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The Association of Serum Aldosterone with Sex, Age, and Sodium Status

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Abstract

Context: In a prior study we observed that adjustment of serum aldosterone for age, sex and sodium status led to confirmation of our hypothesis of bimodality of serum aldosterone in low-renin hypertension; the hypothesis was not statistically supported without this adjustment. Here we aim to further characterize the effect of this statistical adjustment on the normality of the distribution of serum aldosterone.

Methods: We analyzed data from 1486 normotensive men and women, aged 29 to 85, in the sixth examination cycle of the Framingham Offspring Study. We used independent two sample t-tests, regression of natural-log-transformed values of aldosterone on age, sex, and urinary sodium: creatinine ratio, the dip test for unimodality, dotplots, and Q-Q plots to study the normality of the distribution of aldosterone concentrations with and without statistical adjustment for the covariates listed above.

Results: The proportion of variability of serum aldosterone concentrations explained by age, sex, and urine sodium:creatinine ratio was 0.91%,1.3%, and 8%, respectively ($p > 0.005$). The distribution of adjusted serum aldosterone was unimodal (dip test: 2.26 ± 0.17 ng/dL, $p = 0.997$); when unadjusted, the distribution was not unimodal (dip test: 2.26 ± 0.50 ng/dL, $p < 0.00005$). The dotplot and Q-Q plot also showed a more normal distribution of serum aldosterone concentrations after adjustment.

Conclusion: Adjustment of serum aldosterone for age, sex, and urine sodium:creatinine ratio leads to a more normal aldosterone distribution. Further study is needed to determine whether the use of this adjustment in testing for primary aldosteronism may improve the accuracy of clinical testing

Keywords: Aldosterone • Age • Sex • Sodium

Introduction

Primary aldosteronism (PA) is now recognized as the most common cause of secondary hypertension, occurring in at least 5%, and perhaps more than 10%, of individuals with arterial hypertension [1]. Although the aldosterone-to-renin ratio (ARR) is widely recommended for screening or case detection, the rate of screening for primary aldosterone remains very low [1,2]. One cause for the low rate of screening may be the difficulty that providers have in interpreting the results of the ARR, as its interpretation may not be straightforward [3]. Further, even in cases of confirmed PA, there is a wide range of serum aldosterone levels that are found; circulating aldosterone levels may be in the high-normal range, or elevated above the reference limits. This results in a low level of diagnostic accuracy of the ARR that, in most cases, does not lead to a firm diagnosis of PA. The diagnosis then requires confirmatory tests, which usually require potentially harmful salt loading, as well as additional expense and burden [4]. An increase in the diagnostic

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accuracy of the serum aldosterone concentration might simplify and improve the diagnosis of PA.

In a recent study, in which we postulated that circulating aldosterone levels in low-renin hypertension would have a bimodal distribution, we observed that the frequency distribution of unadjusted serum aldosterone conformed to a pattern that was suggestive of a bimodal distribution, but not statistically different from a unimodal pattern (P=0.11). We hypothesized that a possible bimodal distribution of aldosterone might be obscured by factors that are known to affect the serum aldosterone concentration. When we adjusted the serum aldosterone concentration for three such factors that were readily available in the population we studied, namely age, sex, and the urine sodium:creatinine ratio, the pattern was clearly bimodal, and the P value for lack of unimodality was 0.008 [5].

This observation suggested the following hypothesis: Aldosterone, as commonly measured, may be affected by confounders such as age, sex, and sodium status, causing a distribution of serum aldosterone that differs from a normal distribution; adjustment for these factors may result in a more normal distribution of serum aldosterone. Because the measured aldosterone level may be decisive in the interpretation of tests for primary aldosteronism, such as the aldosterone-renin ratio (ARR) and the saline infusion test, the effect of this statistical adjustment would be of interest, and possible clinical value. We selected a population of normotensive individuals in which to study the effect of this statistical adjustment.

Methods

We analyzed data from the cohort of 3,345 individuals who attended the sixth examination cycle of the Framingham Offspring Study. These individuals were the children, and their spouses, of the original members of the Framingham Heart Study [6]. The sixth examination cycle was performed from 1995 to 1998. In addition to medical history, physical examination, and standard laboratory tests, blood was drawn for later measurement of serum aldosterone and plasma renin concentrations. This blood was drawn between 8:00 and 10:00 AM, in subjects who were fasting and ambulatory, but remained recumbent for 5-10 minutes before blood was drawn. Aldosterone and renin were measured in 2004. Further details are presented in reference (5)

Subjects were excluded if they had a condition, or were taking medication, deemed likely to affect the levels of circulating aldosterone or renin. Exclusions were congestive heart failure, eGFR less than 60 ml/minute, diabetes mellitus, bilateral edema, and present treatment with any antihypertensive medication . For this analysis we excluded all individuals with hypertension (systolic BP ≥140 mm Hg, or diastolic BP ≥90 mm Hg.). We also excluded 42 subjects who lacked a measurement of the urine Na:creatinine ratio. After exclusions, the final sample for the present analysis consisted of 1,468 normotensive participants, 652 men and 816 women, aged 29 to 85 years.

We used independent two sample t-tests, regression of natural-log-transformed values of serum aldosterone concentration on age, sex, and urinary sodium:creatinine ratio, the dip test for unimodality, dotplots, and Q-Q plots to evaluate the normality of the distribution of serum aldosterone levels with and without statistical adjustment for these key covariates.

Results and Discussion

The characteristics of the participants are shown in Table 1. All participants in the Framingham Offspring Study were considered to be white.

Variable	Statistics
Age in years (SD)	55.3 (9.23)
Male, No. (%)	652 (43.9)
Body mass index, kg/m2, mean (SD)	26.7 (4.46)
Systolic BP, mm Hg, mean (SD)	118.3 (12.06)
Diastolic BP, mm Hg, mean (SD)	72.9 (8.01)
Current smoking, No. (%)	241 (16.3)
Urine sodium/creatinine, mmol/g, mean (SD)	87 .6 (48.2)
Family history of hypertension, No. (%)	682 (45.9)

Table 1. Characteristics of the study participants (n=1486).

Multiple regression of age, sex and urine sodium:creatinine ratio on the natural log of serum aldosterone is shown in Table 2. Age, sex and urine sodium:creatinine ratio were each significantly associated with serum aldosterone levels.

Variable (per unit)	Coefficient	Standard Error	t	P	95% Confidence Interval	
Age (year)	43426	13384	-3.24	0.001	-.0069679,	-0.00172
Sex (M vs. F)	1216984	251	4.85	<0.0005	072463,	-0.17093
Urine Na/ creatinine ratio	2514505	195221	-12.88	<0.0005	-.2897444,	, -.2131566
Constant	2.583996	848146	30.47	0.001	2.417626	, -.2131566
Model adjusted R-squared = 0.1118						

Table 2. Multiple regression analysis of age, sex and urine Na:creatinine ratio on aldosterone (log) (n=1486)

The relation of age to serum aldosterone is shown in Figure 1. The average unadjusted aldosterone level was lower in older individuals (9 ng/dL) as compared to younger individuals (13 ng/dL).

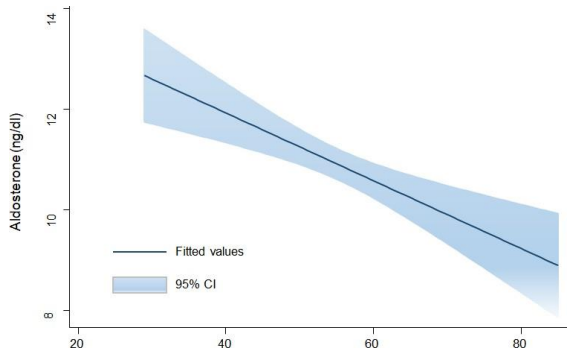

Figure 1. The relation of serum aldosterone concentration to age.

The relation of sex to aldosterone levels is shown in Figure 2. The mean (SD) unadjusted serum aldosterone level was 10.4 (5.89) ng/dl in women, and 11.3 (6.14) ng/dl in men (P=0.0049).

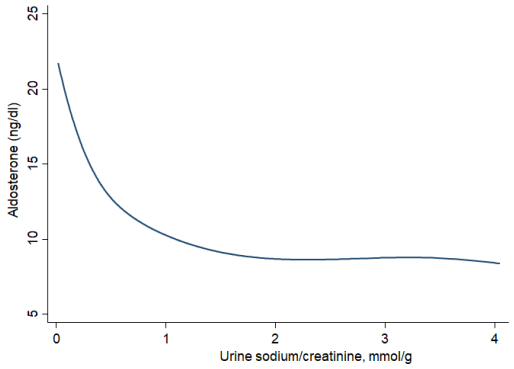

Figure 2. Serum aldosterone concentration in male and female participants.

The relation of urine sodium:creatinine ratio to serum aldosterone is shown in Figure 3. Aldosterone appears to rise sharply when the sodium:creatinine ratio is lower than 100 mEq per gram, but is relatively flat above that ratio.

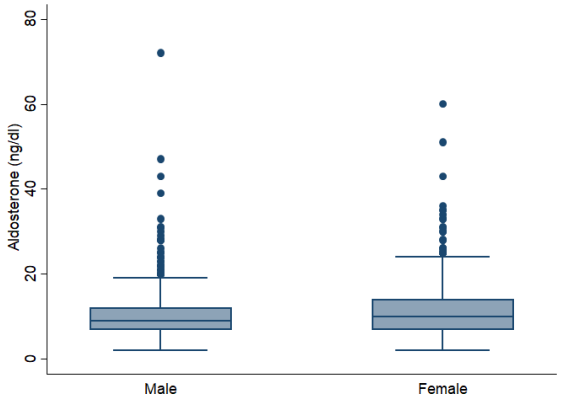

Figure 3. The relation of serum aldosterone concentration to the urine sodium/creatinine ratio.

The proportion of variability explained by age was about 1%, the variability explained by sex was about 1%, and the variability explained by the urine sodium:creatinine ratio was about 8% (Table 3).

Variable	Proportion of Variability Explained	95% Confidence Interval (lower – upper)
Age	(Omega-Squared)	0.00217 - 0.02018
Sex	0.0091	0.00417 - 0.02509
Urine sodium/creatinine ratio	0.0126	0.05729 - 0.10459
Model adjusted R-squared = 0.0948		

Table 3. Proportion of variability of serum aldosterone explained (n=1486)

The results of the dip test for unimodality are shown in Table 4. The dip statistic measures the departure of a sample from unimodality [7]. The non-significant P-values achieved when serum aldosterone concentration was adjusted for urine sodium:creatinine ratio, and when it was adjusted for age, sex, and urine sodium:creatinine ratio, indicate unimodality. The significant P-values achieved when aldosterone level was unadjusted, or adjusted only for age or for sex, indicate that the distribution of unadjusted or minimally adjusted aldosterone was not unimodal.

Aldosterone (ng/dl) (log)	Mean (SD)	Median (Min, Max)	dip statistics	P-value
Unadjusted	2.26 (0.5)	2.3 (0.69, 4.28)	0.0501	<0.00005
Age adjusted	2.26 (0.047)	2.27 (2.11, 2.4)	0.0269	<0.00005
Gender adjusted	2.29 (2.22, 2.29)	2.29 (2.22, 2.29)	0.2806	<0.00005
Na adjusted	2.26 (0.154)	2.29 (1.55, 2.52)	0.0058	0.997
Age, gender and Na adjusted	2.26 (0.17)	2.28 (1.5, 2.63)	0.0051	0.997
Dip statistics measure departure of a sample from unimodality. Non-significant P-value indicates unimodality.				

Table 4. Summary of dip test (n=1486)

Figure 4 shows the highly skewed distribution of unadjusted serum aldosterone concentration, while Figure 5 shows an apparently normal distribution after adjusting aldosterone concentration for age, sex, and sodium:creatinine ratio.

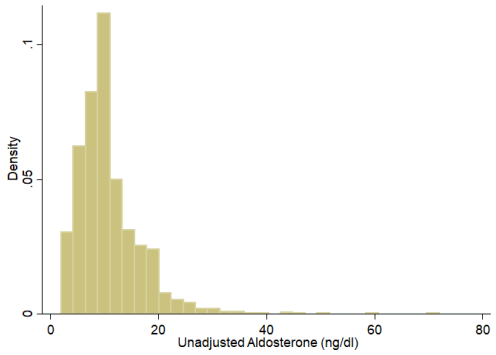

Figure 4. The distribution of unadjusted serum aldosterone concentration.

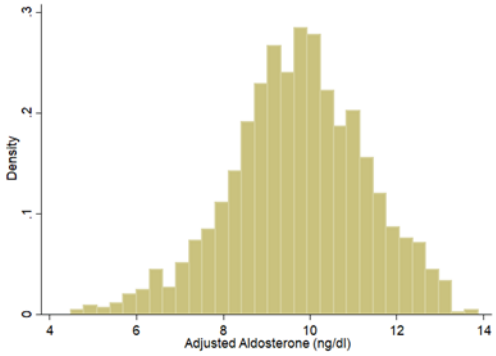

Figure 5. The distribution of adjusted serum aldosterone concentration.

Figure 6 shows the Q-Q plot for serum aldosterone concentration before adjustment for age, sex and urine sodium:creatinine ratio, and Figure 7 shows the more normal distribution after the adjustment.

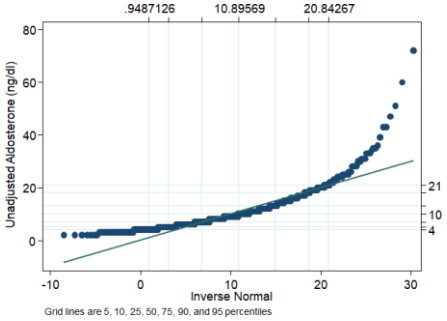

Figure 6. Q-Q plot of unadjusted serum aldosterone concentration.

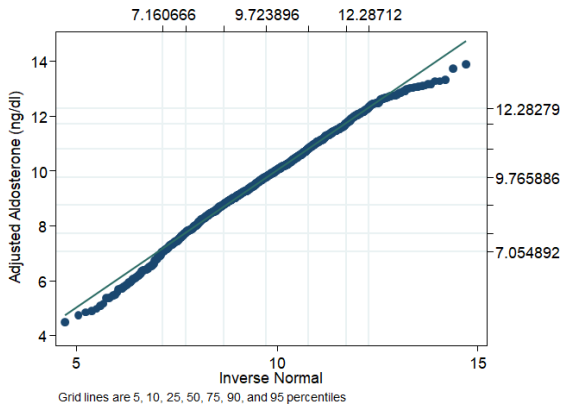

Figure 7. Q-Q plot of adjusted serum aldosterone concentration.

Conclusion

In this investigation we aimed to better understand the factors responsible for an observation made in our previous report [5]. In that report our hypothesis that serum aldosterone concentrations would have a bimodal distribution in individuals with low-renin hypertension was statistically confirmed when we adjusted aldosterone concentrations for age, sex, and the urine sodium:creatinine ratio, but was not supported without this statistical adjustment.

In the present investigation we confirm, in the same large, community-based population, looking at normotensive individuals, that age and sex were weakly associated with serum aldosterone concentrations, but, as expected, urine sodium was more strongly associated [8]. When we adjusted for all three variables several statistical indicators revealed a more normal distribution of the adjusted serum aldosterone concentrations.

In the present investigation we confirm, in the same large, community-based population, looking at normotensive individuals, that age and sex were weakly associated with serum aldosterone concentrations, but, as expected, urine sodium was more strongly associated [8-10]. When we adjusted for all three variables several statistical indicators revealed a more normal distribution of the adjusted serum aldosterone concentrations [1].

It is recognized that an elevated ARR is more likely to be associated with a low renin level than with an elevated aldosterone level [4]. Many investigators therefore recommend that a minimal level of serum aldosterone concentration be present before the ARR is considered to be positive, that is, suggestive of a diagnosis of primary aldosteronism. We suggest that an adjustment of the measured serum aldosterone concentration that provides a more accurate approximation of the actual physiologic activity of the hormone (or at least a more normal distribution) may improve the test.

Characteristics of the ARR. Such a correction might also improve the performance of confirmatory tests for PA, several of which also depend on precise estimation of the levels of serum aldosterone.

Our study does have some limitations. We utilized available urinary indices for sodium status (spot urine sodium measurements). Although there may be inherent variability in spot urine sodium measurements, it does reflect a variable that would be readily available to a clinician at the point of care. We recognize the role of potassium on aldosterone activity; however urine potassium measurements were not available in the Framingham Offspring Study

These considerations lead to the following hypothesis: Adjustment of serum aldosterone levels for age, sex, and a measure of urine sodium excretion may result in a more normal distribution of the serum aldosterone concentration. This may lead to an improvement in the diagnostic performance of the ARR, and of other tests whose interpretation depends on the serum aldosterone level, such as the saline infusion test and Captopril challenge test.

In populations similar to those described in the sixth examination cycle of the Framingham Offspring Study, i.e. white men and women older than 30 years; we suggest that the coefficients and constants

shown in Table 2 may be used to test this hypothesis. In other populations appropriate normative data would be required. Widely used statistical software makes this adjustment relatively simple.

Acknowledgments

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