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Relationships of blood pressure and control with microvascular dysfunction in type 2 diabetes

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ABSTRACT

Background: In type 2 diabetes mellitus (T2D), cardiovascular risk factors including glycemic control differentially affect various microcirculatory beds. To date, studies comparing the impact of blood pressure (BP) on various microvascular beds in T2D are limited. We assessed the associations of BP and its control with neural, renal, and retinal microvascular dysfunction.

Methods: This was a cross-sectional study among 403 adults with T2D. Microvascular dysfunction was based on nephropathy (albumin-creatinine ratio ≥ 30 mg/g), neuropathy (vibration perception threshold ≥ 25 V and/or Diabetic Neuropathy Symptom score > 1), and retinopathy (based on retinal photography). Logistic regression was used to examine the associations of hypertension, systolic BP, and diastolic BP with microvascular dysfunction with adjustments for age, sex, diabetes duration, smoking pack years, HbA1c concentration, total cholesterol concentration, and BMI.

Results: The mean age (± SD), proportion of females, and proportion of hypertensives were 56.35 (± 9.91) years, 75.7%, and 49.1%, respectively. In a fully adjusted model, hypertension was significantly associated with neuropathy [odds ratio 3.44, 95% confidence interval 1.96−6.04, $P < 0.001$] and nephropathy [2.05 (1.09 −3.85), 0.026] but not for retinopathy [0.98 (0.42−2.31), 0.970]. Increasing Z-score systolic BP was significantly associated with nephropathy [1.43 (1.05−1.97), 0.025] but not for neuropathy [1.28 (0.98−1.67), 0.075] or retinopathy [1.27 (0.84−1.91), 0.261]. Increasing Z-score diastolic BP was significantly associated with nephropathy [1.81 (1.32 − 2.49), < 0.001] but not retinopathy [1.38 (0.92−2.05), 0.120] or neuropathy [0.86 (0.67−1.10), 0.230].

Conclusion: Our study shows varying strengths of associations of hypertension, systolic BP, and diastolic BP with microvascular dysfunction in different microcirculatory beds. Hypertension prevention and/or control may be valuable in the prevention/treatment of microvascular disease, especially nephropathy, and neuropathy.

Introduction

Diabetes mellitus remains a global public health problem, affecting over ten percent of the world's adult population [1]. A characteristic complication of diabetes mellitus is microvascular disease including retinopathy, neuropathy, and nephropathy [2]. These microvascular complications are important causes of disability. For example, diabetic retinopathy is the commonest cause of blindness in adults [3], diabetic nephropathy is the commonest cause of

Abbreviations: BMI, body mass index; BP, blood pressure.; CI, confidence interval.; DNS, Diabetic neuropathy symptom; HBA_1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NPDR, Non-proliferative diabetic retinopathy; OR, odds ratio; PDR, Proliferative diabetic retinopathy; SBP, systolic blood pressure; T2D, type 2 diabetes mellitus; VPT, Vibration perception threshold

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end-stage renal failure [4], and diabetic neuropathy is a leading cause of leg ulcers, gangrene, and lower limb amputations [5]. Type 2 diabetes mellitus (T2D), the commonest type of diabetes, is associated with other vascular risk factors including hypertension, obesity, and dyslipidemia [1].

There are important gaps in the treatment of diabetes-related microvascular complications. For example, there is currently no effective treatment for diabetic neuropathy [6]. Given this, a multifactorial approach targeting glycemia and other conventional risk factors has been recommended for the prevention of diabetic microvascular disease [6]. Targeting optimum glucose control may not always be effective in the prevention of microvascular complications in T2D. For example, while enhanced glucose control limits the progression of neuropathy in type 1 diabetes, there is limited evidence for the same in T2D [7]. This has warranted the need for identifying alternative strategies for preventing the development and progression of microvascular disease in T2D. Based on work done by our team among sub-Saharan Africans [8–11], and those of other researchers in other populations [2,12,13], non-conventional candidate risk factors including low-grade inflammation, hyperuricemia, and macrovascular dysfunction also do not fully explain the burden of vascular dysfunction. One potential factor is the impact of blood pressure (BP) control on systemic microvascular injury. It has previously been reported that patients with T2D have a loss of myogenic tone and vascular hypertrophy in resistance vessels [14]. There is also evidence that deranged myogenic tone and vascular hypertrophy in T2D may be partially ameliorated after treatment with the angiotensin-receptor blocker candesartan [15]. Given the above, BP and its control could play an important role in the development and/or progressions of microvascular complications. However, the prognostic potency of the individual vascular risk factors for vascular injury is known to vary in the different vascular beds [16]. We hypothesize that the associations of BP and its control with microvascular dysfunction differ by microvascular beds. Therefore, we assessed the associations of BP and its control with neural, renal, and retinal microvascular dysfunction.

Methods

Study design

This cross-sectional study among adult Ghanaians with T2D managed at a National Diabetes Management and Research center in Ghana has been previously described [17]. Between 2019 and 2022, a total of 500 adults with established diagnoses of T2D and who did not have primary heart disease and/or previous/current heart failure were recruited for pulmonary, cardiac, and vascular functional assessment. The patients were systematically sampled from patients who reported for clinic visits. The diagnosis of T2D was based on fasting plasma glucose (FPG) $\geq$ 7.0 mmol/l and/or 2−h plasma glucose $\geq$ 11.1 mmol/l and/or on hypoglycemic agents who reported the start of their diabetes age > 30 years, and whose diabetes initially did not require insulin for management. The current analyses included 403 participants with data on at least one measure of microvascular function. 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 Korle Bu Teaching Hospital (KBTH-IRB/000,124/2019). All participants provided written informed consent before enrolment in the study.

Measurements

Assessment of baseline sociodemographic/clinical characteristics including smoking and diabetes duration, measurement of height, weight, and concentrations of fasting plasma glucose, HbA1c, cholesterol, and serum creatinine has also been previously described [17].

BP measurement and control

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 systolic BP (SBP) $\geq$ 140 mmHg and/or diastolic BP (DBP) $\geq$ 90 mmHg, and/or being on antihypertensive medication treatment [18]. 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 [19]. These cutoff values are consistent with the American Diabetes Association's recommendation for individuals with diabetes with higher cardiovascular risk [20].

Assessment of neural microvascular dysfunction

Neural microvascular dysfunction was based on the presence of neuropathy. Vibration perception threshold (VPT) was measured using the Horwell Neurothesiometer (Scientific Laboratory Supplies Ltd, Nottingham) at the metatarsophalangeal joint of both feet in a two-step manner (ascending and descending methods). The VPT procedure was demonstrated to each participant before the VPT testing was done. To explain the nature of the vibration to be perceived, the vibration was demonstrated at the planter surface of the participant's thumb. VPT testing was done while the patient was in the supine position and the neurothesiometer was placed in a position where the patient could not see the vibration settings. Using light pressure, the plastic tip of the neurothesiometer was applied against the plantar surface of the great toe of the foot. For the ascending method, the induced vibrations were gradually increased by increasing the device voltage at a rate of 0.5 Vs/second until the participant first detected the vibration. The voltage at which the participant first detected the vibration was documented as the ascending VPT. Two other ascending vibrating tests were performed, and the arithmetic mean of consistent values was used as the final ascending VPT used in the analyses. The consistent voltages were voltages whose values do not differ by > 0.5 V. The technique was repeated using a descending approach by decreasing the voltage from 50 V at a rate of 0.5 Vs/second and identifying the lowest voltage at which no vibration was perceived; this voltage was documented as the descending VPT. The average of consistent descending voltages was used in the final descending VPT used in the analyses. Symptoms of diabetic neuropathy were scored with the Diabetic Neuropathy Symptom (DNS) score [21]. Neuropathy was diagnosed if the VPT was $\geq$ 25 V [22] and/or a DNS score $\geq$ 1 [21].

Assessment of renal microvascular dysfunction

Renal microvascular dysfunction was based on the presence of albuminuria. 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 based on the urinary albumin-creatinine ratio (ACR) $\geq$ 30 mg/g [category $\geq$ A2]) according to the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines [23].

Assessment of retinal microvascular dysfunction

Retinal microvascular dysfunction was based on the presence of retinopathy. The ZEISS 500 Fundus Camera (ZEISS Inc. JENA) was

used for retinal photography after dilatation with tropicamide (1%) and phenylephrine (2.5%) ophthalmic solutions. Retinal images were analyzed and graded by a certified ophthalmologist according to the Early Treatment Diabetic Retinopathy Study (ETDRS) criteria [24]. 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.

Statistical analysis

Data were analyzed using the IBM SPSS version 25 for Windows. Differences in clinical characteristics between individuals with and without hypertension or sub-optimal BP control were assessed by the chi−square test or Fisher's exact test for categorical variables, t−test for continuous variables, or the Mann−Whitney U−test for variables not normally distributed. Multivariate logistic regression analyses were used to examine the associations of hypertension, sub-optimal BP control, and increasing z-score systolic BP or diastolic BP (independent variables) with measures of microvascular dysfunction (dependent variables), with adjustment for potential covariates. The minimal sufficient adjustment sets for estimating the direct effect of impaired spirometry on microvascular dysfunction were determined by a directed acyclic graph (DAG) (Fig. 1). Based on the DAG, the minimal sufficient adjustment sets were age, sex, diabetes duration, smoking pack years, HbA1c concentration, total cholesterol concentration, and BMI. Three models were used to examine the data. Model 1 was unadjusted. Model 2 was adjusted for age and sex. Model 3 was adjusted for age, sex, diabetes duration, smoking pack years, HbA1c concentration, total cholesterol concentration, and BMI. Odds ratios (ORs) and their corresponding 95% CI were estimated. A statistical test of significance was set at a P-value < 0.05.

Results

General characteristics of the study participants

The baseline characteristics of the study population are summarized in Table 1. Compared with individuals with T2D without hypertension, individuals with T2D with hypertension were much older, had a longer mean duration of diabetes, and were more frequently users of statins and insulin. The mean BMI, waist circumference, and WHR were higher in T2D individuals with hypertension compared with their non-hypertensive comparative group. There were no significant differences in the mean HbA1C and cholesterol concentrations between the two groups. Similar observations were made when the two groups were compared in terms of hypertensive control, except for the observations that the T2D with suboptimal BP control had a higher female-to-male ratio and a similar mean WHR compared with the T2D with optimal BP control group.

Microvascular dysfunction in the study population

Table 2 compares the measures of neural, renal, and retinal microvascular function in the study population. Respectively 31.0%, 25.4%, and 28.8% had markers of neural, renal, and retinal microvascular dysfunction. The mean VPT in the left and right legs were respectively 38% higher (12.30 Vs vs. 8.94 Vs, P < 0.001) and 34% higher (12.04 Vs vs. 8.96 Vs, P < 0.001) in the T2D with hypertension group compared to the T2D without hypertension group (P < 0.001 for both). The prevalence rate of neuropathy was nearly thrice as high in the T2D with hypertension group compared with the T2D without hypertension group (46.5% vs 16.1, P < 0.001). These observed disparities were

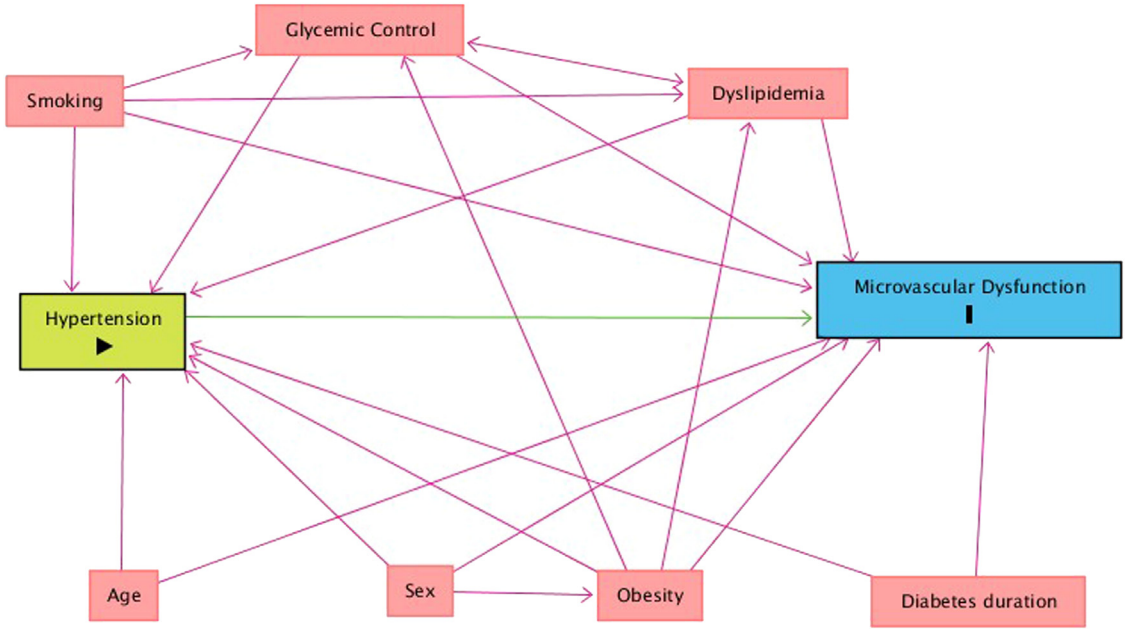

Fig. 1. Directed acyclic graph for estimating the direct effect of hypertension or blood pressure measures on microvascular dysfunction.

Table 1
General characteristics of the study participants.

	All Participants *(N = 403)*	Hypertension Status *			BP Control *		
		Normotensive (N = 205)	*Hypertensive (N = 198)*	*p-value*	*Optimum (N = 111)*	*Suboptimum (N = 293)*	*P-value*
Sex (%)				0.165			0.027
Female	305 (75.7%)	149 (72.7%)	156 (78.8%)		75 (67.6%)	230 (78.8%)	
Male	98 (24.3%)	56 (27.3%)	42 (21.1%)		36 (32.4%)	62 (21.2%)	
Age (years)	56.35 (±9.91)	53.74 (±11.11)	59.05(±7.63)	<0.001	53.05 (±10.58)	57.61 (±9.36)	<0.001
Higher education (%)	149 (43.2%)	68 (42.2%)	81 (44.0%)	0.745	49 (55.1%)	100 (39.1%)	0.009
Smoking status (%)				0.747			0.711
Never smoker	394 (97.8%)	201 (98.0%)	193 (97.5%)		108 (97.3%)	286 (97.9%)	
Current/previous smoker	9 (2.2%)	4 (2.0%)	5 (2.5%)		3 (2.7%)	6 (2.1%)	
Smoking pack years*	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.687	0.0 (0.0)	0.0 (0.0)	0.703
Duration of diabetes (years)	11.15 (±7.17)	9.44(±7.48)	12.73 (±6.48)	<0.001	8.71 (±6.65)	11.99 (±7.15)	<0.001
Insulin use (%)	138 (34.2%)	47 (22.9%)	91 (46.0%)	<0.001	28 (25.2%)	110 (37.7%)	0.019
Statin use (%)	191 (47.4%)	58 (28.3%)	133 (67.2%)	<0.001	42 (37.8%)	149 (51.1%)	0.019
Systolic BP, mmHg	136.51 (±16.23)	128.60 (±32)	144.70 (±16.50)	<0.001	119.48 (±7.29)	142.98 (±13.82)	<0.001
Diastolic BP, mmHg	79.47 (±8.40)	77.61 (±7.38)	81.40 (±8.95)	<0.001	72.36 (±5.21)	82.18 (±7.78)	<0.001
Pulse rate, beats per minute	79.62 (±11.15)	78.70 (±11.40)	80.57 (±10.83)	0.093	78.60 (±10.82)	80.00 (±11.26)	0.262
Anthropometry							
BMI, kg/m^2	29.55 (±6.07)	28.48 (±5.84)	30.65 (±6.12)	<0.001	28.4 (±5.47)	29.98 (±6.24)	0.019
Waist circumference, cm	96.16 (±12.18)	93.83 (±11.34)	98.56 (±12.57)	<0.001	93.70 (±10.82)	97.09 (±12.55)	0.012
WHR	0.90 (±0.07)	0.89 (±0.08)	0.91 (±0.74)	0.047	0.89 (±0.08)	0.90 (±0.07)	0.799
Biochemical Measurements							
HbA1c,%	7.98 (±1.78)	8.03 (±1.85)	7.93 (±1.70)	0.596	8.00 (±1.87)	8.00 (±1.74)	0.903
Total cholesterol, mmol/l	4.88 (±1.27)	4.91 (±1.23)	4.85 (±1.31)	0.712	4.6 (±1.13)	4.95 (±1.32)	0.110
Triglyceride, mmol/l	1.23 (±0.51)	1.20 (±0.49)	1.26 (±0.52)	0.374	1.18 (±0.44)	1.25 (±0.36)	0.228
HDL- cholesterol, mmol/l	1.34 (±0.35)	1.37 (±0.36)	1.32 (±0.33)	0.171	1.37 (±0.36)	1.33 (±0.34)	0.339
LDL-cholesterol, mmol/l	2.97 (±1.15)	2.98 (±1.14)	2.95 (±1.16)	0.783	2.78 (±1.05)	3.04 (±1.18)	0.078

Obesity is defined as BMI ≥ 30 kg/m2; Central obesity defined as waist to hip ratio ≥ 0.90 for males and ≥ 0.85 for females.
Higher education is defined as secondary school education or higher.
Abbreviations: BMI = body mass index, HBA1c = glycated hemoglobin; WC = waist circumference.

less masked when individuals with T2D with and without suboptimal BP control were compared.

The median ACR was 63% higher in the in the T2D with hypertension group compared to the T2D without hypertension group (19.50 mg/g vs. 12.00 mg/g, $P < 0.001$). Similarly, the proportion of individuals with albuminuria was nearly 80% higher in individuals with T2D with hypertension compared with those with T2D without hypertension (32.6% vs. 18.2%, $P = 0.003$). Similar observations were made when individuals with T2D with and without suboptimal BP control were compared.

The rates, types, and grades of retinopathy were similar in the T2D with hypertension and T2D without hypertension groups. However, differences were observed when individuals with T2D with and without suboptimal BP control were compared. For example, the prevalence of retinopathy was over twice as high in individuals with T2D with suboptimal BP control compared with those with optimal BP control (33.6% vs. 14.0%, $P = 0.013$). Also, individuals with T2D with suboptimal BP control were less likely to have mild NPDR or early PDR compared with those with optimal BP control (29.1% vs. 14.0%, $P = 0.036$).

Relationship between measures of BP and microvascular dysfunction

In the unadjusted and age and sex-adjusted models, hypertension was positively associated with higher odds of neuropathy and

Table 2
Microvascular Dysfunction in the Study Population.

Microvascular circulation		Hypertension Status *			BP Control *		
A. Neural microvascular	**All Participants *(N = 403)***	***Normotensive (N = 205)***	***Hypertensive (N = 198)***	***p-value***	***Optimum (N = 111)***	***Suboptimum (N = 292)***	***P-value***
VPT left leg, volts	10.59 (±7.93)	8.94 (±5.77)	12.30 (±9.38)	<0.001	9.24 (±6.67)	11.10 (±8.31)	0.021
VPT right leg, volts	10.47 (±8.06)	8.96 (±6.22)	12.04 (±9.36)	<0.001	9.77 (±7.47)	10.74 (±8.27)	0.291
Neuropathy (%)	125 (31.0%)	33 (16.1%)	92 (46.5%)	<0.001	27 (24.3%)	98 (33.6%)	0.091
B. Renal microvascular	**All Participants *(N = 342)***	***Normotensive (N = 170)***	***Hypertensive (N = 172)***	***p-value***	***Optimum (N = 92)***	***Suboptimum (N = 250)***	***P-value***
ACR, mg/g	12.00 (24.00)	12.00 (18.00)	19.50 (34.00)	<0.001	11.00 (18.00)	17.00 (29.00)	0.001
Nephropathy	87 (25.4%)	31 (18.2%)	56 (32.6%)	0.003	14 (15.2%)	73 (29.2%)	0.008
C. Retinal microvascular	**All Participants *(N = 177)***	***Normotensive (N = 77)***	***Hypertensive (N = 100)***	***p-value***	***Optimum (N = 43)***	***Suboptimum (N = 134)***	***P-value***
Retinopathy	51 (28.8%)	19 (24.7%)	32 (32.0%)	0.318	6 (14.0%)	45 (33.6%)	0.013
Retinopathy type				0.496			0.040
PDR	4 (2.3%)	1 (1.3%)	3 (3.0%)		0 (0.0%)	4 (3.0%)	
NPDR	47 (26.6%)	18 (23.4%)	29 (29.0%)		6 (14.0%)	41 (30.6%)	
Retinopathy Grade				0.315			0.036
Mild NPDR / early PDR	45 (25.4%)	18 (23.4%)	27 (27.0%)		6 (14.0%)	39 (29.1%)	
Moderate to severe NPDR / high risk or severe PDR	6 (3.4%)	1 (1.3%)	5 (5.0%)		0 (0.0%)	6 (4.4%)	

ACR expressed as median 9interquartile range).
Abbreviations: ACR = urinary albumin to creatinine ratio; DNS = Diabetic Neuropathy Symptom; NPDR = non-proliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy; VPT = vibration perception threshold.

nephropathy but not retinopathy (Table 3). The association remained statistically significant in the fully adjusted model for neuropathy [odds ratio 3.44, 95% confidence interval 1.96−6.04, $P < 0.001$] and nephropathy [2.05 (1.09−3.85), 0.026] but not for retinopathy [0.98 (0.42−2.31), 0.970]. While suboptimal BP control was positively associated with nephropathy and retinopathy in both unadjusted and age-sex-adjusted models, the strength of associations was not statistically significant in the fully adjusted model for each of the measures of microvascular dysfunction: neuropathy [1.11 (0.61 −2.04), 0.732]; nephropathy [1.63 (0.77−3.47), 0.205]; retinopathy [2.18 (0.72−6.61), 0.170].

Increasing Z-score systolic BP was positively associated with higher odds of neuropathy, nephropathy, and retinopathy in the unadjusted and age and sex-adjusted models. In the fully adjusted model, the positive association between Increasing Z-score systolic BP and microvascular dysfunction was significant for nephropathy [1.43 (1.05−1.97), 0.025] but not for neuropathy [1.28 (0.98−1.67), 0.075] or retinopathy [1.27 (0.84−1.91), 0.261].

Increasing Z-score diastolic BP was not significantly associated with neuropathy in all three models including the fully adjusted model [0.86 (0.67−1.10), 0.230]. Increasing Z-score diastolic BP was positively associated with higher odds of nephropathy and retinopathy in the unadjusted and age and sex-adjusted models. In the fully adjusted model, the strength of association was significant in the fully adjusted model for nephropathy [1.81 (1.32−2.49), < 0.001) but not for retinopathy [1.38 (0.92−2.05), 0.120].

Discussion

Summary of key findings

Our study has four key findings. First, neuropathy was the most common microvascular complication and nephropathy was the least common microvascular complication in our study population of West Africans with T2D. Secondly, coexisting hypertension and/or suboptimal BP control was associated with an increased likelihood of microvascular dysfunction in individuals with T2D; hypertension diagnosis was significantly associated with neuropathy and nephropathy, while suboptimal BP was significantly associated with nephropathy and retinopathy. Thirdly, the positive associations of hypertension with neuropathy and nephropathy were independent of the conventional vascular risk factors. Finally, there were differential associations of measures of BP and control with microvascular dysfunctions in different microcirculation.

Discussion of key findings

In our study population of West Africans with T2D managed at a national diabetes management and referral center, neuropathy was the commonest microvascular complication, while nephropathy was the least common. To the best of our knowledge, no study among West Africans has compared the burden of microvascular dysfunctions in the three key microcirculations affected by diabetes. Our finding of neuropathy as the commonest complication is consistent with prior studies among individuals of European ethnic origins as well as those living in high-income settings [6,25]. Similar reports exist for individuals of Asian ethnic origin living in low-resource settings [26]. While about 50% of individuals with T2D may eventually develop diabetic neuropathy [27], prevalence rates from cross-sectional studies have varied based on the population studied. Our reported diabetic neuropathy prevalence rate of 31.0% is slightly higher than that reported in high-income settings such as a cross-sectional multicenter hospital clinic-based study in the UK that reported a prevalence rate of 28.5 [28]. We have previously reported on how the prevalence of retinopathy and nephropathy in our study population compared with other populations [17]. The biological

Table 3
Logistic regression models for the between measures of obesity (independent variable) and pulmonary dysfunction (dependent variable).

	Neuropathy ($N = 125$)			Nephropathy ($N = 87$)			Retinopathy ($N = 51$)		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
Hypertension	4.52 (2.84 – 7.21), <0.001	4.74 (2.91 – 7.74), <0.001	3.44 (1.96 – 6.04), <0.001	2.17 (1.31 – 3.58), 0.003	1.88 (1.11 – 3.19), 0.018	2.05 (1.09 – 3.85), 0.026	1.44 (0.74 – 2.80), 0.287	1.38 (0.69 – 2.75), 0.360	0.98 (0.42 – 2.31), 0.970
Suboptimal BP control	1.57 (0.96 – 2.58), 0.075	1.51 (0.90 – 2.51), 0.116	1.11 (0.61 – 2.04), 0.732	2.30 (1.22 – 4.32), 0.010	1.94 (1.01 – 3.72), 0.046	1.63 (0.77 – 3.47), 0.205	3.12 (1.23 – 7.94), 0.017	3.02 (1.16 – 7.88), 0.024	2.18 (0.72 – 6.61), 0.170
Z-score systolic BP	1.44 (1.16 – 1.79), 0.001	1.44 (1.14 – 1.81), 0.002	1.28 (0.98 – 1.67), 0.075	1.62 (1.26 – 2.07), <0.001	1.49 (1.15 – 1.94), 0.003	1.43 (1.05 – 1.97), 0.025	1.58 (1.13 – 2.21), 0.007	1.56 (1.10 – 2.22), 0.013	1.27 (0.84 – 1.91), 0.261
Z-score diastolic BP	0.97 (0.78 – 1.19), 0.749	0.97 (0.78 – 1.20), 0.770	0.86 (0.67 – 1.10), 0.230	1.65 (1.26 – 2.16), <0.001	1.69 (1.29 – 2.22), <0.001	1.81 (1.32 – 2.49), <0.001	1.45 (1.05 – 2.01), 0.025	1.47 (1.06 – 2.04), 0.022	1.38 (0.92 – 2.05), 0.120

Model 1 = unadjusted.
Model 2 = adjusted for age and sex.
Model 3 = Adjusted for age, sex, diabetes duration, smoking pack years, HbA1c concentration, total cholesterol concentration, and BMI.
Abbreviations: BMI = body mass index; BP = BP.

basis of increased susceptibility of the neural microcirculation to dysfunction, compared with other microcirculations, is not fully understood. Proposed explanations include enhanced hyperglycemia-induced oxidative stress in diabetic neurons [25] or the fact that some nondiabetic neuropathies may be misdiagnosed as diabetic neuropathy [6].

The current study shows that coexisting hypertension and/or suboptimal BP control is associated with an increased likelihood of microvascular dysfunction in individuals with T2D. Our findings agree with a limited study that assessed the impact of hypertension on diabetes-related complications based on questionnaires [29]. Kesavamoorthy *et al*. reported that the proportion of individuals reporting diabetes neuropathy and retinopathy was higher among individuals with diabetes and hypertension compared with those without hypertension [29]. Our findings and that of Kesavamoorthy et al. are supported by evidence that hypertension or elevated BP alone can cause derangements in the microvascular circulation [30–33]. Mechanistically, hypertension alters the mechanisms regulating vasomotor tone resulting in enhanced vasoconstriction or reduced vasodilator responses to various vasodilators [34]. In addition, the loss of myogenic tone and vascular hypertrophy in resistance vessels of hypertensive patients with T2D results in increased wall thickness to radius ratio, resulting in microcirculatory dysfunction [14]. Regardless of the above mechanistic model, some studies have not found hypertension to substantially enhance the risk of microvascular injury in T2D. For example in the Wisconsin Epidemiologic Study of Diabetic Retinopathy, a diagnosis of hypertension, systolic BP, and diastolic BP were not associated with the incidence and progression of retinopathy in individuals with T2D [35]. Our findings suggest that in individuals with T2D of West African ethnic origin, coexisting hypertension and/or suboptimal BP control are associated with an increased likelihood of microvascular injury. BP control in West Africans with T2D may thus have protective benefits including enhanced microvascular function.

A novel contribution of our study to the existing literature is our comparison of the differential effects of BP and control measures on different microcirculation. While prior studies have compared the differential effects of hypertension on different microcirculatory beds, none has done so in the setting of T2D. Our results show that measures of abnormal BP are more strongly associated with renal microvascular dysfunction than neural and retinal microvascular dysfunction. In the fully adjusted model, both increasing systolic BP and diastolic BP were independently associated with an increased likelihood of nephropathy, but not neuropathy or retinopathy. Our findings are consistent with previous observations that show that high-flow, low-impedance organs including the brain and kidney are particularly vulnerable to high BP pulsatility since the pulsatile load in these organs penetrates deeply into their microvascular beds [36]. T2D is independently associated with stiffness of the elastic proximal arteries including the aorta [37,38]. In the setting of aortic stiffness, there is a loss in the ability to dampen the pulsatility of ventricular ejection [36]. However, the distal muscular arteries may not stiffen. Therefore, there is a decrease in the difference or gradient of stiffness between the proximal elastic arteries and distal muscular arteries, resulting in a reduction in the backward reflection of pulsatile energy. The pulsatile energy that is not reflected backward may be transmitted toward the small arteries of target organs [36]. Because the renal microvasculature is more susceptible to high BP pulsatility compared with the neural and retinal microcirculation, measures of increasing BP are more likely to be associated with renal microvascular dysfunction, compared with neural and retinal microvascular dysfunction,

Like systolic and diastolic BP, a diagnosis of hypertension was independently associated with nephropathy. However, a diagnosis of hypertension was also independently associated with neuropathy. The strength of the association between hypertension diagnosis and neuropathy was more pronounced than that of nephropathy. For example, in a fully adjusted model, hypertension diagnosis was associated with 244% increased odds of neuropathy ($P < 0.001$) and 105% increased odds of nephropathy ($P = 0.026$); there was no significant association with retinopathy. Given the evidence of no effective treatment for diabetic neuropathy [6], interventions aimed at preventing hypertension in individuals with T2D may be valuable in reducing the risk of diabetic neuropathy. It remains unclear why a diagnosis of hypertension had different strengths of associations with microvascular dysfunction, compared with measures of BP. It may well be the case that hypertension per se is more strongly associated with neuropathy, but poor BP control more adversely affects high-flow, low-impedance organs including the kidney [36]. Future longitudinal studies may confirm or refute this claim.

Strengths and limitations

To the best of our knowledge, our study is the first to compare the impact of BP and its control on complementary measures of systemic microvascular dysfunction in individuals with T2D. The strengths of our study include an objective assessment of three complementary measures of microvascular dysfunction and the adjustments for a wide range of confounders. Our study has limitations. First, the cross-sectional design limits us from precluding reverse caus. Secondly, we did not assess microvascular dysfunctions of the coronary and cerebral microcirculation due to the current technical challenges associated with microvascular functional testing in these circulations. For example, coronary microcirculation is beyond the resolution of invasive or noninvasive coronary angiography [39].

Conclusions

The current study demonstrates differential strengths of associations of hypertension and increasing BP with dysfunction in the renal, neural, and retinal microcirculation in T2D. The positive associations of hypertension with neuropathy and nephropathy persisted after adjustment for a wide range of conventional risk factors. Increasing systolic and diastolic BP were independently associated with an increased likelihood of nephropathy but not neuropathy or retinopathy. Based on our findings, individuals with T2D may benefit from interventions aimed at hypertension prevention, to prevent the likelihood of developing neuropathy or nephropathy. In the setting of T2D, BP control aimed at reducing the likelihood of microvascular dysfunction may most benefit the kidneys. Our findings provide useful insights into the possible role of BP control in systemic microvascular dysfunction and provide opportunities for future research aimed at determining the mechanisms linking differential impacts of hypertension and/or BP control to microvascular dysfunction in different microcirculatory beds, as well as studies targeting strategies for microvascular dysfunction prevention and/or treatment.

Authorship contributions

All authors contributed substantially to this article and approved the submission. C.F.H-B and T.R.Q-P conceived the idea. C.F.H-B and P.V. performed the experiment. C.F.H-B, T.A-N., and K.A.O. were responsible for statistical analysis and data 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.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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