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Research Article

Aldosterone and aldosterone: renin ratio associations with insulin resistance and blood pressure in African Americans

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Abstract

African Americans have more hypertension and hypertension-related morbidity than whites. Aldosterone, in presence of a high salt intake, contributes to hypertension and tissue injury. Inappropriately elevated aldosterone levels could explain this racial disparity. Our study was conducted to determine if aldosterone is associated with elevated blood pressure (BP) or insulin resistance, independent of obesity. A study was conducted on 483 young adult African Americans without cardiovascular or renal disease. Measurements included anthropometrics, BP, lipids, glucose, insulin, aldosterone, and renin. Urine sodium and potassium estimated sodium intake. The cohort was stratified by tertiles of aldosterone and tertiles of aldosterone/renin ratio (ARR). Average urine sodium/potassium ratio was >3.0 in all groups. Insulin resistance, estimated by homeostasis model, was lowest in the low aldosterone group (geometric mean 1.5 [0.6, 2.2]) compared with the high aldosterone group (1.7 [0.9, 2.7], $P < .01$). Adjusted analyses detected a significant association of aldosterone with insulin resistance, independent of other variables. BP was significantly higher in the high ARR group compared with low and mid ARR groups ($P < .01$). The significant association of ARR with BP with high dietary sodium suggests that insufficiently suppressed aldosterone may contribute to BP sensitivity to sodium in African Americans. J Am Soc Hypertens 2012;6(1):56–65.

Keywords: Aldosterone; renin; insulin resistance; blood pressure; African Americans.

Introduction

Among African Americans, hypertension is more prevalent,[1] develops at a younger age, and is associated with greater hypertension-related morbidity compared with whites.[2] In African Americans, as well as other race/ethnic groups, hypertension is commonly associated with insulin resistance[3,4] and heightened expression of metabolic risk factors[5]; these conditions together increase risk for cardiovascular disease and poor outcomes.

The renin-angiotensin-aldosterone system has a well-established role in blood pressure (BP) regulation and in hypertension. Hyperaldosteronism is a recognized cause of secondary hypertension, mediated, at least in part, by its promotion of sodium retention.[6] In a community-based prospective study, however, Vasan et al[7] found that relatively high levels of plasma aldosterone, although not sufficiently elevated to diagnose hyperaldosteronism, were associated with increased BP and incident hypertension, raising the possibility that modest elevations in circulating aldosterone could play a causal role in the hypertension of African Americans.

Previous studies demonstrated a consistent positive association of body mass index (BMI) and visceral obesity with plasma aldosterone levels,[8,9] suggesting that obesity could

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mediate modest elevations in aldosterone. Emerging reports indicate that aldosterone may play an important role in insulin resistance[10,11] and the metabolic syndrome,[12] suggesting that aldosterone may contribute to the hypertension associated with obesity and the metabolic syndrome.

In addition to the effects of aldosterone on renal sodium reabsorption, experimental studies indicate that aldosterone plays a pathogenic role in cardiovascular inflammation and fibrosis.[13] Clinical trial results demonstrate benefits of aldosterone antagonists on heart failure[14,15] and cardiac hypertrophy.[16]

These reports raise the possibility that aldosterone could also contribute to the excess prevalence and morbidity of hypertension in African Americans, especially obesity-associated hypertension. We conducted a study on a cohort of young adult African Americans, without cardiovascular or renal disease, to determine if aldosterone is associated with insulin resistance, obesity, and/or BP.

Methods

Study Population

Healthy young adult African Americans were recruited in urban Philadelphia through local advertisements between 2006 and 2009. Criteria for enrollment included African Americans between ages 18 and 45 years, with or without obesity (defined as BMI $\geq$ 30 kg/m^2) and with or without high blood pressure (HBP) (defined as BP $\geq$ 130/85 mm Hg or on any antihypertensive medications). Exclusion criteria included known diabetes, secondary hypertension, renal disease, cardiovascular disease, autoimmune disease, thyroid disease, sickle cell disease, eating disorders, and use of steroids. The study protocol was approved by the Institutional Review Board of Thomas Jefferson University. Written informed consent was obtained from each participant at enrollment.

Study Procedures

Each participant was given instructions to collect the first voided urine sample (with void-to-void times recorded) on the morning of the visit to the clinical research center. On their arrival to the clinical research center in the early morning, BP and anthropometric measurements (height, weight, and waist circumference) were obtained from all participants. BP measurements were obtained from each subject following a 10-minute rest period in the seated position using auscultation with an aneroid sphygmomanometer. The average of 4 separate measurements of systolic BP (SBP) and diastolic BP (DBP) was used as the BP value for each participant. BMI was calculated as weight (kg) divided by height squared (m^2). Data on health status, medication use, and health-related behaviors were obtained by self-report.

An oral glucose tolerance test (OGTT) was conducted after a 12-hour overnight fast. A fasting blood sample was obtained for plasma glucose, insulin, and lipids. Following the ingestion of 75 g of glucose solution (Glucola; Ames Diagnostics, Elkhart, IN), blood samples were then obtained at 30, 60, and 120 minutes postingestion and assayed for plasma glucose and insulin concentrations. Plasma glucose concentration was analyzed by the glucose oxidase technique (YSI Model 27; Glucostat, Yellow Springs, OH). Plasma insulin concentration was determined with a solid-phase radioimmunoassay (RIA) (Coat-a-Count; Diagnostic Products Corp, Los Angeles, CA). Coefficients of variation for intra- and interassay variability for glucose and insulin assays were less than 5%. Insulin resistance was estimated using the homeostasis model assessment of insulin resistance (HOMR-IR).[17] Fasting lipids, including total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides, were measured using the Hitachi 704 (Boehringer Mannheim, Mannheim, Germany) standard enzymatic method in the Lipid Laboratory of Thomas Jefferson University. Urine albumin excretion (UAE) was measured by ELISA (Exocell, Philadelphia, PA) and corrected for creatinine (cr) (mg/g cr). These assays were highly reliable with a consistently low coefficients of variation (<5%). Urine sodium, potassium, and creatinine were measured with a Nova 16 clinical analyzer (Nova Biomedical, Waltham, MA).

Plasma renin activity and aldosterone levels were measured in fasting blood samples stored at –70°C. Serum aldosterone was determined using a solid-phase ^{125}I radioimmunoassay with sensitivity of 1.1 ng/dL (Coat-a Count, Siemens Healthcare Diagnostics Inc, Los Angeles, CA). Plasma renin activity was determined using radioimmunoassay of generated angiotensin I with sensitivity of 0.132 ng/mL/h (GammaCoat Plasma Renin Activity ^{125}I RIA Kit, DiaSorin, Stillwater, MN).

Statistical Analyses

Frequency counts and percentages were used to summarize the categorical study variables including BMI group (not overweight: BMI <25, overweight: 25$\leq$BMI<30, obese: BMI$\geq$30), BP group (hypertension: SBP $\geq$140 mm Hg or DBP $\geq$90 mm Hg or BP medication, prehypertension: nonhypertensives having 120<SBP<140 mm Hg or 80<DBP<90 mm Hg, normal: SBP $\leq$120 mm Hg and DBP $\leq$80 mm Hg and no BP medication), BP medication usage (all types and diuretics), glucose tolerance status (GTS) group (normal: fasting blood glucose <100 mg/dL and 2-hour post-OGTT glucose < 140 mg/dL, impaired glucose tolerance: fasting blood glucose 100–125 mg/dL or 2-hour glucose of 140–199 mg/dL, diabetic: fasting blood glucose >125 mg/dL or 2-hour post OGTT glucose >199 mg/dL), family history of diabetes (in parents or siblings), and metabolic syndrome (any 3 of the following 5 criteria:

waist circumference ≥ 102 cm for men or ≥ 88 cm for women; BP ≥ 130/85 mm Hg or taking antihypertensive medication; HDL <40 mg/dL for men or <50 mg/dL for women; triglycerides ≥ 150 mg/dL; fasting glucose ≥ 110 mg/dL[18]). Study variables based on continuous measurements were summarized with measures of central tendency and spread. Means and standard deviations were used to summarize approximately normally distributed data (eg, age and BMI). When the data were substantially skewed (eg, HOMA and aldosterone), the central tendency was measured by the geometric mean and, as an alternative to standard deviation, the spread was measured by the first and third quartiles of the data.

Unadjusted group comparisons were conducted for each study variable by either Fisher's exact test of independence (categorical variables) or Student *t* test (2-group comparison of continuous variables) or analysis of variance (ANOVA) F-test (3-group comparison of continuous variables).

Statistical Modeling

Adjusted analyses of HOMA were conducted by multiple regression of log-transformed HOMA on aldosterone/renin ratio (ARR) (or aldosterone and renin) with covariate adjustment for gender, age, smoking (yes/no), alcohol consumption (yes/no), obesity (BMI ≥ 30), and high blood pressure (BP ≥ 130/85 mm Hg or BP medication). These covariates were selected before beginning analyses and no variable selection procedures were used to reduce the number of variables in the models. Some participants were missing renin and were not included in the regression models. Aldosterone and renin were not linearly related to log-HOMA and were categorized by their tertiles for use in modeling (aldosterone tertile cutpoints were 1.37 and 2.79 ng/dL; renin tertile cutpoints were 0.6 and 1.8 ng/mL/h). ARR values were also categorized by tertiles with cutpoints at 1.23 and 3.38. Results on the associations between HOMA and tertiles of aldosterone or ARR are presented as geometric mean ratios (GMR: the anti-log of the log-HOMA regression parameters) with 95% confidence intervals (CIs) and Wald test *P* values. The low level serves as reference category and the GMRs represent the multiplicative change in HOMA associated with a higher level (moderate or high) compared with low when all other variables in the model are held constant. The significance level for all tests was set at $\alpha = 0.05$. All analyses were conducted using SAS version 9.2 (SAS Institute, Inc., Cary, NC).

Results

A total of 505 young adult African Americans were enrolled into the study. Twenty-two participants were removed from data analysis for either insufficient data (n = 11), inability to verify reported antihypertensive medication use (n = 7), or suspected renal disease based on albuminuria of 300 mg/g creatinine or higher and/or serum creatinine of 1.5 mg/dL or higher (n = 4). Data analyses were conducted on 483 study participants, although renin activity was not measured in 21 of these participants. Characteristics of the cohort are described in Table 1. The cohort included 50% women. Compared with men, women had higher mean BMI and a higher prevalence of obesity, but lower mean SBP and DBP. Serum aldosterone levels in our cohort ranged from 0.3 to 19.0 ng/dL. No cases of primary hyperaldosteronism were identified, based on the criteria of aldosterone of 15 ng/dL or higher with ARR of 25 or higher. Plasma renin activities ranged from 0.02 to 43.3 ng/mL/h. Half of the cohort had renin activity less than 1 ng/mL/h. Of the19 participants with renin activity greater than 10 ng/mL/h, 15 were taking antihypertensive medication and 4 were normotensive but obese. The geometric mean of urinary sodium to potassium excretion ratios was above 3.0 in the cohort, indicating a high salt intake.

The cohort was stratified by tertiles based on aldosterone levels to examine the relationships of aldosterone with age, gender, BMI, waist circumference, BP, and metabolic parameters. These results are presented in Table 2. There were no significant differences in age, gender distribution, BMI, or waist circumference across the aldosterone groups. There were no differences in mean systolic or diastolic blood pressures across the aldosterone groups. The geometric mean of urinary sodium to potassium excretion ratios were above 3.0 in all aldosterone groups, indicating high salt intake in all 3 groups.

There were statistically significant differences across the aldosterone groups in metabolic parameters including fasting glucose, fasting insulin, HOMA-IR, and triglycerides. As shown in Table 2, the differences in fasting glucose, fasting insulin, and HOMR-IR emerged between the low and the moderate aldosterone groups. The rates of metabolic syndrome increased progressively from 17% in the low aldosterone group to 27% in the moderate aldosterone group, and 33% in the high aldosterone group.

ARR has been used to assess the dependence of aldosterone secretion on its classical secretagogue angiotensin. We stratified the cohort by tertiles of ARR and examined its relationships with age, gender, BMI, waist circumference, BP, and metabolic parameters. These results are presented in Table 3. There were no significant differences in age, gender distribution, BMI, and waist circumference across the ARR groups. There were also no significant differences in the metabolic parameters, including fasting glucose, fasting insulin, HOMA-IR, and lipid parameters across the ARR groups. Rates of metabolic syndrome were comparable across ARR groups. There were, however, statistically significant differences in blood pressures across the ARR groups ($P < .01$). Both SBP and DBP increased progressively across the ARR groups. There were also statistically significant differences in UAE ($P = .01$) across ARR

Table 1
Characteristics of study participants by gender

	Men (n = 241)	Women (n = 242)	*P* Value*
	Categorical Variables: Frequencies (Percents)		
BMI group			
Overweight	85 (35%)	52 (21%)	<.01
Obese	85 (35%)	158 (65%)	
BP group			<.01
Prehypertension	56 (23%)	46 (19%)	
Hypertension	116 (48%)	91 (38%)	
BP medications			
All types	87 (36%)	82 (34%)	.63
Diuretic	38 (16%)	36 (15%)	.80
GTS group (ordinal)			.97
Prediabetic	72 (30%)	70 (29%)	
Diabetic	22 (9%)	23 (10%)	
Metabolic syndrome	42 (17%)	84 (35%)	<.01
Family history of diabetes†	78 (32%)	79 (33%)	1.000
Family history of hypertension†	133 (55%)	145 (60%)	.31
	Continuous Variables: Mean (SD) or Geometric Mean [Q1,Q3]		
Age, y	38.7 (7.1)	36.7 (7.8)	<.01
BMI, kg/m^2	29.2 (6.9)	33.9 (8.5)	<.01
Waist circumference, cm	95.4 (17.6)	101.4 (17.4)	<.01
Systolic BP, mm Hg	124 (17)	120 (17)	<.01
Diastolic BP, mm Hg	78 (12)	73 (12)	<.01
Fasting glucose, mg/dL	103.6 (16.4)	103.7 (21.1)	.94
Fasting insulin, μU/mL	7.7 (7.2)	9.4 (10.5)	.03
HDL, mg/dL	48.1 (15.4)	47.9 (14.2)	.88
LDL, mg/dL	107.2 (30.3)	109.7 (28.0)	.35
Triglycerides, mg/dL‡	73.6 [52.0, 102]	71.0 [51.0, 94.0]	.42
Total cholesterol, mg/dL	172.1 (33.9)	173.2 (31.0)	.71
UAE, mg/g creatinine ‡	4.9 [1.6, 14.3]	5.2 [2.2, 13.8]	.63
HOMA-IR‡	1.5 [0.8, 2.2]	1.7 [0.9, 2.7]	.08
Aldosterone, ng/dL‡	2.1 [1.2, 3.3]	2.4 [1.2, 3.9]	.02
Renin, ng/mL/h‡	1.0 [0.4, 2.2]	1.0 [0.4, 2.5]	.98
ARR‡	2.0 [0.9, 4.6]	2.4 [1.0, 5.5]	.21
Urinary Na/Cr ratio, meq/g‡	82.8 [60.0, 120]	78.5 [56.4, 112]	.32
Urinary K/Cr ratio, meq/g‡	22.5 [16.0, 31.4]	24.1 [18.0, 29.9]	.11

ARR, aldosterone/renin ratio; BMI, body mass index; BP, blood pressure; GTS, glucose tolerance status; HDL, high-density lipoprotein; HOMA-IR, homeostatis model assessment–insulin resistance; LDL, low-density lipoprotein; UAE, urine albumin excretion.

Hypertension: BP $\geq$ 140/90 mm Hg or BP medication, prehypertension: BP $>$ 120/80 mm Hg, but not hypertensive.

Metabolic syndrome: 3 or more of following: waist circumference $\geq$102 cm (men), $\geq$88 cm (women); BP $\geq$130/85 mm Hg or BP medication; HDL $<$40 (men), $<$50 (women); triglycerides $\geq$150 mg/dL; fasting glucose $\geq$110 mg/dL.

* Fishers exact test (categorical variables) or Student *t* test (continuous variables).

† Family history of diabetes: parent or sibling.

‡ Data natural log transformed: geometric means with the first and third quartiles [Q1,Q3] presented.

groups, with UAE being the highest in the high ARR group. Based on calculations of estimated glomerular filtration rates, there were no significant differences in renal function between ARR groups or between aldosterone groups (data not shown).

Analyses were conducted to determine possible association of aldosterone with insulin resistance (HOMA-IR) after adjusting for variables, including age, gender, smoking, alcohol use, obesity, and BP. As shown in Table 4, the geometric mean of HOMA-IR was higher by 35% in the moderate aldosterone group and 26% in the high aldosterone group when compared with the low aldosterone group. On the other hand, HOMA-IR was similar across the ARR groups. Based on this analysis, the significant association of aldosterone with insulin resistance, estimated by HOMA, is independent of obesity. Replacing obesity assessed by BMI with obesity assessed by waist circumference ($\geq$102 cm in men or $\geq$88 cm in women) did not influence the presence or absence of associations between HOMA-IR and aldosterone or ARR (data not shown). Because the

Table 2
Characteristics of study subjects by aldosterone groups

	Aldosterone (ng/dL)			*P* Value*
	Low (<1.37) (n = 160)	Moderate (1.37≤ to <2.79) (n = 161)	High (≥2.79) (n = 162)	
	Categorical Variables: Frequencies (Percents)			
Gender (female)	77 (48%)	76 (47%)	89 (55%)	.32
BMI group				.76
Overweight	51 (32%)	42 (26%)	44 (27%)	
Obese	74 (46%)	85 (53%)	84 (52%)	
BP group				.63
Prehypertension	30 (19%)	40 (25%)	32 (20%)	
Hypertension	70 (44%)	63 (39%)	74 (46%)	
BP medications				
All types	57 (36%)	58 (36%)	54 (33%)	.86
Diuretics	18 (11%)	21 (13%)	35 (22%)	.03
GTS group (ordinal)				.14
Prediabetic	40 (25%)	54 (34%)	48 (30%)	
Diabetic	10 (6%)	18 (11%)	17 (10%)	
Metabolic syndrome	27 (17%)	44 (27%)	55 (34%)	<.01
Family history of diabetes†	53 (33%)	53 (33%)	51 (31%)	.95
Family history of hypertension†	94 (59%)	81 (50%)	103 (64%)	.05
	Continuous Variables: Mean (SD) or Geometric Mean [Q1,Q3]			
Age, y	37.5 (7.7)	37.2 (7.7)	38.5 (7.0)	.26
BMI, kg/m^2	31.0 (7.8)	32.3 (8.8)	31.4 (7.6)	.35
Waist circumference, cm	97.3 (17.0)	99.9 (19.5)	97.9 (16.5)	.44
Systolic BP, mm Hg	123 (16)	120 (16)	123 (19)	.19
Diastolic BP, mm Hg	75 (12)	75 (11)	76 (13)	.46
Fasting glucose, mg/dL	100.5 (14.1)	106.5 (24.9)	104.0 (15.4)	.01
Fasting insulin, μU/mL	6.5 (6.2)	10.3 (11.7)	8.8 (7.9)	<.01
HDL, mg/dL	48.6 (14.2)	47.8 (14.9)	47.4 (15.2)	.75
LDL, mg/dL	106.4 (26.6)	107.2 (29.1)	111.7 (31.5)	.23
Triglycerides, mg/dL ‡	67.0 [50.0, 91.5]	71.9 [51.0, 94.0]	78.3 [53.0, 112]	.03
Total cholesterol, mg/dL	170.0 (31.3)	171.1 (31.8)	177.0 (33.9)	.13
UAE, mg/g creatinine‡	5.3 [1.8, 15.3]	4.9 [1.8, 14.3]	4.9 [2.2, 12.0]	.82
HOMA-IR‡	1.2 [0.8, 1.7]	1.8 [0.9, 3.1]	1.7 [0.9, 2.7]	<.01
Aldosterone, ng/dL‡	1.1 [1.1, 1.2]	1.9 [1.7, 2.3]	5.1 [3.5, 7.0]	n/a
Renin, ng/mL/h ‡	0.7 [0.3, 1.4]	1.1 [0.5, 2.3]	1.5 [0.6, 3.0]	<.01
ARR‡	1.7 [0.8, 3.7]	1.8 [0.8, 3.8]	3.6 [1.5, 7.9]	<.01
Urinary Na/Cr ratio, meq/g‡	82.6 [60.9, 118]	78.0 [52.7, 112]	81.4 [63.4, 114]	.66
Urinary K/Cr ratio, meq/g ‡	21.5 [15.7, 28.2]	24.4 [17.5, 34.6]	24.0 [18.3, 29.1]	.03

ARR, aldosterone/renin ratio; BMI, body mass index; BP, blood pressure; GTS, glucose tolerance status; HDL, high-density lipoprotein; HOMA-IR, homeostatis model assessment–insulin resistance; LDL, low-density lipoprotein; UAE, urine albumin excretion; n/a, not applicable.

Metabolic syndrome: 3 or more of following: waist circumference ≥102 cm (men), ≥88 cm (women); BP ≥130/85 mm Hg or BP medication; HDL <40 (men), <50 (women); triglycerides ≥150 mg/dL; fasting glucose ≥110 mg/dL.

* Fishers exact test (categorical) or analysis of variance F-test (continuous).

† Family history of diabetes: parent or sibling.

‡ Data natural log transformed: geometric means with first and third quartiles [Q1,Q3] presented.

aldosterone and renin measurements were below the assay sensitivity levels in a portion of our cohort, we reanalyzed the data by setting the lowest aldosterone level and lowest renin activity level at the lower limit of sensitivity level of 1.1 ng/dL and 0.132 ng/mL/h, respectively, per assay manufacturers. This resulted in no change in the participant stratification by aldosterone tertiles. The overall results and the significant findings in the regression modeling were not affected by the reanalysis.

Using ATP III criteria,[18] 26% of our study cohort had metabolic syndrome. Table 5 provides the data on subjects with and without metabolic syndrome. Aldosterone and renin levels are higher in the metabolic syndrome group compared with the nonmetabolic syndrome group, but

Table 3
Characteristics of study subjects by ARR groups

	Low ARR (<1.38) (n = 153)	Moderate ARR (1.38≤ to <3.67) (n = 162)	High ARR (≥3.67) (n = 148)	*P* Value*
	Categorical Variables: Frequencies (Percents)			
Gender (female)	72 (47%)	78 (48%)	84 (57%)	.19
BMI group				.08
Overweight	39 (25%)	52 (32%)	40 (27%)	
Obese	73 (48%)	87 (54%)	74 (50%)	
BP group				.34
Prehypertension	27 (18%)	35 (22%)	31 (21%)	
Hypertension	67 (44%)	63 (39%)	72 (49%)	
BP medications				
All types	62 (41%)	50 (31%)	55 (37%)	.19
Diuretics	24 (16%)	23 (14%)	26 (18%)	.72
GTS group (ordinal)				.54
Prediabetic	51 (33%)	45 (28%)	42 (28%)	
Diabetic	17 (11%)	15 (9%)	11 (7%)	
Metabolic syndrome	41 (27%)	40 (25%)	40 (27%)	.88
Family history of diabetes†	39 (25%)	60 (37%)	50 (34%)	.08
Family history of hypertension†	86 (56%)	87 (54%)	93 (63%)	.24
	Continuous Variables: Mean (SD) or Geometric Mean [Q1,Q3]			
Age, y	37.2 (8.0)	37.6 (7.8)	38.3 (6.8)	.20
BMI, kg/m^2	31.4 (8.6)	32.2 (8.3)	31.3 (7.6)	.31
Waist circumference, cm	97.4 (17.6)	100.9 (18.8)	97.4 (17.2)	.09
Systolic BP, mm Hg	118 (14)	122 (18)	125 (17)	<.01
Diastolic BP, mm Hg	73 (10)	75 (13)	78 (13)	<.01
Fasting glucose, mg/dL	103.2 (13.8)	104.7 (19.3)	103.4 (23.1)	.94
Fasting insulin, μU/mL	9.6 (11.4)	8.0 (7.7)	8.2 (7.9)	.35
HDL, mg/dL	47.6 (13.5)	48.5 (15.4)	48.1 (15.7)	.72
LDL, mg/dL	107.8 (27.6)	108.2 (31.6)	109.5 (28.8)	.96
Triglycerides, mg/dL‡	74.6 [53.0, 102]	72.2 [51.0, 99.0]	69.8 [50.0, 91.0]	.39
Total cholesterol, mg/dL	172.2 (32.6)	172.8 (34.3)	173.5 (31.5)	.92
UAE, mg/g creatinine‡	4.7 [1.8, 14.1]	4.0 [1.3, 10.5]	6.4 [3.0, 16.8]	.03
HOMA-IR‡	1.6 [0.8, 2.6]	1.5 [0.8, 2.4]	1.5 [0.9, 2.4]	.51
Aldosterone (ng/dl)‡	1.6 [0.9, 2.2]	1.9 [1.1, 2.9]	2.8 [1.6, 4.9]	<.01
Renin, ng/mL/h‡	3.1 [1.6, 4.6]	0.9 [0.5, 1.8]	0.3 [0.2, 0.7]	<.01
ARR‡	0.5 [0.3, 0.9]	2.1 [1.6, 2.8]	8.3 [4.7, 12.1]	n/a
Urinary Na/Cr, meq/g‡	75.6 [52.4, 112]	79.5 [57.8, 110]	84.7 [61.6, 125]	.25
Urinary K/Cr, meq/g‡	23.8 [17.5, 33.2]	22.9 [16.5, 30.0]	22.7 [16.8, 28.5]	.70

ARR, aldosterone/renin ratio; BMI, body mass index; BP, blood pressure; GTS, glucose tolerance status; HDL, high-density lipoprotein; HOMA-IR, homeostatis model assessment–insulin resistance; LDL, low-density lipoprotein; UAE, urine albumin excretion; n/a, not applicable.

Metabolic syndrome: 3 or more of following: waist circumference ≥102 cm (men), ≥88 cm (women); BP ≥130/85 mm Hg or BP medication; HDL <40 (men), <50 (women); triglycerides ≥150 mg/dL; fasting glucose ≥110 mg/dL.

* Fisher's exact test (categorical) or analysis of variance F-test (continuous).

† Family history of diabetes: parent or sibling.

‡ Data natural log transformed: geometric means with first and third quartiles [Q1,Q3] presented.

there is no significant difference in ARR between these groups.

Discussion

Analysis of data from our study of young adult African Americans detected a significant association of aldosterone with insulin resistance that is independent of age, gender, obesity (assessed either by BMI or waist circumference), and BP. In addition, higher aldosterone is associated with higher triglyceride levels and higher rates of metabolic syndrome. Although we did not detect a significant direct association of aldosterone with BP, there was a significant association of ARR with both SBP and DBP. Participants in our cohort were ingesting high amounts of salt, as indicated by the urinary sodium:potassium ratio. Considering the

Table 4
Associations of HOMA-IR with aldosterone and ARR groups by tertile

	GMR (95% CI)	*P* Value
Aldosterone		
Moderate vs Low	1.35 (1.13, 1.60)	<.01
High vs Low	1.26 (1.05, 1.50)	.01
ARR		
Moderate vs Low	0.93 (0.78, 1.11)	.41
High vs Low	0.92 (0.78, 1.10)	.37

ARR, aldosterone/renin ratio; CI, confidence interval; GMR, geometric mean ratio; HOMA-IR, homeostatis model assessment–insulin resistance.

positive association of insulin resistance with aldosterone, it is possible that insulin, acting as an adrenal secretagogue, mediates an increase in aldosterone. Alternatively, aldosterone secretion may be stimulated by an unidentified secretagogue independent of renin. This unidentified substance may also be responsible for the glomerular damage indicated by the increased urinary albumin excretion in the highest ARR subgroup. Our results indicate that a modest increase in aldosterone, in the presence of high salt intake and renin suppression, is associated with higher BP.

A significant association of aldosterone with insulin resistance and metabolic syndrome has been reported in African Americans[12,19] as well as whites.[20] In a study of 182 hypertensive and 215 normotensive African Americans between ages 18 and 55, Kidambi et al[19] found significant correlations of aldosterone with fasting insulin and HOMA-IR, as well as higher aldosterone levels in those with metabolic syndrome than those without metabolic syndrome. These investigators acknowledged that their findings could have been confounded by the association of aldosterone with BMI and waist circumference. They speculated that the relatively high aldosterone and low plasma renin among hypertensives might reflect a mild variant of primary aldosteronism. The results of our study differ somewhat from that study. We used the same definition of high BP in our study, and although our cohort was slightly younger, we identified a significant association of aldosterone with insulin resistance that was independent of obesity and high BP (Tables 2 and 4). Bochud et al[12] reported a similar study of families with a strong history of hypertension (defined as at least 2 hypertensive siblings in each family) of East African descent in the Seychelles islands. Based on data from 356 individuals, these investigators reported significantly higher aldosterone levels in those with metabolic syndrome compared with those without metabolic syndrome, and the association of aldosterone with metabolic syndrome appeared to be independent of individual components of the metabolic syndrome, including BP and waist circumference. In that cohort, plasma aldosterone was associated with daytime ambulatory BP only in the older participants.

The relationship of aldosterone with insulin resistance has also been reported in whites. Colussi et al[20] detected a significant positive relationship between aldosterone and HOMA-IR that was independent of BMI and BP. The significant positive association was replicated in a subgroup of the cohort using an insulin clamp procedure to quantify insulin resistance. Compared with the previously mentioned studies, the distribution of plasma aldosterone levels in our cohort was at a lower range and salt intake was high. Our results indicate that even in the low normal range, relatively higher aldosterone is associated with greater insulin resistance and higher rates of metabolic syndrome independent of age, gender, obesity, and BP.

Several reports describe a significant positive association of both aldosterone and plasma renin activity with obesity,[8,9] and with components of the metabolic syndrome.[21] Both aldosterone and plasma renin activity decrease following reduction in body weight among obese individuals.[22] Based on these observations, aldosterone and renin have been thought to play a causal role in obesity-associated hypertension. Despite a substantial amount of obesity in our African American cohort, we did not detect a significant association of aldosterone or plasma renin activity with either BMI or waist circumference.

Despite higher rates of hypertension and greater insulin resistance,[23] African Americans, on average, have lower levels of renin activity and aldosterone than whites.[24,25] It has been shown experimentally in rodents that by slightly overexpressing the aldosterone synthase gene, subsequent exposure to a high salt diet results in high BP, even with normal or only slightly elevated plasma aldosterone.[26] Much earlier clinical studies on aldosterone secretion in humans by Collins and colleagues[27] demonstrated that during salt-loading conditions, a large portion of patients with ''benign essential'' hypertension do not suppress aldosterone secretion to a level observed in normotensive individuals. It has been proposed that modest increases or insufficiently suppressed aldosterone in the presence of a high salt intake can contribute to sodium retention and salt-sensitive hypertension.[26,28] Our data are consistent with this concept. Although our data demonstrate a significant independent association of aldosterone with insulin resistance, there were no detectable direct associations of aldosterone or plasma renin activity with BP or incidence of hypertension. The distributions of both aldosterone and renin activity were low, and dietary salt intake was consistently high in our study cohort. When the cohort was stratified by ARR tertile, both SBP and DBP were significantly higher in the high ARR tertile group. Based on these findings, it is plausible that insufficient suppression of aldosterone in the presence of high sodium intake may explain the positive association of ARR with blood pressure in African Americans. It is also possible that relative hyperinsulinemia, as a consequence of insulin resistance, may blunt suppression of aldosterone and explain, to some extent,

Table 5
Characteristics of study subjects by metabolic syndrome

	Metabolic Syndrome		*P* Value*
	No (n = 357)	Yes (n = 126)	
	Categorical Variables: Frequencies (Percents)		
Gender (female)	158 (44%)	84 (67%)	<.01
BMI group			<.01
Overweight	113 (32%)	24 (19%)	
Obese	143 (40%)	100 (79%)	
BP group			<.01
Prehypertension	81 (23%)	21 (17%)	
Hypertension	119 (33%)	88 (70%)	
BP medications			
All types	95 (27%)	74 (59%)	<.01
Diuretics	38 (11%)	36 (29%)	<.01
GTS group (ordinal)			<.01
Prediabetic	86 (24%)	56 (44%)	
Diabetic	13 (4%)	32 (25%)	
Family history of diabetes†	114 (32%)	43 (34%)	.66
Family history of hypertension†	202 (57%)	76 (60%)	.53
	Continuous Variables: Mean (SD) or Geometric Mean [Q1,Q3]		
Age, y	37.2 (7.8)	39.2 (6.3)	<.01
BMI, kg/m^2	29.8 (7.4)	36.6 (7.8)	<.01
Waist circumference, cm	94.4 (16.6)	109.6 (15.7)	<.01
Systolic BP, mm Hg	120 (16)	127 (19)	<.01
Diastolic BP, mm Hg	75 (12)	78 (12)	.03
Fasting glucose, mg/dL	99.2 (11.2)	116.4 (28.2)	<.01
Fasting insulin, μU/mL	7.2 (7.4)	12.4 (11.7)	<.01
HDL, mg/dL	50.8 (14.8)	39.8 (11.1)	<.01
LDL, mg/dL	106.8 (28.7)	113.0 (30.2)	.05
Triglycerides, mg/dL‡	65.1 [49.0, 87.0]	97.4 [68.0, 145.0]	<.01
Total cholesterol, mg/dL	171.9 (31.7)	174.9 (34.6)	.39
UAE, mg/g creatinine‡	4.9 [1.8, 13.2]	5.4 [2.0, 14.7]	.47
HOMA-IR‡	1.3 [0.8, 2.0]	2.6 [1.5, 4.5]	<.01
Aldosterone, ng/dL‡	2.1 [1.1, 3.3]	2.6 [1.5, 3.9]	<.01
Renin, ng/mL/h‡	0.9 [0.4, 2.1]	1.3 [0.5, 3.0]	<.01
ARR‡	2.3 [1.0, 5.3]	1.9 [0.8, 5.3]	.22
Urinary Na/Cr ratio, meq/g‡	84.2 [60.6, 120]	71.4 [50.8, 108]	<.01
Urinary K/Cr ratio, meq/g‡	22.9 [16.8, 30.5]	24.1 [18.3, 30.0]	.28

ARR, aldosterone/renin ratio; BMI, body mass index; BP, blood pressure; GTS, glucose tolerance status; HDL, high-density lipoprotein; HOMA-IR, homeostatis model assessment–insulin resistance; LDL, low-density lipoprotein; UAE, urine albumin excretion.

Metabolic syndrome: 3 or more of following: waist circumference ≥102 cm (men), ≥88 cm (women); systolic ≥130 or diastolic ≥85 or hypertension medication; HDL <40 (men), <50 (women); triglycerides ≥150; fasting glucose ≥110.

* Fisher's exact test (categorical) or analysis of variance F-test (continuous).

† Family history of diabetes: parent or sibling.

‡ Data natural log transformed: geometric means with [Q1,Q3] presented.

the link between insulin resistance and high blood pressure in African Americans.

There are some limitations in this study. Our data are based on a cross-sectional study, and we do not have evidence to support a causal role of aldosterone in development of insulin resistance or increasing BP. Longitudinal prospective studies on a similar or younger African American cohort would be required to determine if relatively high aldosterone precedes the onset of insulin resistance or increasing BP level. Our study was conducted on African Americans, which limits generalizability to other races and ethnic groups. Although our cohort was relatively healthy, 35% were taking antihypertensive medications based on their self-report. Because participants were recruited from the community and were not our own patients, we did not request that they stop taking their medication before study participation. Medication usage was similar across the aldosterone, renin, and ARR tertiles. As described earlier, elevated plasma renin

activity in a few subjects could be explained by diuretic or angiotensin-converting enzyme inhibitor use. These subjects were not in the high-ARR tertile. Use of diuretics, according to self-report, was higher in the high aldosterone group. It is possible that our results were confounded to some extent by antihypertensive medication usage.

Conclusion

Among young adult African Americans, there is a positive association of aldosterone with insulin resistance that is independent of obesity and is present within a normal range of plasma aldosterone. In the presence of high salt intake, a higher ARR is associated with higher BP, suggesting that insufficiently suppressed aldosterone contributes to blood pressure elevation and sensitivity to sodium.

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