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Plasma Aldosterone Is Independently Associated With the Metabolic Syndrome

Murielle Bochud, Jürg Nussberger, Pascal Bovet, Marc R. Maillard, Robert C. Elston, Fred Paccaud, Conrad Shamlaye, Michel Burnier

Abstract—The aim of this study was to analyze the associations of plasma aldosterone and plasma renin activity with the metabolic syndrome and each of its components. We analyzed data from a family based study in the Seychelles made up of 356 participants (160 men and 196 women) from 69 families of African descent. In multivariable models, plasma aldosterone was associated positively ($P<0.05$) with blood pressure in older individuals (interaction with age, $P<0.05$) and with waist circumference in men (interaction with sex, $P<0.05$) and negatively with high-density lipoprotein cholesterol, in particular in individuals with elevated urinary potassium excretion (interaction with urinary potassium, $P<0.05$); plasma renin activity was significantly associated with triglycerides and fasting blood glucose. Plasma aldosterone, but not plasma renin activity, was associated with the metabolic syndrome per se, independently of the association with its separate components. The observation that plasma renin activity was associated with some components of the metabolic syndrome, whereas plasma aldosterone was associated with other components of the metabolic syndrome, suggests different underlying mechanisms. These findings reinforce previous observations suggesting that aldosterone is associated with several cardiovascular risk factors and also suggest that aldosterone might contribute to the increased cardiovascular disease risk in individuals of African descent with the metabolic syndrome. (*Hypertension*. 2006;48:1-7.)

Key Words: aldosterone ■ metabolism ■ blood pressure ■ genetics

The metabolic syndrome (MS) represents a clustering of several cardiovascular risk factors, which include hypertension, dyslipidemia (low high-density lipoprotein [HDL] cholesterol and elevated triglycerides), abdominal obesity, glucose intolerance, and a proinflammatory and prothrombotic state.¹ The mechanisms linking these abnormalities are, however, not well understood.² The MS is associated with increased cardiovascular morbidity and mortality,^{3–6} although the underlying mechanisms responsible for these associations are not yet fully known.⁷

The renin–angiotensin–aldosterone system plays a crucial role in blood pressure (BP) control, as well as in the progression of cardiovascular and renal diseases.⁸ A large body of evidence now suggests that aldosterone exerts cardiovascular effects that might go beyond the classically described kidney-mediated electrolyte and water homeostasis.⁹ In the last decades, much of the attention focused on the potentially deleterious effects of angiotensin II. However, recent observations have suggested that increased aldosterone levels are much more frequent in “essential” hypertension than thought previously.^{10–14} The Randomized ALdactone Evaluation Study (RALES)¹⁵ and Eplerenone Post-acute myo-

cardial infarction Heart failure Efficacy and SURvival Study (EPHESUS) trials^{16,17} have highlighted the key role of aldosterone in cardiovascular morbidity and mortality in patients with heart failure. Because both aldosterone and renin are associated with BP, and high BP is part of the MS, they may be associated independently with the MS in general and with specific components of it in particular.

Although the role of renin and aldosterone in BP regulation is well known, less is known about association of renin and aldosterone with the MS. Several observations suggest that plasma aldosterone (PA) plays a role in BP regulation in obesity.^{18–21} In addition, several studies have reported an association between aldosterone and/or plasma renin activity (PRA) and blood lipids^{22–24} and insulin resistance,^{22,25–27} which are components of the MS. Although Egan et al²⁸ found that an activated renin–angiotensin–aldosterone system was associated with cardiovascular risk factor clustering, no association was found between the MS and aldosterone or PRA in a recent TROPHY substudy.²⁷ The aim of this study was to analyze the association in an East African population of PA and PRA with: (1) the MS, and (2) each of its components.

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Methods

The study took place in the Seychelles islands, which are populated predominantly by individuals of East African descent. Participants were recruited between August 1999 and January 2002. The selection process for families has been described previously.²⁹ The protocol was accepted by the local ethical committee in Lausanne, Switzerland, and also accepted by the Ministry of Health of the Seychelles Islands. The main purpose of the study aimed at examining genetic determinants of hypertension within families including ≥ 2 hypertensive siblings. Therefore, we conducted these analyses post hoc. Patients treated with statins (n=4) were excluded. In addition, 134 individuals were excluded because data on hormones (n=54) or on one of the MS components (n=84) were not available. This study was composed of 356 individuals from 69 families.

We used a standard definition of the MS.¹ The MS is defined for subjects with ≥ 3 of the following 4 factors: waist circumference >102 cm (40 in) in men and >88 cm (35 in) in women, triglycerides ≥ 150 mg/dL (1.69 mmol/L), HDL cholesterol <40 mg/dL (1.04 mmol/L) in men and <50 mg/dL (1.30 mmol/L) in women, office BP $\geq 130/85$ mm Hg or on antihypertensive treatment, and fasting blood glucose ≥ 110 mg/dL (6.1 mmol/L) or on an antidiabetic agent.

Office BP was measured using a standard mercury sphygmomanometer with a cuff that automatically adapts the bladder to the arm circumference (TriCuff) in seated subjects who had been quiet for ≥ 10 minutes. The average of 3 readings was used for the definition of the MS. Antihypertensive therapy, if any, was stopped for 2 weeks before conducting ambulatory BP monitoring and measuring PRA and PA. Antihypertensive treatment was stopped in 149 participants for a median of 15 days (interquartile range, 12 to 22). Diuretics, angiotensin-converting enzyme (ACE) inhibitors, β -blockers, and calcium-channel blockers were stopped in, respectively, 73, 46, 42, and 65 participants. Ambulatory BP was measured using Diasys Integra devices (Novacor SA). Additional methodologic criteria have been described previously.³⁰ For the analyses, we used the average of 10 randomly selected daytime BP measures to have the same number of measures for each participant. Body mass index (BMI) was calculated as weight (kilograms) divided by squared height (square meters). Waist was measured at the umbilicus level, on standing patients wearing only underwear, to the nearest 1 cm.

After an overnight fast, protocols began between 7:00 AM and 8:00 AM in a quiet room with the subject lying on a bed for 1 hour. Venous plasma was collected into prechilled glass tubes containing potassium EDTA and immediately centrifuged at 4°C. PRA was measured according to the antibody-trapping principle.³¹ We used high-affinity antibodies to protect angiotensin I generated in plasma against degradation during a 30-minute incubation at 37°C.³² The same antibodies after 100-fold dilution were subsequently used for radioimmunoassay.³² PA was measured by a direct radioimmunoassay using a very sensitive and specific antiserum raised in a New Zealand white rabbit.³³ The coefficients of variation for within- and between-assay precision were 0.04 to 0.13 for the PRA and PA assays.^{32,33} The lower detection limits for PA and PRA were 2 pg/mL (5.548 pmol/L) and 0.05 ng/mL per hour (0.014 ng/Ls), respectively. PA and PRA are converted to SI units on multiplying by 2.774 and 0.2778, respectively. For the analyses, we assumed the 26 samples below detection limit for PRA to have half the value of the detection limit. No participant was below the detection limit for PA.

Participants were given, on the same day as ambulatory BP monitoring was performed, plastic containers to collect urine for a 24-hour period under their usual diet. Urinary and plasma sodium and potassium concentrations were measured by flame photometry (IL-943, Instrumentation Laboratory). Fasting blood glucose was measured twice using a Glycotronic C reflectometer (Macherey-Nagel).

Statistical Methods

To compare data in participants with and without the MS, we obtained approximate *P* values (ie, not accounting for the correlated family data) using *t* tests for continuous and χ^2 tests for dichotomous

variables. Spearman rank correlations were calculated between PA and PRA (after adjustment for age, sex, urinary sodium, and potassium) in participants with 0, 1, 2, 3, and >3 MS criteria. We used the ASSOC program in SAGE³⁴ to conduct multiple linear regressions using centered continuous independent variables to avoid multicollinearity problems when adding interaction terms. ASSOC analyzes the association between a continuous trait and 1 or more covariates on the assumption that a power transformation of the trait leads to multivariate normality across pedigree members from pedigree data in the presence of familial correlations. Because this is a cross-sectional study and none of the variables can be considered to be measured with less error than the others, we conducted regression analyses both ways, that is, once using the MS components as the dependent variables and once using the hormones (PA and PRA) as the dependent variables. Regression coefficients and their SEs are presented on an untransformed scale. For independent observations, the following relationship relates the estimated regression coefficient *b* of *Y* on *X* to Pearson's correlation coefficient *r*: $b=r(s_y/s_x)$, where s_x and s_y represent the sample SDs of *X* and *Y*. No such simple relationship exists for correlated family data. All of the models included age and sex as covariates and were corrected for ascertainment as described previously.³⁰ To analyze whether PA or PRA was associated with the entity MS, as defined by the National Cholesterol Education Program (NCEP) criteria,¹ independent of the MS components, we added a variable (coded 1/0 for the presence/absence of MS) to a model containing all of the MS components. We repeated the analyses (1) after removing 26 individuals who were the most susceptible to having a primary aldosteronism (ie, those with hypertension [NCEP criteria] and both PA/PRA ratio and PA above the 75th percentile), and (2) adding BMI as a covariate.

Results

Participants' characteristics are presented in Table 1. Most participants fulfilled the NCEP criteria for hypertension, which reflects the fact that families were ascertained on the

TABLE 1. Descriptive Statistics

Characteristic	MS		<i>P</i> Value
	Absent	Present	
N	249	107	
Age, y	45.0 (11.5)	48.5 (12.9)	0.01
Sex, % women	50	67	0.002
BMI, kg/m ²	26.0 (4.7)	31.2 (4.5)	<0.0001
Overweight (BMI ≤ 25), %	58	93	<0.0001
Taken off treatment, %	36	56	<0.0001
Plasma aldosterone, pg/mL*	49 (20)	59 (27)	<0.0001
Plasma renin activity, ng/L per hour*	0.33 (0.41)	0.44 (0.49)	0.17
Plasma potassium, mmol/L	3.8 (0.3)	3.7 (0.3)	0.60
Fasting blood glucose, mmol/L	4.4 (1.3)	5.8 (3.0)	<0.0001
HDL cholesterol, mmol/L	1.34 (0.35)	1.07 (0.26)	<0.0001
Triglycerides, mmol/L	1.0 (0.5)	1.6 (0.9)	<0.0001
Waist circumference, cm	90 (12)	104 (10)	<0.0001
Office hypertension, %†	65	94	<0.0001
Day systolic BP, mm Hg	129.5 (17.5)	135.0 (15.2)	0.005
Day diastolic BP, mm Hg	84.1 (12.2)	85.7 (9.5)	0.23

Results are means (SD) unless specified otherwise. MS was defined using National Cholesterol Education Adult Treatment Panel III criteria.

*Results are medians (interquartile range).

†Hypertension, defined as office BP $\geq 130/85$ mm Hg or on antihypertensive treatment.

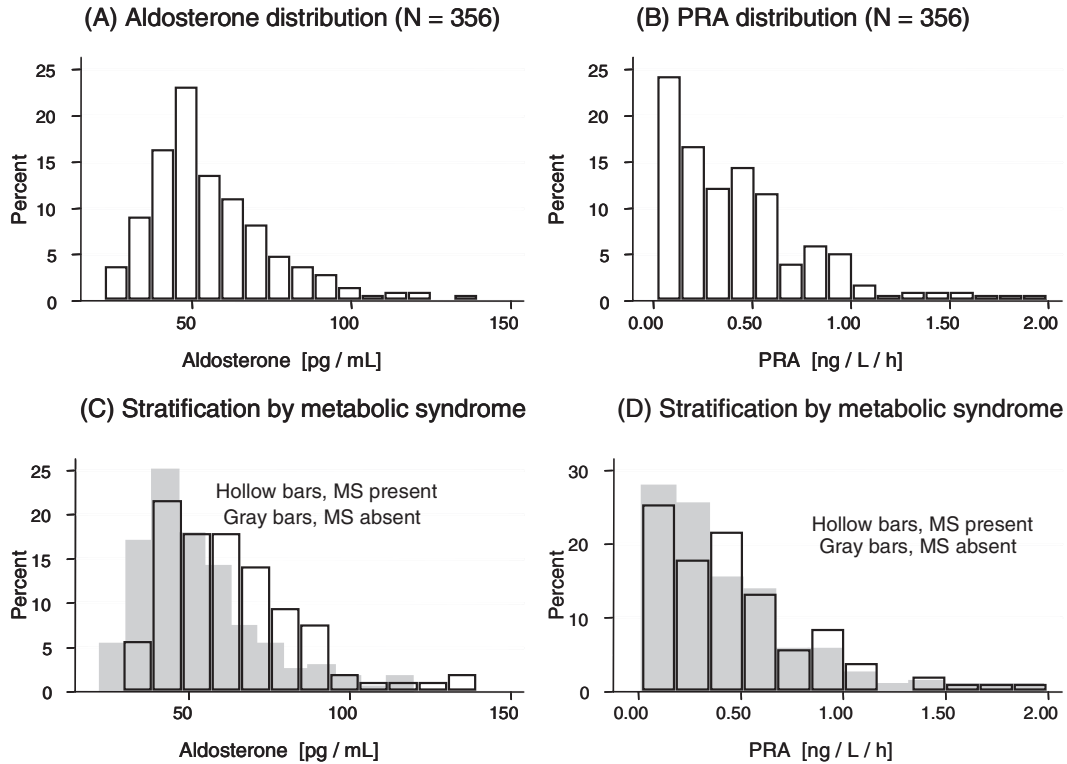


Figure 1. Distribution of PA and PRA. A and B, Distributions of PA and PRA in the whole sample (N=356). C and D, Distribution according to the presence (□) or the absence (■) of MS.

basis of the presence of ≥ 2 hypertensive siblings. PA was significantly higher, and PRA tended to be higher, in participants with than without the MS. Figure 1 illustrates the rightward shift in distribution of PA, but not PRA, in participants with, as compared with those without, the MS. PA tended to increase, and the positive correlation between PA and PRA tended to decrease, with an increasing number of MS risk factors (Figure 2). After removing participants with any suspicion of primary aldosteronism, the rank correlations between PA and PRA were, for participants with,

respectively, 0, 1, 2, 3, and >3 MS components, 0.32 (n=29; $P=0.09$), 0.27 (n=93; $P=0.008$), 0.13 (n=114; $P=0.16$), 0.17 (n=55; $P=0.22$), and 0.17 (n=39; $P=0.30$). The near 0 correlation between PA and PRA in participants with the MS may, therefore, be, in part, because of primary aldosteronism.

Table 2 presents regression coefficients of components of the MS on hormones. PA was significantly associated with all components of the MS except for fasting blood glucose. In contrast, PRA was significantly associated with only triglycerides and fasting blood glucose. The different associations

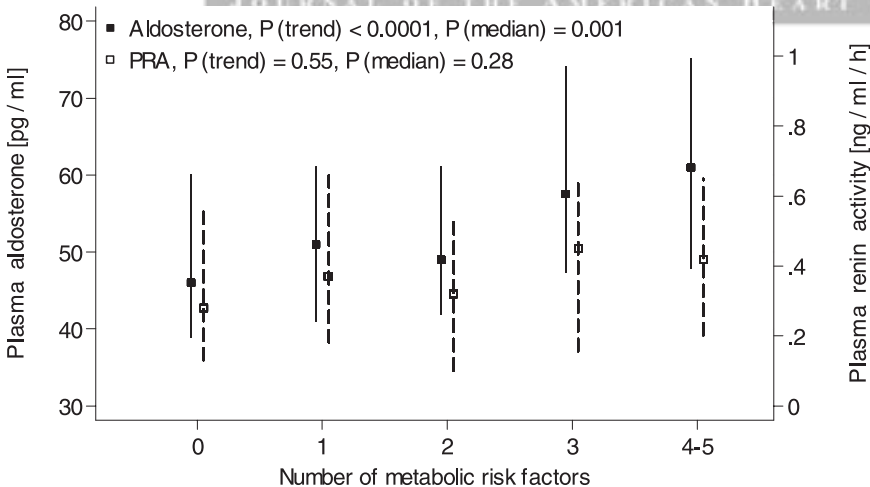


Figure 2. PA and PRA by number of metabolic risk factors. Results are medians and interquartile ranges. Solid lines and ■ represent PA. Dashed lines and □ represent PRA. P (trend) is the P value for a nonparametric test for trend, P (median) is the P value for a test of equal medians across all categories. r is the Spearman rank correlation between PA and PRA levels within each category. Na/K represents the 24-hour urinary sodium/potassium excretion, expressed in mmol/24 hour.

N	29	99	129	64	43
r	0.32	0.14	0.04	-0.12	0.06
Na/K	100/40	94/42	108/43	117/45	113/51

TABLE 2. Regression Coefficients of Components of the MS on PA and PRA and Their Significant Interactions

Factor	Type of Analysis	Dependent Variable					
		Day SBP, mm Hg	Day DBP, mm Hg	Waist, cm	HDL, mmol/L	Triglycerides, mmol/L	FBG, mmol/L
PA							
Model A	Main effect	-0.02 (0.04)	0.007 (0.03)	0.14 (0.04)*	-0.003 (0.001)*	0.003 (0.001)†	0.004 (0.004)
	Interaction	0.007 (0.003)†	0.007 (0.002)*	-0.18 (0.06)*			
		(PA×age)	(PA×age)	(PA×sex)			
Model B	Main effect	-0.005 (0.04)	0.012 (0.027)	0.16 (0.04)*	-0.003 (0.001)*	0.004 (0.001)*	0.005 (0.003)
	Interaction	0.006 (0.003)†	0.007 (0.002)*	-0.17 (0.06)*	-0.0001 (0.00005)*	0.0001 (0.00003)†	
		(PA×age)	(PA×age)	(PA×sex)	(PA×urine K)		
	Interaction			0.004 (0.002)†			
				(PA×urine K)			
PRA							
Model A	Main effect	2.49 (2.03)	1.00 (1.39)	1.47 (1.65)	-0.01 (0.04)	0.13 (0.07)	0.34 (0.18)
Model B	Main effect	2.95 (1.98)	1.12 (1.38)	1.96 (1.64)	-0.03 (0.04)	0.13 (0.07)†	0.36 (0.18)†

This table presents regression coefficients (SE) for the main effects of PA and PRA and their interactions with other covariates from 24 models. Dependent variables are the components of the MS. Continuous predictors were mean centered. In addition to PA or PRA, models A included age, sex, ascertainment, and their significant 2-way interactions as covariates. In models B, urine sodium and potassium and plasma potassium were added as covariates (also including significant 2-way interactions). Only significant interactions with PA or PRA are reported in the table. SBP/DBP indicates systolic/diastolic daytime ambulatory blood pressure; FBG, fasting blood glucose.

* $P \leq 0.01$; † $0.01 < P \leq 0.05$.

further suggest that the association of PA with the MS is independent of PRA. No significant interaction between PRA and any of the covariates used in the models was found. In

contrast, a positive linear trend between PA and BP was only observed among older participants; a positive linear trend between PA and waist was only observed in men and increased

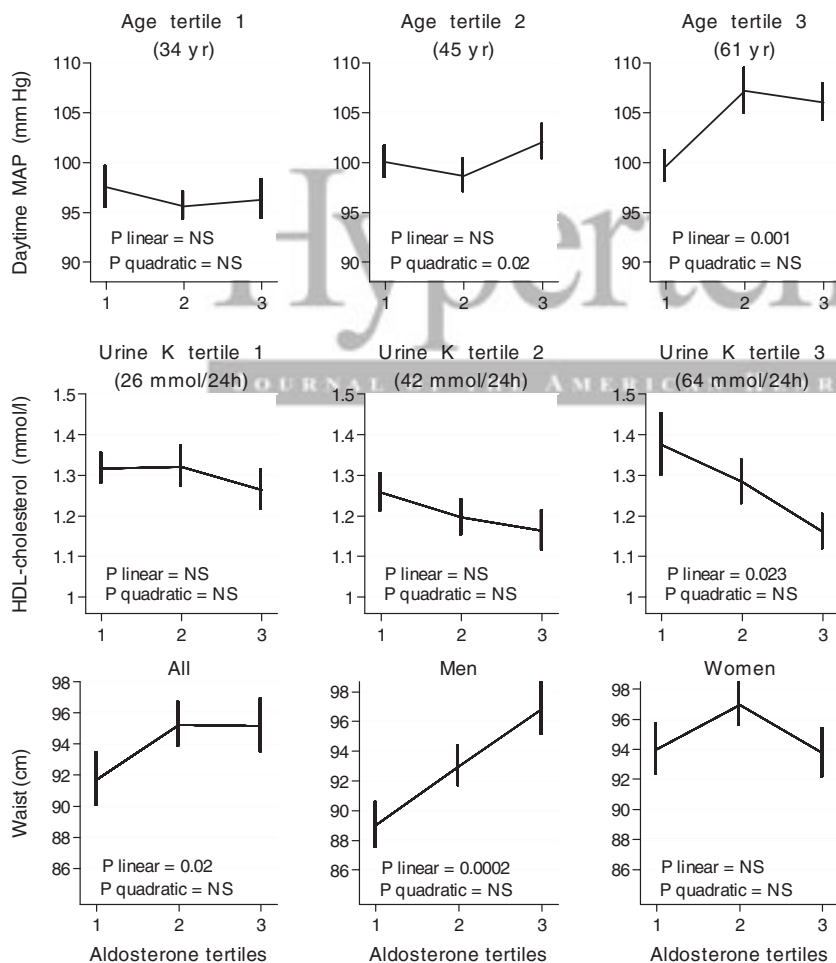


Figure 3. Relationships of selected MS components with selected tertiles. Horizontal lines connect means across aldosterone tertiles. Vertical bars represent SE. Traits are unadjusted. P linear and P quadratic are the P values of the regression coefficients for aldosterone in ASSOC models containing the mean-centered continuous aldosterone and its square with the dependent variable being MAP in the top, HDL cholesterol in the middle, and waist in the bottom. Separate models were fit in each tertile of age (top), urinary K excretion (middle), and by sex (bottom). MAP indicates mean blood pressure.

TABLE 3. Regression Coefficients of PA and PRA on MS Components

Independent Variables	Dependent Variable					
	Model 1		Model 2		Model 3	
	PA	PRA	PA	PRA	PA	PRA
MAP	0.06 (0.08)	0.001 (0.001)	0.06 (0.08)	-0.001 (0.001)	0.09 (0.07)	0.001 (0.001)
HDL	-6.10 (2.64)†	-0.004 (0.052)	-4.11 (2.71)	0.01 (0.05)	-5.01 (2.69)	-0.01 (0.05)
Triglycerides	0.73 (1.52)	0.06 (0.03)†	-1.25 (1.54)	0.05 (0.03)	-1.15 (1.48)	0.05 (0.03)
Waist	0.26 (0.11)†	-0.001 (0.001)	0.22 (0.11)	0.01 (0.01)	0.27 (0.11)†	-0.001 (0.001)
FBG	0.33 (0.47)	0.02 (0.01)†	-0.05 (0.48)	0.009 (0.004)	0.13 (0.47)	0.015 (0.009)
MS, 0, no; 1, yes	-	-	9.21 (2.62)*	0.05 (0.04)	8.65 (2.57)*	0.04 (0.04)
Urine Na					-0.05 (0.02)*	-0.0011 (0.0004)*
Plasma K					8.60 (3.01)*	-0.02 (0.05)
Interaction 1	0.02 (0.01)*	0.009 (0.004)†	0.02 (0.01)*	0.04 (0.01)†	0.02 (0.01)*	0.011 (0.004)*
	(age×MAP)	(age×HDL)	(age×MAP)	(age×HDL)	(age×MAP)	(age×HDL)
Interaction 2	-0.31 (0.13)†	-0.04 (0.01)*	-0.34 (0.13)*	-0.04 (0.01)*	-0.38 (0.13)*	-0.04 (0.01)†
	(sex×waist)	(trig×FBG)	(sex×waist)	(trig×FBG)	(sex×waist)	(trig×FBG)
Interaction 3						0.001 (0.001)†
						(sex×urine Na)

This table presents regression coefficients (SE). MAP indicates mean blood pressure; FBG, fasting blood glucose. * $P \leq 0.01$; † $0.01 < P \leq 0.05$.

with increasing urinary potassium excretion; the association between PA and HDL became more negative with increasing urinary potassium excretion (see also Figure 3). Analyses without participants with a suspicion of primary aldosteronism led to very similar results (ie, all estimates differed by <1 SE) and did not change our conclusions. Adding BMI as a covariate in the models eliminated the association between PA and waist. All of the other associations were robust to BMI adjustment.

Table 3 presents the regression coefficients of hormones on MS components together with their significant interactions. Unlike what is reported in Table 2, PA and PRA are now the dependent variables. With such models, one can assess the association of PA or PRA with each of the MS components (model 1). PA was significantly associated with mean ambulatory BP in older individuals, with waist circumference in men, and with HDL cholesterol, whereas PRA was associated with triglycerides, HDL cholesterol interacting with age, and fasting blood glucose interacting with triglycerides. An indicator variable for the MS was added in model 2, which showed that the incremental risk for the presence of the MS was significant for PA but not for PRA. This suggests that PA was associated with the clustering of cardiovascular risk factors per se, independently of its associations with BP, waist, and HDL. In model 3, potential confounding factors or variables on the pathway of the association, such as urinary sodium and plasma potassium, were added as covariates, but this did not substantially modify the observed associations. Because urinary potassium excretion was a significant determinant neither for PA nor for PRA (results not shown), it was not included as a covariate in these models. Similar results were obtained if BMI was added as a covariate or after excluding the participants with a suspicion of primary aldosteronism (data not shown).

Discussion

These results demonstrate that MS is independently associated with aldosterone levels (ie, PA levels are 20% higher in the presence versus the absence of the MS), independent of the MS components. This is not because of only a few MS individuals with elevated PA, because the whole PA distribution is shifted to the right in those with the MS. This finding is highly relevant in view of: (1) the increased mortality associated with the MS,⁶ (2) the potential role of aldosterone in the development of cardiovascular complications,^{16,17} and (3) the high prevalence of hypertension (40%) and MS (22%) in the general Seychelles population.³⁵ El-Gharbawy et al³⁶ found a positive association between aldosterone and left-ventricular hypertrophy in obese hypertensive blacks who had similar aldosterone values as those found in our study. We, therefore, consider the magnitude of the observed effect, although modest at the individual level, to potentially represent a substantial burden at the population level.

So far only 1 study has reported increased aldosterone in patients with a clustering of cardiovascular risk factors.²⁸ That study, which included 29 volunteers of unidentified ethnicity, also found increased PRA, in particular under a low-salt diet. In a recent TROPHY substudy,²⁷ no evidence for elevated aldosterone or PRA was found in subjects with the MS when compared with controls without the syndrome. That study, however, included mostly white participants and the results may, therefore, not apply to individuals of African descent.

The fact that PA and PRA were less correlated in participants with the MS and were associated differently with components of the MS suggest that these factors are related to the MS, at least in part, through independent mechanisms. The control of aldosterone secretion is complex.⁹ Although angiotensin II repre-

sents a major regulator of aldosterone, recent evidence from clinical trials underscores the role of aldosterone even in the presence of a blunted renin–angiotensin system. For instance, mineralocorticoid receptor blockade (spironolactone) further lowers BP in type 2 diabetic patients with nephropathy already treated with ACE inhibitors and angiotensin II receptor blockers (ARBs).³⁷ In the RALES¹⁵ and EPHEsus¹⁶ trials, spironolactone and eplerenone (2 aldosterone receptor blockers) significantly reduced all-cause and cardiovascular mortality compared with placebo when added to standard therapy.

In our study, which included 66% overweight participants, only PA, but not PRA, was significantly associated with daytime ambulatory BP. We found a significant interaction with age that showed aldosterone to be positively associated with BP only in older participants. Similarly, Grim et al³⁸ found that aldosterone, but not PRA, correlated positively with BP in individuals of African descent. In the latter study,³⁸ the correlation between BP and aldosterone was much stronger in blacks than in whites. El-Gharbawy et al³⁶ had shown previously that a positive correlation between aldosterone and BP in blacks was significant only among obese individuals. The selective aldosterone blocker eplerenone effectively lowered BP in black and white hypertensive patients³⁹ but was more effective than losartan only in blacks. These observations give further credence to the role of aldosterone in BP control, specifically in subjects of African descent.

We found that PA and PRA were negatively associated with HDL cholesterol, independent of all other MS components. This is consistent with previous reports.^{22–24} Recently, Gaudio et al⁴⁰ found HDL cholesterol to increase in response to a combination therapy of an ACE inhibitor and an ARB, which provides experimental evidence that the renin–angiotensin–aldosterone system interacts with lipid metabolism in humans. We have now demonstrated that these associations can also be found in individuals of African descent.

In our study PRA, but not aldosterone, was associated with fasting blood glucose. Although we did not measure insulin resistance, our results are consistent with previous observations showing an association between PRA and insulin resistance.^{26,27,41} Lind et al²⁶ found that insulin resistance was associated more strongly with PRA than aldosterone. Haenni et al⁴¹ found an increase in PRA, but not aldosterone, during a euglycemic hyperinsulinemic clamp test in 49 hypertensive patients. In a recent meta-analysis,⁴² ARB and ACE inhibitors seemed to decrease the incidence of diabetes mellitus by $\approx 20\%$ when compared with placebo, β -blockers, diuretics, or amlodipine. These findings would also suggest that the renin–angiotensin system is related to glucose intolerance independent of BP control.

Findings from in vitro studies provide some insight as to which mechanisms might explain the relationships between metabolic disturbances and the renin–angiotensin–aldosterone system. Human fat is now recognized to be a highly active endocrine tissue. It has been postulated that visceral fat might affect adrenal steroidogenesis.¹⁹ Goodfriend et al⁴³ observed that an oxidized derivative of linoleic acid, a fatty acid that is increased in obesity, stimulated aldosterone secretion by rat adrenal cells and correlated positively with PA and BP in humans. Ehrhart-Bornstein et al⁴⁴ have shown

that some (as yet unidentified) products secreted by adipocytes directly stimulate the secretion of aldosterone by human adrenocortical cells. Other potential links between the renin–angiotensin system and the MS point to plasma leptin⁴⁵ and adiponectin.⁴⁶

Our study has some limitations. Participants came from families with a history of hypertension: this common background clearly limits the generalizability of our results to the general population. However, because we also recruited family members with normal BP, the full BP range was represented. Furthermore, we corrected our models for ascertainment (ie, for the fact that recruitment was constrained to include 2 hypertensive siblings in each family). Such a correction aims to determine what would have been the results had the participants not been ascertained this way. This correction results in a better generalizability of our observations.²⁹

Perspectives

We report that aldosterone, but not PRA, is associated with the MS, even after adjusting for all of its separate components, which would indicate that the clustering of these factors per se is associated with aldosterone. Although an association does not necessarily imply a cause-effect relationship, this finding suggests that aldosterone might contribute to the increased cardiovascular disease risk in individuals of African descent with the MS. So far, there is no evidence that specific aldosterone blockade favorably impacts the clinical course of patients with the MS and/or is superior to other antihypertensive medications, but these hypotheses would be worth testing experimentally.

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Disclosures

None.

References

1. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report. *Circulation*. 2002;106:3143–3145.
2. Grundy SM, Hansen B, Smith SC Jr, Cleeman JI, Kahn RA, for Conference. Clinical Management of Metabolic Syndrome: Report of the American Heart Association/National Heart, Lung, and Blood Institute/American Diabetes Association Conference on Scientific Issues Related to Management. *Circulation*. 2004;109:551–556.
3. Dekker JM, Girman C, Rhodes T, Nijpels G, Stehouwer CDA, Bouter LM, Heine RJ. Metabolic syndrome and 10-year cardiovascular disease risk in the Hoorn Study. *Circulation*. 2005;112:666–673.

4. Isomaa B, Almgren P, Tuomi T, Forsen B, Lahti K, Nissen M, Taskinen MR, Groop L. Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care*. 2001;24:683–689.
5. Ford ES. The metabolic syndrome and mortality from cardiovascular disease and all-causes: findings from the National Health and Nutrition Examination Survey II Mortality Study. *Atherosclerosis*. 2004;173:309–314.
6. McNeill AM, Rosamond WD, Girman CJ, Golden SH, Schmidt MI, East HE, Ballantyne CM, Heiss G. The metabolic syndrome and 11-year risk of incident cardiovascular disease in the atherosclerosis risk in communities study. *Diabetes Care*. 2005;28:385–390.
7. Kohli P, Greenland P. Role of the metabolic syndrome in risk assessment for coronary heart disease. *JAMA*. 2006;295:819–821.
8. Laragh J. Laragh's lessons in pathophysiology and clinical pearls for treating hypertension. *Am J Hypertens*. 2001;14:307–310.
9. Connell JMC, Davies E. The new biology of aldosterone. *J Endocrinol*. 2005;186:1–20.
10. Vasan RS, Evans JC, Larson MG, Wilson PWF, Meigs JB, Rifai N, Benjamin EJ, Levy D. Serum aldosterone and the incidence of hypertension in nonhypertensive persons. *N Engl J Med*. 2004;351:33–41.
11. Freel EM, Connell JM. Mechanisms of hypertension: the expanding role of aldosterone. *J Am Soc Nephrol*. 2004;15:1993–2001.
12. Lim PO, Dow E, Brennan G, Jung RT, MacDonald TM. High prevalence of primary aldosteronism in the Tayside hypertension clinic population. *J Hum Hypertens*. 2000;14:311–315.
13. Lim PO, Rodgers P, Cardale K, Watson AD, MacDonald TM. Potentially high prevalence of primary aldosteronism in a primary-care population. *Lancet*. 1999;353:40.
14. Gordon RD, Ziesak MD, Tunny TJ, Stowasser M, Klemm SA. Evidence that primary aldosteronism may not be uncommon: 12% incidence among antihypertensive drug trial volunteers. *Clin Exp Pharmacol Physiol*. 1993;20:296–298.
15. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J. The Randomized Aldactone Evaluation Study Investigators. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med*. 1999;341:709–717.
16. Pitt B, White H, Nicolau J, Martinez F, Gheorghiadu M, Aschermann M, van Veldhuisen DJ, Zannad F, Krum H, Mukherjee R, Vincent J. Eplerenone reduces mortality 30 days after randomization following acute myocardial infarction in patients with left ventricular systolic dysfunction and heart failure. *J Am Coll Cardiol*. 2005;46:425–431.
17. Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, Bittman R, Hurlley S, Kleiman J, Gatlin M. The Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study Investigators. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med*. 2003;348:1309–1321.
18. Engeli S, Bohnke J, Gorzelniak K, Janke J, Schling P, Bader M, Luft FC, Sharma AM. Weight loss and the renin-angiotensin-aldosterone system. *Hypertension*. 2005;45:356–362.
19. Goodfriend TL, Egan BM, Kelley DE. Aldosterone in obesity. *Endocr Res*. 1998;24:789–796.
20. Sowers JR, Nyby M, Stern N, Beck F, Baron S, Catania R, Vlachis N. Blood pressure and hormone changes associated with weight reduction in the obese. *Hypertension*. 1982;4:686–691.
21. Rocchini AP, Katch VL, Grekin R, Moorehead C, Anderson J. Role for aldosterone in blood pressure regulation of obese adolescents. *Am J Cardiol*. 1986;57:613–618.
22. Goodfriend TL, Egan BM, Kelley DE. Plasma aldosterone, plasma lipoproteins, obesity and insulin resistance in humans. *Prostaglandins Leukot Essent Fatty Acids*. 1999;60:401–405.
23. Goodfriend TL, Egan B, Steptniakowski K, Ball DL. Relationships among plasma aldosterone, high-density lipoprotein cholesterol, and insulin in humans. *Hypertension*. 1995;25:30–36.
24. Lind L, Lithell H, Wide L, Ljunghall S. Metabolic cardiovascular risk factors and the renin-aldosterone system in essential hypertension. *J Hum Hypertens*. 1992;6:27–29.
25. Goodfriend TL, Kelley DE, Goodpaster BH, Winters SJ. Visceral obesity and insulin resistance are associated with plasma aldosterone levels in women. *Obes Res*. 1999;7:355–362.
26. Lind L, Reneland R, Andersson PE, Haenni A, Lithell H. Insulin resistance in essential hypertension is related to plasma renin activity. *J Hum Hypertens*. 1998;12:379–382.
27. Egan BM, Papademetriou V, Wofford M, Calhoun D, Fernandes J, Riehle JE, Nesbitt S, Michelson E, Julius S. Metabolic syndrome and insulin resistance in the TROPHY sub-study: contrasting views in patients with high-normal blood pressure. *Am J Hypertens*. 2005;18:3–12.
28. Egan BM, Steptniakowski K, Goodfriend TL. Renin and aldosterone are higher and the hyperinsulinemic effect of salt restriction greater in subjects with risk factors clustering. *Am J Hypertens*. 1994;7:886–893.
29. Bochud M, Elston RC, Maillard M, Bovet P, Schild L, Burnier M. Heritability of renal function in hypertensive families of African descent in the Seychelles (Indian Ocean). *Kidney Int*. 2005;67:61–69.
30. Bochud M, Bovet P, Elston RC, Paccaud F, Falconnet C, Shamlaye C, Burnier M. High heritability of ambulatory blood pressure in families of East African descent. *Hypertension*. 2005;45:445–450.
31. Poulsen K, Jorgensen J. An easy radioimmunological microassay of renin activity, concentration and substrate in human and animal plasma and tissues based on angiotensin I trapping by antibody. *J Clin Endocrinol Metab*. 1974;39:816–825.
32. Nussberger J, Fasanella d'Amore T, Porchet M, Waeber B, Brunner DB, Brunner HR, Kler L, Brown AN, Francis RJ. Repeated administration of the converting enzyme inhibitor cilazapril to normal volunteers. *J Cardiovasc Pharmacol*. 1987;9:39–44.
33. Nussberger J, Waeber B, Brunner HR, Burris J, Vetter W. Highly sensitive microassay for aldosterone in unextracted plasma: comparison with two other methods. *J Lab Clin Med*. 1984;104:789–796.
34. S.A.G.E. (Statistical Analysis for Genetic Epidemiology) [computer program]. Version 5.0. Available at: <http://darwin.cwru.edu/sage/index.php>. Accessed May 20, 2006.
35. Bovet P, Shamlaye C, Gabriel A, Riesen W, Paccaud F. Prevalence of cardiovascular risk factors in a middle-income country and estimated cost of a treatment strategy. *BMC Public Health*. 2006;6:9. Available at: www.biomedcentral.com/1471-2458/6/9. Accessed May 23, 2006.
36. El-Gharbawy AH, Nadig VS, Kotchen JM, Grim CE, Sagar KB, Kaldunski M, Hamet P, Pausova Z, Gaudet D, Gossard F, Kotchen TA. Arterial pressure, left ventricular mass, and aldosterone in essential hypertension. *Hypertension*. 2001;37:845–850.
37. Rossing K, Schjoedt KJ, Smidt UM, Boomsma F, Parving HH. Beneficial effects of adding spironolactone to recommended antihypertensive treatment in diabetic nephropathy: a randomized, double-masked, cross-over study. *Diabetes Care*. 2005;28:2106–2112.
38. Grim CE, Cowley AW Jr, Hamet P, Gaudet D, Kaldunski ML, Kotchen JM, Krishnaswami S, Pausova Z, Roman R, Tremblay J, Kotchen TA. Hyperaldosteronism and hypertension: ethnic differences. *Hypertension*. 2005;45:766–772.
39. Flack JM, Oparil S, Pratt JH, Roniker B, Garthwaite S, Kleiman JH, Yang Y, Krause SL, Workman D, Saunders E. Efficacy and tolerability of eplerenone and losartan in hypertensive black and white patients. *J Am Coll Cardiol*. 2003;41:1148–1155.
40. Gaudio G, Guasti L, Schizzarotto A, Simoni C, Crespi C, Cimpanelli M, Klersy C, Grandi AM, Riganti G, Venco A. Changes in plasma lipids during renin-angiotensin system blockade by combination therapy (enalapril plus valsartan) in patients with diabetes and hypertension. *J Cardiovasc Pharmacol*. 2005;45:362–366.
41. Haenni A, Reneland R, Lind L, Lithell H. Serum aldosterone changes during hyperinsulinemia are correlated to body mass index and insulin sensitivity in patients with essential hypertension. *J Hypertens*. 2001;19:107–112.
42. Scheen AJ. Renin-angiotensin system inhibition prevents type 2 diabetes mellitus. Part 1. A meta-analysis of randomised clinical trials. *Diabetes and Metabolism*. 2004;30:487–496.
43. Goodfriend TL, Ball DL, Egan BM, Campbell WB, Nithipatikom K. Epoxy-keto derivative of linoleic acid stimulates aldosterone secretion. *Hypertension*. 2004;43:358–363.
44. Ehrhart-Bornstein M, Lamounier-Zepter V, Schraven A, Langenbach J, Willenberg HS, Barthel A, Hauner H, McCann SM, Scherbaum WA, Bornstein SR. Human adipocytes secrete mineralocorticoid-releasing factors. *Proc Natl Acad Sci U S A*. 2003;100:14211–14216.
45. Suter PM, Locher R, Hasler E, Vetter W. Is there a role for the ob gene product leptin in essential hypertension? *Am J Hypertens*. 1998;11:1305–1311.
46. Rahmouni K, Correia MLG, Haynes WG, Mark AL. Obesity-associated hypertension: new insights into mechanisms. *Hypertension*. 2005;45:9–14.