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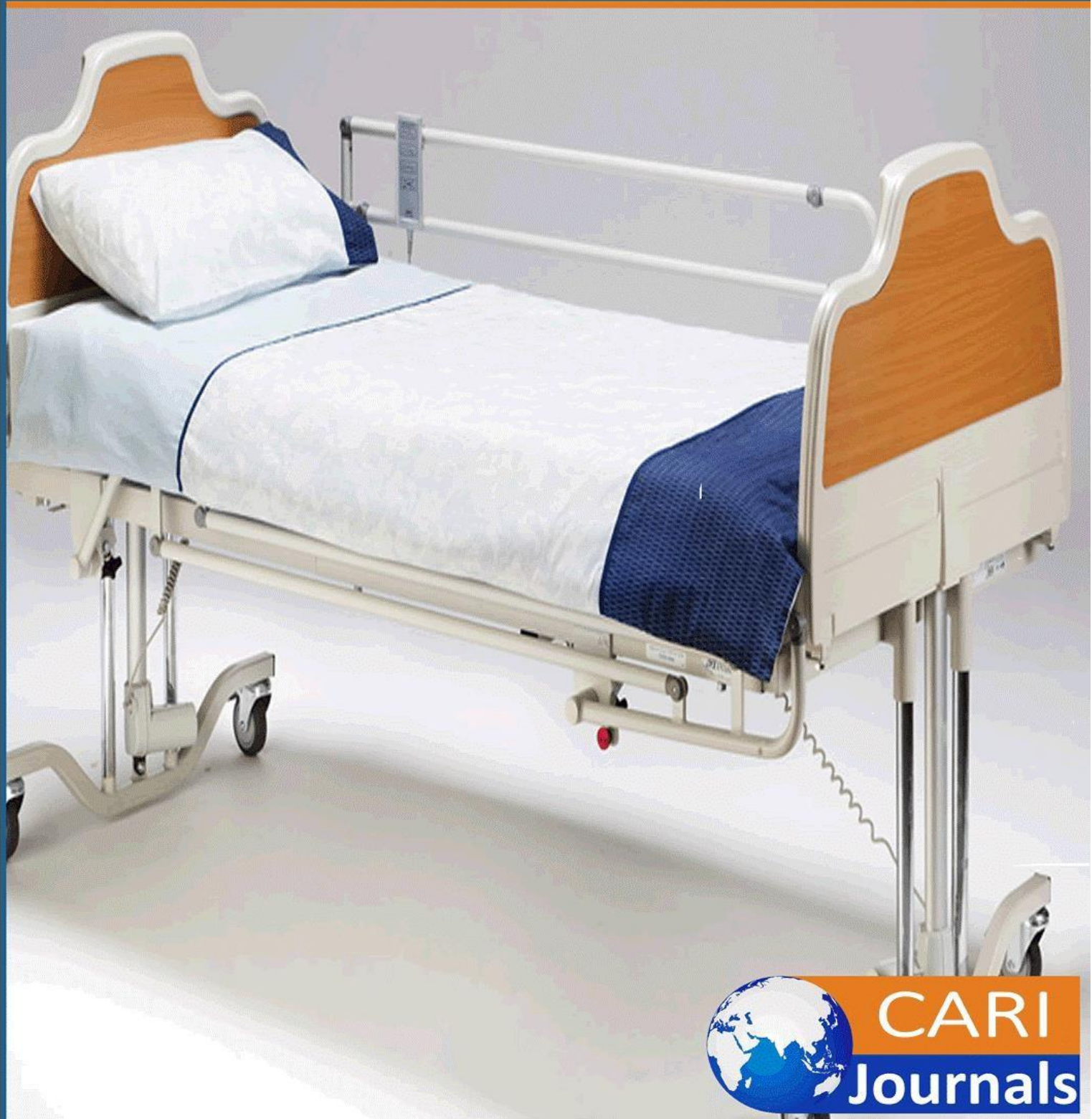

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APOL 1 Risk Genotype is associated with Albuminuria in Sub-Saharan African without Hypertension: A Case Study of Trypanosoma Brucei Gambiense Endemic Area

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Abstract

Purpose. An association between *APOL1* risk genotypes (HRG) and hypertension has been reported in African Americans with chronic kidney diseases (CKD). However, such data from African populations living in a Human African Trypanosomiasis (HAT) endemic area remain limited.This study assessed the association between *APOL1* high-risk genotypes (HRG) and hypertension among sub-Saharan African in T.b. *gambiense* endemic area.

Methodology. This cross-sectional study enrolled 94 HAT-infected and 144 non–infected participants in Masimanimba, the Democratic Republic of the Congo, from April 2019 to April 2021. We evaluated the association between *APOL1* HRG and hypertension in HAT-infected and non–infected participants. *APOL1* HRG was defined as the presence of two risk variants (G1/G1, G2/G2, or G1/G2), and a low-risk genotype (LRG) with the presence of 0 or 1 single variant. The elevated albuminuria was defined as urinary albumin/creatinine ratio ≥ 30 mg/g. Student's and Pearson's Chi^2 tests or Fisher's exact test were used to compare means and proportions. The Wilcoxon/Mann–Whitney test was used to compare medians. A multivariate logistic regression model was used to identify independent determinants of hypertension. Odds ratios were provided with their 95% confidence intervals (Cis). Statistical significance was set at $p < 0.05$, based on 2-tailed test.

Findings. *APOL1* sequence analysis revealed that 3 of 21 (14.3%) hypertensive participants carried *HRG* (G1G1) and 7 of 103 (6.8%) non-hypertensive carried HRG (G1G1, G2G2, and G1G2) (p=0.371). The frequency of *APOL1* HRG among hypertensive participants was 14.3% in both HAT- infected and uninfected individuals. Ten of 21 (47.6%) hypertensive individuals with elevated albuminuria had a higher incidence of CKD (100% vs. 0%; $p < 0.001$) and HRG (30% vs. 0%; $p = 0.09$) than 11 (52.3%) without albuminuria who carried LRG. Of 103 non-hypertensive subjects, 43 (41.7%) with elevated albuminuria had a higher frequency of HRG (16.3% vs. 0%; $p = 0.002$) and CKD (100% vs. 1.7%; $p<0.001$) compared with 60 of 103 (58.3%) without albuminuria who carried LRG.

Unique contributor to theory, policy and practice: *APOL1* HRG was associated with albuminuria and CKD, regardless of the hypertension status in T.b. *gambiense* HAT endemic area. However, further prospective cohort studies are required to confirm these results. The High-risk subjects will benefit from early preventive measures in low-income countries.

Keywords: *APOL1 - Hypertension Trypanosomiasis Endemic Area – Albuminuria*

Introduction

Hypertension is a leading risk factor for cardiovascular disease, and three-quarters of deaths associated with this disease occur in low-and middle-income countries (1). Data from studies conducted among African Americans of West African descent report that *APOL1* high-risk genotypes (HRG) are associated with hypertension, a high rate of mortality and cardiovascular and renal complications (2-4). These case-control studies indicate that *APOL1* renal risk alleles G1 (rs73885319 - S342G, rs60910145 - I384M) and G2 (rs71785313 - D 388:389 NY) on chromosome 22 which conferred protection against Human African Trypanosomiasis (HAT) in sub-Saharan populations, especially the *Trypanosoma brucei rhodesiense*, increase the propensity for hypertension attributed to kidney diseases in their new environment in the United States of America (5,6). Hence the interest in verifying this hypothesis in sub-Saharan Africa, their region of origin, where the HAT is prevalent in order to clarify this relationship between *APOL1* HRG and hypertension knowing that these *APOL1* risk variants do not protect against T.b. *gambiense*, but they are associated with non-diabetic chronic kidney diseases (CKD) (5,7,8). This study assessed the association between *APOL1* HRG and hypertension among sub-Saharan populations in rural areas endemic to T.b *gambiense*.

Methods

Study Design and sampling

This cross-sectional study was conducted in the HAT endemic region of Masimanimba, Democratic Republic of the Congo from April 2019 to April 2021. The inhabitants of Masimanimba belong to the Bantu ethnicity. The criteria for participant selection in this study included individual ≥ 15 years, who have lived in Masimanimba and Mosango Health Zones for more than a year. All participants shared their consent to participate. Individuals currently pregnant were excluded from the study.

Clinical and paraclinical assessment

Trained investigators collected sociodemographic data (age, sex, and ethnicity), lifestyle information (consumption of vegetables and fruits, current or past habit of smoking, and alcohol consumption), and personal and family histories of chronic diseases (including hypertension and diabetes). Anthropometric and physical measurements (height, weight, waist circumference, body mass index [BMI], blood pressure, and heart rate) were obtained. The Blood pressure was measured using an automated sphygmomanometer (Omron M2 Basic (HEM-7120-E), Kyoto, Japan) with an appropriately sized cuff secured to the left or right arm in a seated position, after at least 5 min of rest. The average of three measurements, repeated 1 min apart, was used for the final analysis. The Pulse pressure (PP) was defined as the difference between systolic blood pressure (SBP) and diastolic blood pressure (DBP). Hypertension was defined as systolic blood pressure (SBP) ≥ 140 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg and/or the use of antihypertensive drug treatment (9), while prehypertension was defined as SBP between 120-139

mmHg and DBP 80-89 mmHg (10). Left ventricular hypertrophy (LVH) confirmed by the electrocardiogram was defined using the Kolmogorov-Lyon criterion (SV1+ RV5 >35 mm) (11).

The Height (cm) was measured with the participants in a standing position without shoes, and their body weight was measured using a digital weight-management scale (EKS, Germany). BMI was calculated as the weight of the person in kilograms divided by the square of the height in meters (Kg/m^2). The BMI over the 25–29.9 range is considered overweight, and > 30 kg/m^2 is obesity (12). A tape measure was used to measure the waist circumference at the top of the hip bone. Central obesity was defined as a waist circumference > 94 cm for men and > 80 cm for women (12). The High cardiometabolic risk was defined as a waist-to-height ratio of > 0.5 (13).

HAT was diagnosed using the card agglutination test for trypanosomiasis (CATT) and a parasitological test [mini-anion exchange column (mAECT)]. Participants with HAT included those with either serological or parasitological positive tests, or a CATT plasma dilution ≥ 1/8, parasitology negative. HAT- uninfected had negative or positive CATT plasma dilutions of < 1/8.

Serum creatinine, glucose, total cholesterol, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol, uric acid, C-reactive protein (CRP), and triglycerides were measured with a Cobas c 111 analyzer using a colorimetric enzymatic method at the National Institute for Biomedical Research. We estimated the glomerular filtration rate (eGFR) using the modification of diet in renal disease (MDRD) formula. The urinary albumin-to-creatinine ratio (U-ACR) was evaluated using freshly voided morning urine samples. CKD was an eGFR < 60 mL/min/1.73 m^2 and/or a persistent (>3months) urinary albumin/creatinine ratio ≥30 mg/g (14). Diabetes mellitus was defined as fasting serum glucose ≥126 mg/dl or the use of antidiabetic medications (12). Dyslipidemia was defined as total cholesterol levels >190 mg/dl, triglycerides > 150 mg/dl, or HDL cholesterol value < 40 mg/dl in males and < 50 mg/dl in females (15). Based on International Diabetes Federation (IDF), American Heart Association and the National Heart, Lung, and Blood Institute (AHA/ NHLBI) (2009), the metabolic syndrome was defined when any three of the following five were present: (1) waist circumference of > 94 cm for males and >80 cm for females; (2) SBP > 130 mm Hg and/or DBP > 85 mm Hg or antihypertensive drug treatment; (3) triglycerides ≥ 150 mg g/dl; (4) HDL cholesterol < 40 mg/dl for males and < 50 mg/dl for female; and (5) fasting serum glucose ≥ 100 mg/dl or the use of antidiabetic medications (12). C-reactive protein levels > 6 mg/L are considered inflammatory markers (16), whereas anemia is defined as hematocrit < 37% in women and < 40% in men (17). Hyperuricemia was defined as a uric acid level > 6 mg/dl or 360 µmol/L (18).

Assessment of APOL1 Renal Risk Alleles

DNA was extracted from whole blood samples at the Genetics Laboratory of the National Institute for Biomedical Research (INRB) using the Maxwell method, following the manufacturer's instructions. The extracted DNA was transferred to the Laboratory of Development and Regeneration at Katholieke University, Leuven (Belgium) for storage and genotyping. *APOL1* genotyping was performed for two renal risk alleles: G1 (coding variants rs73885319A>G [p.Ser342Gly] and rs60910145G>T [p.Ile384Met]) and G2 (6-bp deletion, rs71785313). Exon 7

(883 bp) of *APOL1* was amplified using gene-specific primer pairs (Fw50-GTCACTGAGCCAATCTCAGC-30 and Rv50-CATATCTCTCCTGGTGGCTG-30). Polymerase chain reaction experiments were performed on genomic DNA using GoTaq Green DNA Polymerase (Promega Corporation, Fitchburg, Wisconsin) and consisted of 35 cycles with at an annealing temperature of 55 ^{o}C. Alkaline phosphatase and exonuclease exoSAP IT (Affymetrix, Santa Clara, CA, USA) were used for polymerase chain reaction purification. Sanger sequencing was performed with an ABI 3100XL High-Throughput DNA Sequencer (Applied Biosystems, Foster City, CA, USA). *APOL1* HRG was defined as the presence of two risk alleles (G1/G1, G2/G2, or G1/G2), and low-risk genotype (LRG) was defined as the presence of zero or one risk allele.

Statistical analysis

Data analysis was performed using the SPSS software (SPSS Inc. Chicago, IL, USA, 2013) for Windows software version 21.

Student's and Pearson's Chi2 test or Fisher's exact tests were used to compare the means and proportions, where appropriate. The Wilcoxon/Mann-Whitney test was used to compare the median. A multivariate logistic regression model was used to identify the independent determinants of hypertension. Odds ratios were provided with 95% confidence intervals (Cis). The statistical significance was set at P value < 0.05 based on a 2-tailed test. A chi-square test was used to test the deviation from Hardy-Weinberg equilibrium.

Results

General Characteristics of the study population

As shown in table 1, the prevalence of hypertension in the study population was 12.6 %. It was similar in HAT- infected and non - infected individuals (17% vs. 9.7%, p = 0.112) and in males (14.4%) and females (11.5%) (p = 0.112). The hypertensive participants were ten years older than the non - hypertensive ones (48.2 vs. 38.4 years; p=0.003).

Table 1: General Characteristics of the study population

Characteristics	All n=238	Hypertensives participants n=30 (12.6)	Non-Hypertensive participants n=208(87.4)	p-value
Age (years)	39.7 ± 17.1	48.2 ± 16.9	38.4 ± 16.9	**0.003**
Sex				0.548
Male	90(37.8)	13(14.4)	77(85.6)	
Female	148(62.2)	17(11.5)	131(88.5)	
HAT Status				0.112
Infected	94(39.5)	16(17)	78(83)	
Non-Infected	144(60.5)	14(9.7)	130(90.3)	

Data are expressed as mean ± SD or absolute (n) and relative (%) frequency. HAT: Human African Trypanosomiasis.

Distribution of Cardiovascular risk factors and *APOL1* risk genotypes by hypertension status

The distribution of cardiovascular risk factors (CVRF) in hypertensive and non - hypertensive participants is shown in table 2. The most common cardiovascular risk factors (CVRF) were low fruit consumption (97%), dyslipidemia (80.2%), alcohol intake (74.7%), low vegetable consumption (46.6%), CKD (43.6%), and smoking (36.9%). Participants with hypertension had a higher frequency of abdominal obesity (30% vs. 9.1%, p=0.003), metabolic syndrome (MS) (16.7% vs. 0.5%, p<0.001), overweight obesity (10% vs. 1.9%, p = 0.045), and electrical LVH (23.3% vs. 7.7%, p = 0.014). The other variables did not differ between the two groups.

APOL1 sequence analysis showed that 3 of 21 (14.3%) participants with hypertension and 7 of 103 (6.8%) without hypertension carried an HRG; the difference between the two groups was not significant (p = 0,371). Hypertensive individuals carried only G1G1, whereas non hypertensive individuals carried G1G1, G2G2, and G1G2. 43% Participants of in both groups carried at least one *APOL1* allele. The frequency of the G1 allele (26.2%) was higher in hypertensive participants compared with non-hypertensive (14.6%) (p = 0.071), while the G2 allele tended to be high in non-hypertensive participants (10.2% vs. 2.4%, p = 0.139).

Table 2: Distribution of Cardiovascular risk factors and *APOL1* risk genotypes by hypertension status

Cardiovascular risk factors	**All n=238**	**Hypertensives participants n=30 (12.6)**	**Non-Hypertensive participants n=208(87.4)**	**p-value**
Low fruits consumption	231(97)	30(100)	201(95,6)	0.600
Dyslipidemia	191(80.2)	24(80)	167(80.3)	1.000
Alcohol intake	178(74,7)	25(83,3)	153(73,6)	0.368
Low vegetable consumption	111(46.6)	11(36.7)	100(48.1)	0.328
Chronic kidney Disease	104(43.6)	14(46.7)	90(43.3)	0.844
Tachycardia	102(42.8)	14(46.7)	88(42.3)	0.696
smoking	88(36.9)	11(36.7)	77(37)	0570
Microalbuminuria	79(33.1)	6(20)	73(35.1)	0.145
High cardiometabolic risk (WHR>0.5)	60(25.2)	11(36.7)	49(23.6)	0.175
Hyperuricemia	39(16.3)	3(10)	36(17.3)	0.432
abdominal obesity	28(11.7)	9(30)	19(9.1)	**0.003**
Electrocardiogram LVH	23(9.7)	7(23.3)	16(7.7)	**0.014**
Diabetes mellitus	9(3.7)	2(6.7)	7(3.4)	0.317
Overweight-obesity	7(2.9)	3(10)	4(1.9)	**0.045**
Metabolic syndrome	6(2.5)	5(16.7)	1(0.5)	**<0.001**
***APOL1* variants**	**All n=124**	**Hypertensives participants (n=21)**	**Non- Hypertensives participants (n=103)**	**p-value**
At least one allele risk	53 (42.7)	9(42.9)	44(42.7)	1.000
High -risk genotypes	10 (8.1)	3(14.3)	7(6.8)	0.371
G1/G1	5 (4)	3(14.3)	2(1.9)	
G2/G2	2 (1.6)	0(0)	2(1.9)	
G1/G2	3 (2.4)	0(0)	3(2,9)	
Low-risk genotypes	114 (91.9)	18(85.7)	96(93.2)	0.371
G1/G0	28 (22.6)	5(23.8)	23(22.3)	
G2/G0	15 (12.1)	1(4.8)	14(13.6)	
G0/G0	71 (57.3)	12(57.1)	59(57.3)	
****Alleles**				
G1	41(16.5%)	11(26.2%)	30(14,6%)	0.071
G2	22 (8.8%)	1(2.4%)	21(10.2%)	0.139

Data were expressed as absolute (n) or relative (%) frequencies. * All the chromosomes were considered.

Cardiovascular risk factors in the study population by HAT status.

The distribution of cardiovascular risk factors according to the HAT infection status is shown in table 3 for participants with and without hypertension. HAT- uninfected participants were older than HAT- infected participants with hypertension (53.8 vs. 43.2 yrs, p = 0.088) and those without hypertension (40.6 vs. 34.9 yrs, p = 0.018). All HAT-infected patients with hypertension had dyslipidemia (p = 0.005). The frequency of *APOL1* HRG was similar in HAT- infected and non - infected patients with hypertension (14.3%). Among the participants without hypertension, men appeared to be more susceptible to HAT infection than women (p = 0.008). Dyslipidemia (89.7% vs. 74.6%, p = 0.011) and anemia (48.7% vs. 28.5%, p = 0.004) were predominant in the HAT-infected individuals. The trend towards a higher HRG frequency in HAT- infected patients was not significant (10.5 vs. 2.2%, p = 0.127).

Table 3: Cardiovascular risk factors in the study population by HAT status

Cardiovascular risk factors	All n=238	Hypertensives Participants n=30			Non-Hypertensives Participants n=208		
		HAT+ 16(53.3)	HAT- 14(46.7)	p-value	HAT+ 78(37.5)	HAT- 130(62.5)	p- value
Age (Yrs)	39.7 ± 17.1	43.2±16.7	53.8±15.9	0.088	34.9±16.5	40.6±16.6	**0.018**
Sex							
Male	90(37.8)	6(37.5)	7(50)	0.713	38(48.7)	39(30)	**0.008**
Female	148(62.2)	10(62.5)	7(50)	0.374	40(51.3)	91(70)	
smoking	88(36.9)	3(18.8)	8(57.1)	0.057	21(26.9)	56(43.1)	**0.026**
Alcohol intake	178(74.7)	15(93.8)	10(71.4)	0.126	59(75.6)	94(72.3)	0.360
Low fruits consumption	231(97)	16(100)	14(100)	0.157	77(98.7)	124(95.4)	0.189
Low vegetable consumption	111(46.6)	3(18.8)	8(57.1)	0.057	35(44.9)	65(50)	0.283
Diabetes	9(3.7)	2(12.5)	0(0)	0.276	5(6.4)	2(1.5)	0.071
Dyslipidemia	191(80.2)	16(100)	8(57.1)	**0.005**	70(89.7)	97(74.6)	**0.011**
Metabolic syndrome	6(2.5)	3(18.8)	2(14.3)	0.567	1(1.3)	0(0)	0.375
Hyperuricemia	39(16,3)	1(6,2)	2(14,3)	0,448	15(19,2)	21(16,2)	0.349
Overweight-Obesity	7(2,9)	0(0)	3(21,4)	0,090	1(1,3)	3(2,3)	0.518
Abdominal Obesity	28(11,7)	5(31,2)	4(28,6)	0,596	5(6,4)	14(10,8)	0.332
Electrocardiogram LVH	23(9,7%)	2(12,5)	5(35,7)	0,143	8(10,3)	8(6,2)	0.208
Anemia	88(36,9)	8(50)	5(35,7)	0,339	38(48,7)	37(28,5)	**0.004**
Inflammation	56(23.5)	6(37.5)	1(7.1)	0.061	18(23.1)	31(23.8)	0.520
Microalbuminuria	79(33.1)	2(12.5)	4(28.6)	0.261	31(39.7)	42(32.3)	0.296
Tachycardia	102(42.8)	7(43.8)	7(50)	0.509	31(39.7)	57(43.8)	0.664
Chronic Kidney disease	104(43.6)	7(43.8)	7(50)	0.509	36(46.2)	54(41.5)	0.564
***APOL1* risk variants**	**N=124**	**n=14 (66.7)**	**n=7 (33.3)**		**n=57 (55.3)**	**n=46 (44.7)**	
High-risk genotypes	10 (8.1)	2(14.3)	1(14.3)	1.000	6(10.5)	1(2.2)	0.127
G1/G1	5 (4)	2(14.3)	1(14.3)		2(3.5)	0(0)	
G2/G2	2 (1.6)	0(0)	0(0)		2(3.5)	0(0)	
G1/G2	3 (2.4)	0(0)	0(0)		2(3.5)	1(2.2)	
0 risk allele	71 (57,3)	8(57.1)	4(57.1)	1.000	33(57.9)	26(56.5)	0.451
G0/G0	71 (57.3)	8(57.1)	4(57.1)		33(57.9)	26(56.5)	
1 risk allele	43 (34.7)	4(28.6)	2(28.6)	0.726	18(31.6)	19(41.3)	0.409
G1/G0	28 (22.6)	4(28.6)	1(14.3)		10(17.5)	13(28.3)	
G2/G0	15 (12.1)	0(0)	1(14.3)		8(14)	6(13)	

Data are expressed as mean ± SD or absolute (n) and relative (%) frequency. LVH, left ventricular hypertrophy

HAT+ = infected participants HAT- = non-infected participants

Participant characteristics by level of microalbuminuria

Table 4 indicates that hypertensive participants with microalbuminuria were older than those without it (51.3 vs. 44.2 yrs, p = 0.377), as well as among non - hypertensives (43 vs. 31.8 yrs, p< 0.001). Hypertensive individuals with microalbuminuria had a higher mean blood pressure (SBP,

DBP, MAP, and PP) than those without microalbuminuria; however, the difference was not significant. Moreover, they had a higher frequency of HRG (30% vs. 0%, p = 0.09) and CKD (100% vs. 0%, p<0.001). Among non- hypertensive participants, those with microalbuminuria had higher WHR (0.47 vs. 0.45, p = 0.040), a frequency of at least one *APOL1* risk allele (60.5% vs. 30%; p = 0.003), HRG (16.3% vs. 0%; p = 0.002) and CKD (100% vs. 1.7%; p < 0.001) than those without microalbuminuria with LRG (100% vs. 83.7%; p = 0.002).

Table 4: characteristics of study population by level of microalbuminuria status

Variables	All n=124	Hypertensive Participants n=21(16.9)			Non-Hypertensive Participants n=103(83.1)		
		U-ACR ≥30mg/g N=10(47.6)	U-ACR <30mg/g N=11(52.4)	p	U-ACR ≥30mg/g N=43(41.7)	U-ACR <30mg/g N=60(85.3)	p
Age (Yrs)	38.3±17	51.3±18.3	44.2±17.3	0.377	43±16.3	31.8±14.7	**<0.001**
Gender				0.425			0.204
Male	51(41.1)	5(50)	7(63.6)		28(65.1)	33(55)	
Female	73(58.9)	5(50)	4(36.4)		15(34.9)	27(45)	
SBP (mm Hg)	119.5±19.9	154.2±38,9	141.7±9.1	0.314	113±13.2	114.3±10.1	0.566
DBP (mm Hg)	74.1±14	96.4±19.07	90.3±7.6	0.345	69±11.1	71.1±97	0.302
MAP ((mm Hg)	89.2±15.5	115.6±25.1	107.5±5.8	0.313	82.9±10.9	85.6±9.2	0.187
PP ((mm Hg)	45.4±11.2	57.6±23.6	51.4±12.2	0.458	44±9.1	43.3±7.4	0.645
ABI anormal	1.1±0.3	1.10±0.31	1.00±0.00	0.306	1.17±0.37	1.20±0.40	0.686
WC (cm)	72.9±6.7	78.4±10.3	76.3±7.9	0.616	73.1±5.1	71.3±6.3	0.136
BMI (Kg/m^2)	19±2.7	20.7±3.4	20.6±3.0	0.965	19.1±1.9	18.4±2.8	0.197
High cardiometabolic risk (WHR≥0.5)	0.41±0.22	0.47±0.06	0.47±0.05	0.931	0.47±0.03	0.45±0.04	**0.040**
HR (bpm)	79.1±14.6	82.6±18.3	76.9±17.9	0.481	77±13.7	80.5±14.1	0.218
Fasting serum glucose (mg/dl)	78[55-93]	51.5[14-81]	80[59-99]	0.063	80[48-99]	78.5 [58.3-92.5]	0.293
*Total Cholesterol(mg/dl)	69[50-94.7]	62[47.5-85]	50[41-96]	0.726	70[55-98]	71[49.5-94.7]	0.859
*HDL-c (mg/dl)	25[17-34]	28.5 [13,3-34.7]	24[13-35]	0.807	26[18-38]	26[14,2-33]	0.161
*LDL-c (mg/dl)	38[22,2-55,7]	36.5 [21-56,5]	33[16-56]	0.733	41[27-55]	38[20-56]	0.557
*Triglycerides (mg/dl)	41[31.2-53.5]	41[38.5-48.2]	35[26-48]	0.990	36[29-56]	44[32.2-52]	0.887
*uric acid (mg/dl)	6.1±3.1	6.3±1.5	5.5±1.8	0.260	6.6±3.6	5.9±3.2	0.390
CRP (g/L)	3[1-9.7]	3.5[1.7-14.5]	3[2-22]	0.943	2[1-6]	3[1-10]	0.453
Hematocrit (%)	39.2±6.4	38.6±7.4	40.3±48	0.543	39.5±4.7	38.9±7.7	0.641
eGFR, mL/min/ 1.73 m^2	99[74,2-129.2]	88.5 [60,7-115]	106[84-171]	0.066	83[67-100]	109.5 [90.2-150.7]	**<0.001**
CKD (n, %)	54(43.5)	10(100)	0(0.0)	**<0.001**	43(100)	1(1.7)	**<0.001**
***APOL1* risk variants**							
At least one *APOL1* allele	53 (42.7)	6(60)	3(27.3)	0.198	26(60.5)	18(30)	**0.003**
High-risk genotypes	10 (8.1)	3(30)	0(0.0)	0.090	7(16.3)	0(0.0)	**0.002**
G1/G1	5 (4)	3(30)	0(0.0)		2(4.7)	0(0.0)	
G2/G2	2 (1.6)	0(0.0)	0(0.0)		2(4.7)	0(0.0)	
G1/G2	3 (2.4)	0(0.0)	0(0.0)		3(7)	0(0.0)	
Low -risk genotypes	114 (91.9)	7(70)	11(100)	0.090	36(83.7)	60(100)	**0.002**
G1/G0	28 (22.6)	3(30)	2(18.2)		13(30.2)	10(16.7)	
G2/G0	15 (12.1)	0(0.0)	1(9.1)		6(14)	8(13.3)	
G0/G0	71 (57.3)	4(40)	8(72.7)		17(39.5)	42(70)	

* Analysis of serum SBP= systolic blood pressure; DBP= diastolic blood pressure; MAP= mean arterial pressure; PP= pulse pressure; ABI= ankle-brachial index; WHR= waist height ratio; WC= waist circumference; BMI= body mass index; HR= heart rate; CRP= C-reactive protein;

U-ACR= urinary albumin to creatinine ratio; eGFR= estimated glomerular filtration rate; HRG=high-risk genotypes; LRH=low-risk genotype.

Determinants of Hypertension

As reported in table 5, the univariate analysis showed that HAT- infected status [OR 3.4 (1.1-10.5), p = 0.029], age ≥ 38 years [3.2 (1.3-7.5), p = 0.004], overweight-obesity [5.6 (1.2-26.6), p = 0.045], abdominal obesity [5.6 (1.7-10.6), p = 0.003] were associated with hypertension in these participants. Indeed, there was a 6-fold increased odds of hypertension respectively for individuals with abdominal obesity and overweight-obesity. Likewise, this risk was 3 times higher for HAT-infected individuals and the advanced age. However, diabetes (p = 0.317), smoking (p = 0.570), dyslipidemia (p = 0.568) and CKD (p = 0.437), which are strong cardiovascular risk factors, were not associated with hypertension. The multivariate logistic regression analysis revealed that age ≥ 38 years was the primary independent factor associated with hypertension. Age ≥ 38 years was associated with a five-fold increased susceptibility to hypertension [ORa 4.9 (1.3-18.6), p = 0.018].

Tableau 5. Determinants of Hypertension in the study population

Variables	Univariate Analysis		Multivariate Analysis	
	P value	OR (CI 95%)	P value	ORa (CI 95%)
HAT status				
Non-infected		1		1
Infected	**0,029**	3.4 (1.1 – 10.5)	0.073	1.9 (0.8-4.1)
Sex				
Female				
Male	0.318	1.3 (0.5 – 2.8)	0.083	0.3 (0.09-1.1)
Age (yrs)				
<38		1		1
≥38	**0.004**	**3.2 (1.3-7.5)**	**0.018**	**4.9 (1.3-18.6)**
Smoking				
No		1		1
Yes	0.570	0.9 (0.4-2.1)	0.666	1.2 (0.4-3.6)
Diabetes mellitus				
No		1		1
Yes	0.317	2.0 (0.4-10.3)	0.449	2.4 (0.2-24.3)
Overweight-obesity				
No		1		1
Yes	**0.045**	**5.6 (1.2-26.6)**	0.915	1.1 (0.07-18,1)
Abdominal obesity				
Non		1		1
Oui	**0.003**	**4.2 (1.7-10.6)**	0.060	4.8 (0.9-24.7)
Dyslipidemia				
No		1		1
Yes	0.568	0.9 (0.3-2.5)	0,839	0.8 (0.2-3.4)
Microalbuminuria				
Non		1		1
Oui	0.072	0.4 (0.1-1.1)	0.145	0.1 (0.8-4.6)
Chronic Kidney Disease				
Non		1		1
Oui	0.437	1.1 (0.5-2.4)	0.354	2.0 (0.4-9.3)
APOL1 risk Genotypes				
Low (0,1)		1		1
High (2)	0.118	3.1 (0.7-13.0)	0.468	0.3 (0.03-4.8)

Discussion

This study assessed the association between *APOL1* HRG and hypertension in a rural Congolese population endemic for *T.b. gambiense* HAT. The prevalence of hypertension was similar among HAT-infected and non-infected participants. Regardless of the hypertension status, carrying *APOL1* HRG was associated with microalbuminuria and an increased CKD frequency. Age ≥ 38 years was the only independent factor associated with hypertension.

Prevalence of hypertension and cardiovascular risk factors

In this study, the prevalence of hypertension (12.6%) was similar between males and females. This observation is in line with that reported by Longo et *al* in a rural area of Kinshasa (DRC) (19). However, some previous studies conducted in several provinces of the DRC using various methodological approaches (20,21) have described a predominance among females, whereas data from the literature show that women are not exposed to cardiovascular diseases before 65 years of age (22). In sub-Saharan Africa, other authors found higher cardiovascular mortality among women, which could result from sociocultural inequalities imposed by African traditions, of which most women are victims (23,24). This rate of 12.6% was lower than that the one observed in other rural and semi-urban areas of the DRC (25%-41%). This can be explained by the fact that the rural region of Masimanimba is almost landlocked, and its lifestyle is limited to agricultural activities, which, on the one hand, reduces the risk of a sedentary lifestyle; and on the other hand, the population is less exposed to manufactured foods with high amounts of sodium, sugar, and fat due to the lack of food-processing industries.

The results of this study indicated a higher prevalence of MS, overweight-obesity, abdominal obesity, and electrical LVH in participants with hypertension. Our findings are in accordance with surveys conducted in the general population of the DRC and elsewhere in the world (21,25-27). The inhabitants of the Masimanimba region use tobacco and palm wine as essential stimulants for agricultural hard work, which is unfortunately associated with an insufficient and unbalanced diet and a low consumption of fruits and vegetables. Previous reports have demonstrated that a low consumption of fruits and vegetables leads to the onset of insulin resistance, type 2 diabetes mellitus and MS. (28,29). Smoking contributes to high blood pressure, through oxidative stress (30). Several studies have established that visceral adiposity is associated with insulin resistance and stimulation of the sympathic system and renin-angiotensin, with the onset of diabetes and hypertension (26,27). An oxidative stress leading to chronic inflammation, atherogenic dyslipidemia, and endothelial dysfunction impairs intracellular signaling pathways, leading to insulin resistance (31). Thus, any factor that induces insulin resistance, inflammation, or oxidative stress may increase the cardiometabolic risk (32).

The high prevalence of dyslipidemia and anemia observed in HAT-infected participants with and without hypertension is consistent with previous reports (33,34). In this regard, changes in lipid and lipoprotein profiles induced by HAT infection have already been documented. Some studies have reported that HAT- infected individuals have hypertriglyceridemia, High LDL-c, and low HDL-c levels (33). However, other authors have observed hypertriglyceridemia and reduced plasma phospholipid and sphingolipid levels (34). Anemia can be deficient or inflammatory because HAT is a chronic infectious disease, similar to CKD.

Clinical and paraclinical characteristics

The prevalence of hypertension was similar between HAT- infected and uninfected participants. The two groups had almost the same frequency of *APOL1* HRG, which may explain this similarity, given that neither variant confers any protection against *T.b. gambiense* species (5). Data from this study indicated that non hypertensive participants with microalbuminuria exhibited a higher

frequency of HRG and CKD. This suggests that *APOL1* HRG is associated with microalbuminuria or CKD, and hypertension is secondary to CKD. Previous surveys in sub-Saharan Africa have established that the G1G1 genotype reduces susceptibility to the *T.b. gambiense* infection, whereas G2G2 is associated with a faster progression of the *T. b. gambiense* disease. In both cases, they may expose to CKD (8). Previous studies have shown that the HRG is associated with higher SBP, earlier hypertension in young African Americans, microalbuminuria, and CKD, knowing that genotype–related subclinical nephropathy can also manifest as increased blood pressure (4,35-38). We observed low levels of LDL-c, HDL-c, and triglycerides in participants with and without hypertension carrying the HRG, whereas previous studies found hypertriglyceridemia and low HDL-c levels to be independent determinants of *APOL1* serum levels in non-diabetic individuals (39). Ito et *al*. established that the G2G2 genotype, a deletion of two amino acids, is associated with low total cholesterol and HDL-c levels, inducing divergent molecular processes (36).

Determinants of hypertension

The multivariate logistic regression analysis revealed that only age ≥3 8 years emerged as the main independent factor associated with hypertension. People ≥ 38 years of age had 5-fold increased odds to have hypertension. *APOL1* HRG was not associated with hypertension. Surveys conducted in the general population of the DRC showed that age ≥ 45 years, male sex, overweight/obesity, and diabetes are independent determinants of hypertension (21,22,25). Some studies have suggested that *APOL1* may have a protective or neutral effect in the presence of CKD, as in diabetes. However, almost all participants had CKD (46.7%). This is a strong cardiovascular risk factor that obscures the effects of *APOL1* (40,41).

This study has some limitations, including its cross-sectional design and relatively small sample size, which would have weakened the power of our observations and converted the numerical data into averages. However, this is the merit of being a first study to address the association between *APOL1* HRG and hypertension in a rural Central African environment endemic to T.b. *gambiense* HAT. Further studies involving larger numbers of participants recruited from several T.b. *gambiense* foci are required to confirm these results.

Conclusion

Hypertension is more prevalent in populations living in areas endemic to *T.b. gambiense*. The prevalence was similar between HAT- infected and non-infected participants with the same HRG share. *APOL1* HRG is associated with microalbuminuria and CKD without hypertension in a T.b. *gambiense* endemic area. Age ≥38 years emerged as the only independent factor of Hypertension. However, further prospective cohort studies are required to confirm these results. The High-risk subjects will benefit from early preventive measures in low-income countries.

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