nearly 73.4% higher in individuals with albuminuria compared with individuals without albuminuria (41.7% vs. 24.0%%, $p = 0.026$) (Fig. 1). In terms of severity, all cases of moderate or severe NPDR and high-risk or severe PDR were in the albuminuria group. Also, the proportion of individuals with mild NPDR or early PDR was higher in individuals with albuminuria compared with individuals without albuminuria (Table 2).

Association between albuminuria and RMD

In the unadjusted and age-sex-adjusted models, albuminuria was significantly associated with higher odds of RMD (Table 3). Similar observations were made after further adjustment for socioeconomic status. In the fully adjusted model, albuminuria remained significantly associated with RMD (odds ratio 2.41 [95% CI: 1.00–5.80], $p = 0.049$). In both individuals with and without hypertension, the direction of associations between albuminuria and RMD remained positive. However, the strengths of the associations were different. In the fully adjusted model, the positive association between albuminuria and RMD was more pronounced in individuals with hypertension (3.10 [1.01–9.50], 0.048) than in individuals without hypertension (1.70 [0.33–8.77], 0.523). In analyses stratified by BP control, positive associations between albuminuria and RMD were observed in individuals with suboptimal BP but not in those with optimum blood pressure. In the folly-adjusted model, albuminuria remained significantly associated with RMD in individuals with suboptimal BP (2.76 [1.07–7.14], 0.037) but not in individuals with optimum BP (0.24 [0.00–17.04], 0.512).

Discussions

Key findings

In our study population of West Africans with T2D, RMD was more prevalent in individuals with albuminuria compared with individuals without albuminuria. The severer forms of RMD were also

frequent in individuals with albuminuria compared with individuals without albuminuria. The positive association between RMD and albuminuria remained statistically significant after adjustment for a wide range of conventional vascular risk factors including diabetes duration, systolic BP, total cholesterol concentration, and HbA1c concentrations. The strength of the association between albuminuria and RMD was greater in individuals with T2D with hypertension than in individuals without hypertension. A positive and significant association between albuminuria and RMD was observed in individuals with suboptimum BP but not in individuals with optimum BP control.

Discussion of key findings

In this study population, the observed prevalence of RMD (i.e. 28.8%) is slightly higher than the pooled global prevalence of 22.3% (95% CI 19.73%–25.03%), based on a recent meta-analysis of 59 population-based studies [21]. However, it is substantially lower than the prevalence of 35.9% (29.48–42.87) among sub-Saharan Africans included in that metanalysis [21]. While there are limitations in comparing the current hospital-based (out-patient clinic) study with the population-based studies included in the meta-analysis, the lower prevalence of RMD in our study population compared with the pooled prevalence among Africans could reflect better diabetes care among individuals managed at a tertiary diabetes referral facility. Indeed, a previous hospital-based study among West Africans reported lower prevalence rates of RMD, compared with the population-based studies [21,22]. Albeit, over a quarter of our study population having RMD is clinically relevant as RMD remains a key cause of new cases of blindness in adults [2]. Similar to RMD, the prevalence of albuminuria in this hospital-based study (27.1%) is lower than that observed among Ghanaians with T2D in a population-based study (32.0%) [23].

To the best of our knowledge, our study is the first among sub-Saharan Africans to assess an association between albuminuria and RMD in individuals with T2D. Our study shows a higher prevalence (and more severe forms) of RMD in T2D individuals with albuminuria compared with those without albuminuria. After adjustment for key vascular risk factors, the positive association between albuminuria and RMD remained statistically significant. Our findings generally agree with many previous studies among Asians and Europeans [8,24–26]. However, our findings contrast those of other researchers [27,28]. For example, a cross-sectional study by Wolf et al. among Germans showed discordance of albuminuria and RMD in individuals with T2D [28]. Given the similar methods and study design, it remains unclear why our findings contrast with other studies including Wolf et al. [28]. In addition to possible ethnic differences[27], differences in the healthcare systems including diabetes and vascular care may be relevant. Individuals with albuminuria who receive optimum vascular care including optimum BP control might have lower risks of developing RMD, and vice versa. Indeed, we have previously reported that among West Africans, migrating to a high-income setting substantially reduces the risk of developing microvascular disease[23].

Studies that did not find significant associations between albuminuria and RMD give credence to the hypothesis that there are divergences, at least in some aspects of the pathogenesis of albuminuria and RMD. This current study that showed a positive association between albuminuria and RMD independent of the conventional vascular risk factors may suggest that among West Africans, albuminuria and RMD may share common pathogenic factors including exposure of microcirculation to the diabetic milieu [2,4]. Alternatively, functional impairment in one microcirculation may increase the risk of dysfunction in another microcirculation, as supported by results from a meta-analysis by Gupta et al., 2022 [8]. For example, albuminuria is known to increase the risk of RMD [2]. Similar to worsening albuminuria, declining eGFR has been shown to be independently associated with worsening RMD [29,30]. Regardless, there is also the possibility that the observed association could reflect the management of the underlying risk factors for albuminuria and RMD. For example, the effectiveness of management of the underlying risk factors may impact the rate of progression of retinal and kidney microvascular dysfunctions, resulting in the observed association. This hypothesis partly influenced the idea to stratify the analyses by a major risk factor for microvascular injury – hypertension.

A key contribution of our study to the existing literature is the possible role of hypertension or sub-optimal BP control in the relationship between albuminuria and RMD. We observed that the positive association between albuminuria and RMD is more pronounced in individuals with hypertension than in individuals without hypertension. Also, there was a significant positive association between albuminuria and RMD in individuals with elevated BP, but not in individuals with optimal BP. The mechanistic basis of the observation is uncertain. While similar pathophysiological processes drive diabetes-related microvascular injury in different circulations[4], the susceptibilities of individual microcirculation may differ [31]. The susceptibility of a given microcirculation to injury in the setting of T2D may be increased by the presence of hypertension [32] as blood flow alterations in the setting of hypertension may damage the microcirculatory capillary endothelial cells, resulting in the development and progression of RMD[31]. With hypertension being a key cause of retinopathy [33] and hypertensive kidney disease [34], the coexistence of diabetes and hypertension may increase the susceptibility of both renal and retinal microcirculation to injury. In such cases, the development of albuminuria and RMD will be more predictable in individuals with T2D with coexisting hypertension.

While hypertension may be key in the concordance between albuminuria and RMD, elevated BP may be equally important. Similar to the coexistence of hypertension, individuals with T2D with suboptimal BP control may be at a greater risk of microvascular dysfunction involving multiple circulations. This view is supported by many longitudinal studies including the UK Prospective Diabetes Study have shown that lowering BP in individuals with diabetes with poorly controlled hypertension provides clinically significant benefits including preventing the progression of microvascular dysfunction including RMD [31]; A few studies including the ACCORD study have not shown that lowering BP to much lower cut-off values is associated with decreased progression of microvascular dysfunction[35]. The relationship between BP control (regardless of the diagnosis of hypertension) and the strength of association between albuminuria and RMD may explain why a diagnosis of hypertension per se may sufficiently increase the risk of RMD in individuals with albuminuria, as observed by Wolf et al., 2007 [28]. In the present study, a large proportion of the study participants had sub-optimal BP control. This may reflect poorer vascular risk factor awareness, detection of elevated BP, and control of BP in low-income settings [36].

Other possible mechanisms may explain the greater concordance between albuminuria and RMD in the settings of hypertension or suboptimal BP. For example, impaired microvascular autoregulation [37] and/or greater systolic and diastolic BP in the setting of hypertension[38] may predispose one microcirculation to injury from dysfunction of another microcirculation. This view assumes that the relationship between microvascular dysfunction in different microvascular circulations is causal. Alternatively, albuminuria, a marker of albuminuria is also considered an indicator of generalized systemic microvascular dysfunction [39]. Besides, microvascular dysfunction, by affecting systemic vascular resistance may initiate the pathophysiological processes leading to the development of hypertension [40]. With this model, individuals with impaired retinal or albuminuria are more likely to belong to the hypertension group. Future studies could further characterize the role of hypertension/elevated BP in the associations between microvascular dysfunctions in the various microcirculation, including underlying mechanisms.

Regardless of whether the association between albuminuria and RMD is causal or not, important recommendations can be made

based on the observed association. Traditionally, a recommendation from studies associating RMD and albuminuria had been the periodic evaluation of albuminuria when an ophthalmologic evaluation shows RMD. Unlike renal microvasculature, retinal microvasculature can be directly visualized, and early derangements are observed. Therefore, the identification of early retinal microvascular derangements provides sufficient justification for more frequent screening for albuminuria as well as instituting renal protective strategies including lowering the BP and glycemic thresholds and cut-off values [5,6,16]. Additionally, a reverse recommendation (i.e. screening for RMD in individuals with albuminuria) is clinically relevant, especially in low-income settings. In many low-income settings, periodic evaluation of retinal microvascular function in individuals with T2D is not done due to logistical constraints[41] and a limited number of ophthalmologists or clinicians trained in the interpretation of retinal photographs. However, assessment of albuminuria via measurement of spot urinary ACR is widely available. Therefore, screening for RMD should be prioritized in individuals with albuminuria (especially if they have coexisting hypertension), to aid in early detection and/or institution of prevention and treatment strategies.

Strengths and limitations

To the best of our knowledge, our study is the first to report on the relationships between measures of microvascular function in sub-Saharan Africans who are ethnically distinct and whose vascular risk profiles may vary from individuals of European and Asian ethnic origins[10,11,42]. This study is also the first to report the differential associations between albuminuria and RMD in individuals with T2D with and without hypertension or optimal BP control. In this study, we used well-standardized study protocols including objective measures of kidney and retinal microvascular dysfunction. Finally, we adjusted for a wide range of conventional cardiometabolic risk factors in the regression models. Our study has some limitations. First, the cross-sectional design limits us from claiming causality. Secondly, we defined albuminuria based on a high urinary ACR from a single urine sample; based on the high biological variability of >20% between measurements in urinary albumin excretion, two of three specimens of urinary ACR collected within a 3- to 6-month period should be abnormal before considering an individual to have high or very high albuminuria [43].

Conclusions

The current study shows that in West Africans with T2D, albuminuria was positively associated with RMD, independent of the conventional microvascular risk factors. The observed association was more pronounced in individuals with hypertension (than in individuals without hypertension) and suboptimal BP (than in individuals with optimal BP). Based on our findings, individuals with T2D with albuminuria might benefit from more periodic evaluation of retinal microvascular function, for early detection and treatment of diabetic retinopathy. Similarly, individuals with RMD might benefit from more periodic evaluations of renal microvascular function. These benefits are more likely in individuals with hypertension and/or suboptimal BP control. Our study findings also provide useful insights into the possible role of hypertension and/or BP control in the relationship between albuminuria and RMD. Future studies may explore the mechanisms linking hypertension/poor BP control and the relationship between dysfunctions in the various microcirculation.

Authorship contribution

All authors have contributed substantially to this article and approved the submission. C.F.H-B, A.G.B.A C.A., and C.A-B conceived the idea. C.F.H-B. and K.A.O were responsible for data acquisition; C.F. H-B and K.A.O were responsible for statistical analysis. C.F.H-B, C.A-B, A.G.B.A., and K.A.O were responsible for data analysis/interpretation. Each author contributed important intellectual content during article drafting or revision and accepts accountability for the overall work by ensuring that questions about the accuracy or integrity of any portion of the work are appropriately investigated and resolved. C.F.H-B. takes responsibility for the fact that this study has been reported honestly, accurately, and transparently, that no important aspects of the study have been omitted, and that any discrepancies from the study as planned have been explained

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests

Kwesi N. Amissah-Arthur reports a relationship with African Retinal Society that includes: board membership. None

Acknowledgments

We are very grateful to the study participants for taking part in the study. Patience Vormatu deserves special commendation for coordinating the recruitment and study procedures. We thank the Research Assistants (Abraham Ablor, Alexander Danquah, Maame Boatemaa Ansong, Michael Adjei, and Nii Adjetey Kwaw Wills) for assisting with interviews and anthropometric measurements. We also thank Edem Ahiabor for assisting with the retinal photography. We gratefully acknowledge the leadership and staff of the NDMRC for helping with various aspects of the study. We also acknowledge Elikem Jasper Butsey, Faustina Aba Amoah, Odelia Tamakloe, and Seth Agyemang, and the staff of the National Cardiothoracic Centre Laboratory and the KBTH Accident and Emergency Laboratory for running the biochemical tests. We are grateful to Dr. Charles Antwi-Boasiako, Dr. Yvonne Dei-Adomako, and Mr. Enoch Mensah for their support in biobank management and the high-quality storage of collected samples.

Funding

This work was funded by the Faculty Development Grant of the University of Ghana College of Health Science.

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