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Association of plasma renin activity and aldosterone–renin ratio with prevalence of chronic kidney disease: the Kaiser Permanente Southern California cohort

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Background **Although higher plasma renin activity (PRA) is associated with poor clinical outcomes including higher death and cardiovascular events, its association with prevalence of chronic kidney disease (CKD) is not clear. We hypothesized that higher levels of PRA and lower levels of aldosterone-to-PRA ratios (ARRs) are associated with greater CKD prevalence in a large and ethnically diverse population of southern California who underwent uniform healthcare.**

Methods **During the period 1 January 1998 to 31 October 2009, the adult population who was under the care of Kaiser Permanente Southern California with documented outpatient values of PRA and minimum of 6 months continuous enrollment were examined. CKD defined by an estimated glomerular filtration rate (eGFR) less than 60 ml/min per 1.73 m^2. PRA levels and ARR were categorized into quartiles. Multivariate logistic regressions were used to calculate odds ratios for CKD based on PRA controlling for age, sex, black race, diabetes status, hypertension, and type of medication use.**

Results **We identified 9495 individuals including 7887 with hypertension. Study population included 60% women, 35% whites, 20% blacks, 20% Hispanics, and 26% diabetic patients. Adjusted odds ratios (95% confidence interval) for CKD across second, third, and fourth quartiles of PRA quartile (reference: first quartile) were 1.5 (1.2–1.7), 1.5 (1.3–1.8), and 2.2 (1.9–2.6), respectively. Each 10-unit increase in PRA was associated with odds ratio for CKD of 1.3 (1.2–1.4). ARR showed a similar but inverse trend with CKD.**

Conclusion **Higher levels of PRA are associated with greater rates of CKD in our large ethnically diverse population of primarily hypertensive patients. Whether modulation of PRA can mitigate prevalence of CKD needs to be studied in interventional trials. *J Hypertens* 29:2226–2235 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Keywords: chronic kidney disease, epidemiology, plasma renin activity, risk factors

Abbreviations: ALLHAT, antihypertensive and lipid lowering to prevent heart attack trial; ARR, aldosterone-to-PRA ratio; BUN, blood urea nitrogen; CKD, chronic kidney disease; eGFR, estimate glomerular filtration rate; ICD-9, international classification of diseases, ninth revision; KPSC, Kaiser Permanente Southern California; OR, odds ratio; PRA, plasma renin activity; RAAS, renin–angiotensin–aldosterone system; RAS, renin–angiotensin system

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Introduction

Assessment of plasma renin activity (PRA) is often used as a surrogate of the renin–angiotensin–aldosterone system (RAAS) [1]. Whereas the modulation of RAAS happens frequently under physiologic conditions including preservation of vascular tone and maintenance of volume, inappropriate upregulation of this system can lead to detrimental outcomes namely in the vascular system. Past observations have been inconsistent in determining whether high PRA is associated with vascular diseases, and the same has held true when evaluating PRA as a prognosticator of future outcomes [2,3]. The studies that have demonstrated a prognostic value of PRA have been conducted primarily in patients with hypertension or those with preexistent heart disease [4–8]. Additional studies have demonstrated an association of high PRA and cardiac outcomes, but many of these studies were performed as posthoc analyses of large heart failure or ischemic heart disease trials wherein PRA was not assessed as the primary or independent predictor [9–12]. Whereas these studies have examined cardiovascular and/or cerebrovascular outcomes, to the best of our knowledge, no study has investigated the putative relationship of PRA and prevalence of chronic kidney disease (CKD). In this study, we sought to examine the hypothesis whether higher levels of PRA are associated with moderate to advanced CKD defined using estimated glomerular filtration rate (eGFR) within a large ethnically diverse primarily hypertensive population.

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Methods

Study population

The Kaiser Permanente Southern California (KPSC) health system is a prepaid integrated health plan with 12 medical centers and over 100 satellite clinics. Geographically, the centers span from San Diego to Bakersfield, California. The patient population is ethnically diverse with various socioeconomic backgrounds that reflect the underlying population in southern California. As of October 2009, KPSC had an active membership of 3.3 million. All members have similar benefit structures with co-pays and deductibles for medications and healthcare. Members have similar access to all healthcare facilities, procedures, and referrals. The data for this study were collected during routine clinical practice wherein individual healthcare providers had determined the need for the laboratory measurements, medications, and procedures. The study protocol was approved by the regional institutional review board and exempted from informed consent.

This cross-sectional study covered the period 1 January 1998 through 31 October 2009. Participants included all persons 18 years or older with documented outpatient measurement of PRA and serum aldosterone that were drawn concurrently. Inpatient values for PRA and aldosterone were excluded for consideration in the study. If participants had multiple PRA values, the first value in the observation period was used and all associated results were determined relative to that PRA result date. Participants were categorized into quartiles based on the PRA distribution.

Data on age, sex, race/ethnicity (when available), laboratory values, medication usage, and comorbidities were extracted from internal computerized databases, which included laboratory databases, disease registries, and electronic medical charts. Using electronic medical records that was based on self-description, race/ethnicity was categorized as white, black, Hispanic, Asian, or other. Individuals were categorized as other when they were not classified as any of the above or where no race data were available. Kidney function was determined by eGFR using the four-point abbreviated modification of diet in renal disease formula [13]. Proteinuria was determined using urine dipstick results where available. A dipstick result showing greater than 2+ protein was determined to be positive for proteinuria. The presence of comorbidities was assessed based on inpatient and outpatient diagnoses recorded in the health records. In order to ensure that comorbidities were reliably captured, we required individuals to have had continuous enrollment in the healthplan 3 months prior to and 3 months after the PRA measurement for inclusion in the study.

Patients with hypertension were identified by international classification of diseases, ninth revision (ICD-9) coding according to a previously validated algorithm [14]. Among patients with hypertension, those who required antihypertensive medications were identified. Antihypertensive medication usage was determined by any medication prescribed within 90 days prior to the PRA laboratory date. Given the potential effects of antihypertensive medications on PRA, these medications were further categorized as either diuretics/natriuretics, renin–angiotensin system (RAS) blockers, or RAS suppressors (e.g., as beta-blockers). Laboratory values drawn within 3 months prior to or after PRA were collected and reported.

PRA values used in this study were single measurements obtained at varying times and with different clinical scenarios. Thus, PRA levels can fluctuate and may not necessarily reflect RAS status but rather physiologic variations from activity and daily rhythm [15,16]. We also evaluated both serum aldosterone levels and the aldosterone-to-PRA ratio (ARR) in an attempt to control for confounding variations in PRA. Particularly, the ARR would control for any variations in both PRA and aldosterone, as any clinical scenario that would result in PRA changes would also proportionately affect aldosterone.

All PRA measurements were made with an activity assay measuring angiotensin I generation in an American College of Pathology/Clinical Laboratory Improvement Act (CLIA)-certified laboratory and are reported as ng/ml per h. The test is performed by Quest Diagnostics Nichols Institute using the Sealey PRA test [17], which utilizes radioimmunoassay for quantization.

Analytic approach

The primary objective of the study was to determine whether higher levels of PRA were associated with increased risk for CKD as defined by two different degrees in severity of CKD, that is, less than 60 or less than 30 ml/min per 1.73 m^2. Logistic regression was employed to determine odds ratio (OR) for CKD defined as eGFR less than 60 or less than 30 ml/min per 1.73 m^2 at different PRA quartiles compared with quartile 1. Multivariate adjustments were performed to control for potential confounders of age older than 59 years, sex, black race, diabetes mellitus, and use of antihypertensive medications as categorized above. PRA was also treated as a continuous variable to evaluate the linear trend.

In secondary analyses, logistic regression models were used to estimate OR for aldosterone only and the ratio of aldosterone to PRA (ARR) as explanatory variables controlling for the same confounders as above.

Within each PRA quartile, prevalence of CKD and other comorbidities were determined for each quartile and comparisons were made by either chi-squared test or Cochran–Armitage test (Table 1). Additional data on age, sex, race, and laboratory values were determined among each quartile and trend across the quartiles was investigated (Tables 2 and 3). Mean PRA was also

Table 1 Characteristics of study cohort plasma renin activity distribution

Characteristics	All ($N=9495$)	Quartile 1 (<0.51) ($N=2375$)	Quartile 2 (0.51–1.40) ($N=2434$)	Quartile 3 (1.40–3.70) ($N=2312$)	Quartile 4 (>3.70) ($N=2374$)	P
PRA [median (Q1–Q3)]	1.40 (0.51–3.70)	0.20 (0.19–0.33)	0.92 (0.75–1.18)	2.20 (1.80–2.80)	7.50 (5.01–13.10)	n/a
Aldosterone [median (Q1–Q3)]	10.00 (5.00–18.20)	10.00 (5.00–18.00)	8.35 (4.00–15.00)	10.00 (5.00–17.00)	12.00 (6.00–25.00)	<0.001[a]
ARR [median (Q1–Q3)]	6.36 (2.32–20.00)	45.0 (20.0–90.0)	9.0 (4.3–16.9)	4.3 (2.2–7.9)	1.5 (0.6–3.3)	<0.001[a]
Age [years, mean (SD)]	56.4 (15.6)	59.8 (13.1)	57.3 (15.1)	54.4 (16.5)	53.9 (17.0)	<0.001[a]
Sex						
Female (%)	60.4	58.3	62.5	60.0	60.9	0.2312[b]
Male (%)	39.6	41.7	37.5	40.0	39.1	
Race						
White (%)	35.4	32.0	33.3	37.4	39.1	<0.001[c]
Black (%)	20.3	28.7	21.7	15.4	15.2	
Hispanic (%)	19.6	18.5	19.7	20.3	19.8	
Asian/Pacific (%)	8.9	8.4	9.9	9.4	8.0	
Other (%)	15.8	12.6	15.4	17.5	18.0	
Hypertension (%)	83.1	91.8	82.0	75.1	83.2	<0.001[b]
Diabetes (%)	25.8	28.0	25.5	23.1	26.4	0.0819[b]
Ischemic heart disease (%)	20.4	23.3	18.9	18.5	20.8	0.0364[b]
Congestive heart failure (%)	8.3	8.7	8.3	7.4	8.9	0.9792[b]
Cerebrovascular disease (%)	9.2	11.5	9.4	7.2	8.7	<0.001[b]
CKD (eGFR, ml/min per 1.73 m^2)						
<30 (%)	3.0	2.3	2.9	2.9	4.0	<0.001[c]
<60 (%)	17.8	15.4	17.4	16.0	22.1	
≥60 (%)	71.1	74.9	71.0	72.5	66.2	
Not available (%)	8.1	7.4	8.7	8.6	7.7	

ARR, aldosterone-to-PRA ratio; eGFR, estimated glomerular filtration rate; PRA, plasma renin activity. [a]Test for linear trend. [b]Cochran–Armitage trend test. [c]Chi-squared test.

Table 2 Laboratory characteristics where available in plasma renin activity cohort

	All ($N=9495$)		Quartile 1 (<0.51) ($N=2375$)		Quartile 2 (0.51–1.40) ($N=2434$)		Quartile 3 (1.40–3.70) ($N=2312$)		Quartile 4 (>3.70) ($N=2374$)		
Laboratory findings	Value	*n*	Value	*n*	Value	*n*	Value	*n*	Value	*n*	*P*
Creatinine [mean (SD)]	1.1 (0.7)	8884	1.1 (0.7)	2247	1.1 (0.8)	2261	1.0 (0.7)	2150	1.1 (0.8)	2226	0.010[a]
Serum BUN [mean (SD)]	17.1 (10.2)	6563	15.8 (8.6)	1699	16.9 (10.1)	1673	17.0 (10.3)	1511	18.8 (11.6)	1680	<0.001[a]
eGFR [mean (SD)]	80 (31)	8727	80 (28)	2200	80 (32)	2223	81 (29)	2113	77 (35)	2191	0.005[a]
Urine proteinuria (%)	13.7	3509	15.5	870	14.2	887	12.8	831	12.5	921	0.042[b]
Serum potassium [mean (SD)]	3.9 (0.6)	8926	3.8 (0.6)	2247	4.0 (0.6)	2284	4.0 (0.6)	2164	4.0 (0.6)	2231	<0.001[a]
Serum uric acid [mean (SD)]	6.3 (2.2)	1294	6.0 (2.0)	315	6.1 (2.2)	333	6.4 (2.3)	318	6.7 (2.3)	328	<0.001[a]
Serum sodium [mean (SD)]	139 (3)	8660	139 (4)	2183	139 (3)	2220	139(3)	2083	138 (3)	2174	<0.001[a]
Serum bicarbonate [mean (SD)]	28 (3)	8583	28 (3)	2162	28 (3)	2201	28 (3)	2063	28 (3)	2157	<0.001[a]
Hemoglobin A1C [mean (SD)]	6.8 (1.6)	2908	6.8 (1.6)	755	6.9 (1.6)	713	6.8 (1.5)	654	6.8 (1.6)	786	0.204[a]
Serum hemoglobin [mean (SD)]	13.4 (1.7)	7110	13.3 (1.6)	1756	13.3 (1.7)	1802	13.6 (1.7)	1723	13.6 (1.8)	1829	<0.001[a]
Serum ferritin [mean (SD)]	232 (441)	1361	208 (283)	316	260 (641)	375	212 (355)	315	243 (356)	355	0.619[a]
Serum phosphorous [mean (SD)]	3.5 (0.9)	2661	3.59 (0.9)	695	3.6 (0.8)	684	3.5 (0.9)	581	3.6 (0.9)	701	0.943[a]
Total cholesterol [mean (SD)]	196 (45)	6088	194 (45)	1548	196 (44)	1547	198 (45)	1472	198 (48)	1521	0.011[a]
LDL [mean (SD)]	115 (37)	6004	115 (36)	1545	115 (37)	1529	116 (35)	1441	115 (39)	1489	0.663[a]

BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; LDL, low-density lipoprotein. [a]Test for linear trend. [b]Cochran–Armitage test for trend.

evaluated after categorizing the population based on eGFR (>60, 45–59, 30–44, and <30 ml/min per 1.73 m^2).

Sensitivity analyses were performed to evaluate for confounding from potential hyperaldosteronism, hypertension itself, and serum potassium. Subgroup analysis of the PRA cohort with hypertension were performed separately to calculate OR for CKD. Additionally, we performed a regressions analysis excluding the top quartile of aldosterone levels in efforts to exclude the unidentified hyperaldosteronism. Finally, high potassium has been shown to suppress renin secretion [18], thus additional regressions were performed controlling for serum potassium levels.

All analyses were performed using SAS version 9.1.3 (SAS Institute, Cary, North Carolina, USA).

Results

Participant characteristics

A total of 9495 individuals were identified to have documented outpatient PRA and aldosterone values over 11 years of the predetermined study period. The distribution of the PRA cohort is shown in Fig. 1. Overall values ranged from undetectable to as high as 16.5 ng/ml per h. Similar to the general population distribution nomogram established by Alderman *et al.* [4], approximately 30% of our study population was also in the low PRA group when using a cutoff for low PRA of 0.65 ng/ml per h.

The characteristics of the population are described in Table 1. The study population included 60.4% women. Whites had the greatest representation at 35.4% followed by blacks (20.3%) and Hispanics (19.6%). Blacks had the greatest proportion in the lowest PRA quartile and their proportion decreased across higher PRA quartiles. Conversely, whites had the lowest representation in the lowest PRA quartile, which increased with each quartile and had the highest proportion (39.1%) in the highest PRA quartile. Higher PRA quartiles included younger individuals as demonstrated by a mean age of 53.9 years in the highest quartile compared with mean age of 59.8 years in the lowest quartile. No meaningful differences between sexes were noted within different PRA quartiles.

The PRA cohort mostly comprised of patients with hypertension (83.1%) and also had a fair representation of diabetic patients (25.8%). Data on renal function were available on 91.9% of the cohort. Overall prevalence of CKD stage 3+ as defined by an eGFR less than 60 ml/min per 1.73 m^2 was 20.8%. The highest rate of CKD was present in the highest PRA quartile. The study population also included those with ischemic heart disease (20.4%), congestive heart failure (8.3%), and cerebrovascular disease (9.2%). Cerebrovascular disease showed a trend toward higher rates with lower PRA.

Table 3 Mean plasma renin activity, aldosterone, and aldosterone-to-PRA ratio across different levels of estimated glomerular filtration rate

eGFR (ml/min per 1.73 m^2)	*N*	PRA [ng/ml per h (SE)]	Aldosterone [ng/dl (SE)]	ARR (SE)
No eGFR available	760	3.6 (0.2)	13 (0.4)	21 (1.51)
≥60	6715	3.5 (0.1)	14 (0.2)	24 (0.7)
45–60	1148	4.8 (0.1)	17 (0.6)	25 (2.4)
30–45	510	5.9 (0.5)	17 (1.0)	20 (2.1)
<30	222	5.6 (0.5)	20 (1.2)	16 (33)

ARR, aldosterone-to-PRA ratio; eGFR, estimated glomerular filtration rate; PRA, plasma renin activity; SE, standard error.

Laboratory characteristics

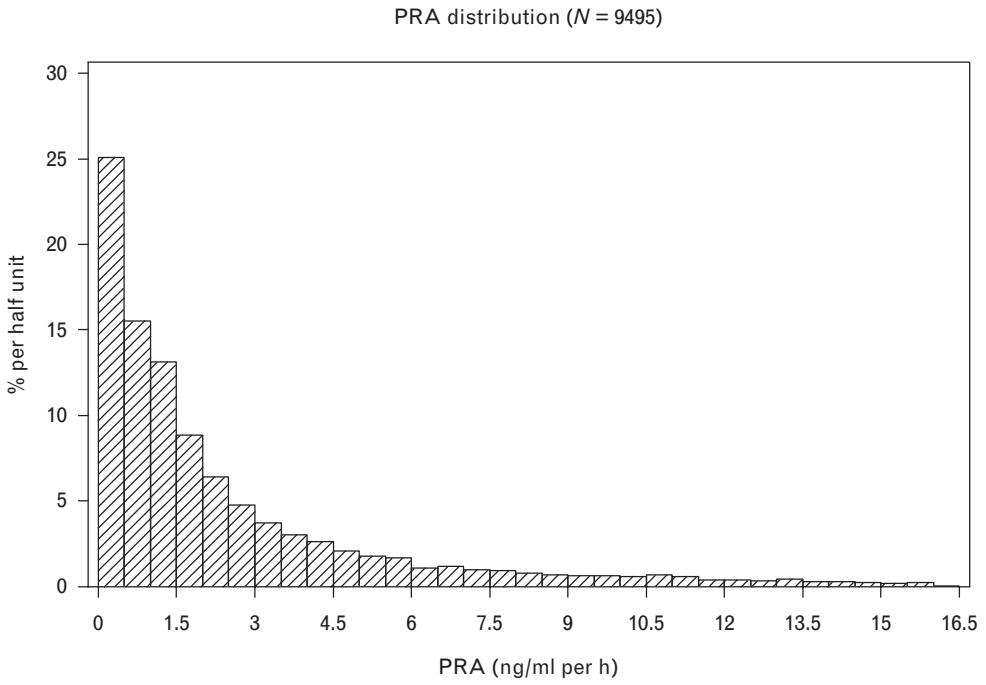
Laboratory characteristics where available are listed in Table 2. Mean serum creatinine and eGFR were similar across all four quartiles of PRA as was serum phosphorous. Serum potassium was lower in the lowest PRA quartile. Qualitative dipstick data for presence of proteinuria were available in 3509 (37%) of the patients. The rates of proteinuria were highest in the lowest PRA quartile (15.5%) and declined with higher quartiles ($P = 0.042$ for trend). The lowest PRA quartile had lower levels of serum hemoglobin, uric acid, and blood urea nitrogen (BUN) and these values increased with subsequently higher quartiles of PRA. Mean PRA increased with declining renal function from 3.5 ng/ml per h in eGFR 60 ml/min per 1.73 m^2 or higher to 4.8, 5.9, and 5.6 ng/ml per h in eGFR 45–59, 30–44, and less than 30 ml/min per 1.73 m^2, respectively (Table 3).

Antihypertensive medication usage was prevalent in 71% of the study population and specifically 86% of the hypertensive population was on medications. Diuretic medication usage was greatest in the cohort at 60% and within the quartiles it was used most frequently in the lowest PRA quartile (Table 4).

Regressions analyses

The crude and multivariate OR for CKD using PRA and other explanatory variables are listed in Tables 5 and 6. Adjusting for age, sex, black race, diabetes status, hypertension, and type of antihypertension medication use, the OR (95% CI) for CKD stage 3+ (eGFR <60 ml/min per 1.73 m^2) using quartile 1 as the reference was 1.5 (1.2–1.7), 1.5 (1.3–1.8), and 2.2 (1.9–2.6) for second to fourth quartiles, respectively. A linear trend was demonstrated between increasing PRA and presence of CKD wherein each five-unit and 10-unit increase in PRA was associated with OR of 1.1 (1.1–1.2) and 1.3 (1.2–1.4), respectively (Table 5). To compare the CKD association of PRA with other CKD risk factors, we also performed logistic regression for a selected number of relevant variables. Age older than 59 years also demonstrated

Fig. 1



Plasma renin activity distribution ($N = 9495$).

Table 4 Antihypertensive medication usage

	All ($N=9495$)	Quartile 1 (<0.51) ($N=2375$)	Quartile 2 (0.51–1.40) ($N=2434$)	Quartile 3 (1.40–3.70) ($N=2312$)	Quartile 4 (>3.70) ($N=2374$)	*P*
Antihypertensive medication usage within entire PRA cohort						
[a]Diuretics/natriuretic (%)	60	67	57	53	63	<0.001
[b]RAS blocker (%)	47	56	42	38	51	<0.001
[c]RAS suppressor (%)	46	66	47	34	35	<0.001
Antihypertensive medication usage among hypertensive patients within PRA cohort						
[a]Diuretics/natriuretic (%)	67	72	67	68	72	<0.001
[b]RAS blocker (%)	56	60	51	50	60	<0.001
[c]RAS suppressor (%)	54	71	55	43	40	<0.001
Any medication (%)	86	90	83	82	87	<0.001

PRA, plasma renin activity; RAS, renin–angiotensin system. [a] Diuretics/natriuretics: aldosterone receptor blockers, thiazide diuretics, calcium channel blockers, alpha-blockers, loop diuretics. [b] RAS blockers: angiotensin-converting enzyme inhibitors, angiotensin receptor blockers. [c] RAS suppressors: beta-receptor blockers, centrally acting alpha-antagonists (guanfacine, clonidine) reserpine, methyl DOPA, direct renin inhibitors.

higher OR of 3.0 (2.7–3.4), but black race in our PRA cohort showed decreased risk for CKD with OR of 0.8 (0.7–0.9). Presence of both hypertension and diabetes mellitus was also associated with higher OR (1.3, 1.1–1.7) and (1.6, 1.4–1.8) for CKD. Usage of both diuretics and renin suppressor drugs also showed greater OR for CKD (see Table 5).

Sensitivity analyses

In sensitivity analyses, we also examined the correlates of more advanced CKD, that is, stage 4+, as defined by eGFR less than 30 ml/min per 1.73 m^2, and found similar associations and trends, although somewhat more pronounced OR across higher quartiles of PRA. OR (95% CI) for eGFR less than 30 ml/min per 1.73 m^2 per each quartile vs. eGFR more than 60 ml/min per 1.73 m^2 (after excluding patients with eGFR between 30 and 60 ml/min per 1.73 m^2) were 1.6 (1.1–2.3), 1.9 (1.3–2.8), and 2.6 (1.8–3.7) for second to fourth quartiles, respectively (reference: first quartile). Linearity was also present with resultant OR of 1.1 (1.1–1.2) and 1.3 (1.1–1.4) for each five-unit and 10-unit increase in PRA. As compared with PRA, older age, hypertension, diabetes, and usage of diuretic and renin suppressor medications also showed significant ORs for eGFR less than 30 ml/min per 1.73 m^2, which were similar to the observations above for eGFR less than 60 ml/min per 1.73 m^2 (Table 6).

In subgroup analyses of the hypertensive population ($n=7887$), the adjusted ORs (95% CIs) for CKD stage 3+ (eGFR <60 ml/min per 1.73 m^2) for second to fourth quartile compared with first quartile were 1.5 (1.3–1.8), 1.5 (1.3–1.8), 2.1 (1.8–2.5), respectively. In another analysis, we removed the top quartile of aldosterone levels and observed OR for CKD stage 3+ to be 1.4 (1.1–1.7), 1.4 (1.1–1.7), and 1.7 (1.4–2.1), respectively for second to fourth quartile compared with first quartile. Finally, adjustment for serum potassium at least 4 vs. less than 4 mEq/dl did not markedly change the OR for CKD stage 3+ (eGFR <60 ml/min per 1.73 m^2) with OR of 1.4 (1.2–1.7), 1.4 (1.2–1.7), and 2.1 (1.7–2.5) for second to fourth quartile compared with first quartile.

Figure 2 displays the ORs of CKD stage 3+ across quartiles of PRA compared with the ORs of CKD derived from serum aldosterone and ARR. The OR of CKD using serum aldosterone alone as the predictor remained flat around 1 with the exception of the highest quartile of aldosterone [OR 1.5 (95% CI 1.3–1.7)]. ARR, however,

Table 5 Logistic regression analyses to calculate odds ratios for chronic kidney disease (estimated glomerular filtration rate <60 ml/min per 1.73 m^2) crude and with adjustment for age, sex, black race, diabetes, hypertension, medication use

PRA	Crude OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*
Quartile 1	–	–	–	–
Quartile 2	1.2 (1.0–1.4)	0.010	1.5 (1.2–1.7)	<0.001
Quartile 3	1.1 (1.0–1.3)	0.191	1.5 (1.3–1.8)	<0.001
Quartile 4	1.7 (1.4–1.9)	<0.001	2.2 (1.9–2.6)	<0.001
Every 5 unit increase in PRA	1.1 (1.1–1.1)	<0.001	1.1 (1.1–1.2)	<0.001
Every 10 unit increase in PRA	1.2 (1.2–1.3)	<0.001	1.3 (1.2–1.4)	<0.001
Hypertension	2.9 (2.4–3.4)	<0.001	1.3 (1.1–1.7)[a]	0.012
Diabetes	2.2 (2.0–2.5)	<0.001	1.6 (1.4–1.8)[a]	<0.001
Age >59 vs. 18–59 years	3.8 (3.4–4.2)	<0.001	3.0 (2.7–3.4)[a]	<0.001
Male	1.1 (1.0–1.2)	0.118	1.1 (1.0–1.3)[a]	0.041
Black vs. non-black	0.8 (0.7–0.9)	<0.001	0.8 (0.7–0.9)[a]	<0.001
Diuretics/natriuretic	2.4 (2.2–2.7)	<0.001	1.5 (1.3–1.7)[a]	<0.001
Blocker	2.0 (1.8–2.2)	<0.001	1.0 (0.9–1.2)[a]	0.858
Suppressor	2.0 (1.8–2.2)	<0.001	1.4 (1.3–1.6)[a]	<0.001

CI, confidence interval; OR, odds ratio; PRA, plasma renin activity. [a] Modeling with PRA as categorical variable.

Table 6 Logistic regression analyses to calculate odds ratios for chronic kidney disease (estimated glomerular filtration rate <30 ml/min per 1.73 m^2) crude and with adjustment for age, sex, black race, diabetes, hypertension, medication use

PRA	OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*
Quartile 1	–	–	–	–
Quartile 2	1.3 (0.9–1.9)	0.118	1.6 (1.1–2.3)	0.012
Quartile 3	1.3 (0.9–1.9)	0.139	1.9 (1.3–2.8)	0.001
Quartile 4	2.0 (1.4–2.8)	<0.001	2.6 (1.8–3.7)	<0.001
Every 5 unit increase in PRA	1.1 (1.0–1.2)	<0.001	1.1 (1.1–1.2)	<0.001
Every 10 unit increase in PRA	1.2 (1.1–1.3)	<0.001	1.3 (1.1–1.4)	<0.001
Hypertension	3.4 (2.1–5.5)	<0.001	2.1 (1.2–3.5)[a]	0.008
Diabetes	3.0 (2.4–3.8)	<0.001	2.4 (1.9–3.1)[a]	<0.001
Age >59 vs. 18–59 years	1.9 (1.5–2.4)	<0.001	1.4 (1.1–1.8)[a]	0.014
Male	1.1 (0.8–1.4)	0.623	1.1 (0.8–1.4)[a]	0.498
Black vs. non-black	1.1 (0.9–1.5)	<0.424	1.1 (0.8–1.4)[a]	0.684
Diuretics/natriuretic	1.9 (1.5–2.4)	<0.001	1.1 (0.8–1.5)[a]	0.449
Blocker	1.5 (1.2–1.9)	<0.001	0.8 (0.6–1.1)[a]	0.114
Suppressor	2.1 (1.7–2.7)	<0.001	1.7 (1.3–2.3)[a]	<0.001

CI, confidence interval; OR, odds ratio; PRA, plasma renin activity. [a]Modeling with PRA as categorical variable.

exhibited a similar trend as PRA but in an inverse manner wherein higher ARR was associated with decreased OR for CKD, though the values are not as pronounced as for PRA (Fig. 2).

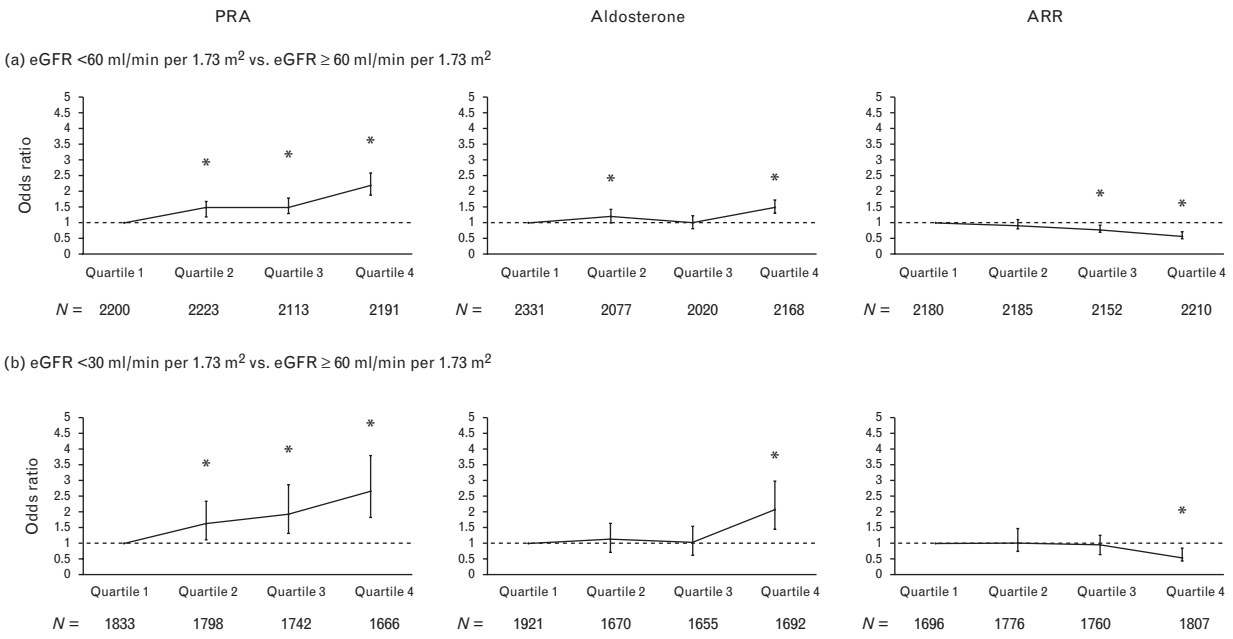
Discussion

Summary of findings

In our large population-based study, we found a positive relationship between higher levels of PRA and higher prevalence of advanced CKD (stages 3+ or 4+) based on eGFR in 9495 individuals from southern California with and without the diagnosis of HTN. OR for CKD increased across higher RPA quartiles and a linear trend was observed where every five-unit increase in PRA raised the prevalence for CKD by 10%. Similarly, mean PRA increased with declining eGFR. Higher values of PRA appear either reflective of coexistent CKD or represent a risk factor for resultant renal disease or damage.

Traditional risk factors including hypertension, diabetes, and older age were compared and demonstrated higher

Fig. 2



Adjusted odds ratios based on plasma renin activity, aldosterone, and aldosterone-to-PRA ratio quartiles for (a) estimated glomerular filtration rate less than 60 vs. an estimated glomerular filtration rate more than 60 ml/min per 1.73 m^2, (b) estimated glomerular filtration rate less than 30 vs. an estimated glomerular filtration rate more than 60 ml/min per 1.73 m^2. ARR, aldosterone-to-PRA ratio; eGFR, estimated glomerular filtration rate; PRA, plasma renin activity. $*P < 0.05$.

risk for CKD. The study cohort included individuals from an ethnically diverse population wherein blacks, Hispanics, and Asians were well represented.

Black race in our PRA cohort showed lower OR for CKD and this may be attributed to the fact that blacks were disproportionately higher in the lower PRA quartiles. When ARR was used as the dependent variable, a similar but inverse trend for CKD was found across quartiles, but this was not seen with serum aldosterone alone as the dependent variable. These finding may have important clinical and public health implications, as they suggest a biologically plausible association between components of RAAS and prevalence of CKD.

PRA reflects the activity of the RAAS wherein the radioimmunoassay quantifies the production of angiotensin I. This value is a functional measurement of renin levels as renin is the upstream and rate-limiting factor for RAAS activity. PRA has been demonstrated to be a better indicator compared with absolute renin concentration due to the fact that certain conditions such as chronic heart failure and chronic liver disease are more prone to alter absolute renin levels, whereas PRA values would not be affected [1].

Implications

The RAAS is a physiologic pathway and essential to maintaining normotension in day-to-day body functions. The direct effects of RAAS are vasoconstriction and downstream volume retention. Theoretically, elevated arterial pressures regardless of the cause should lead to renin suppression, but this does not appear to be the case across the hypertensive population as in our study population. Although vascular injury in hypertension is multifactorial, one pathway that should be explored is the RAAS mechanism of vascular injury. The populations more prone to vascular injury may be the population that fails to suppress renin effectively leaving them susceptible to the vasculopathic consequences of the RAAS system compared with those who protectively shut off or suppress renin. Furthermore, some individuals may actually have overstimulated RAAS activity wherein the PRA is elevated due to positive rather than negative feedback mechanism from downstream angiotensin II and aldosterone. In a subpopulation of hypertensive patients, this pathophysiologic process may partially explain individuals' so called 'bad protoplasm' for certain vascular disease and even mortality [19,20]. Additionally, various interventional studies have demonstrated a beneficial effect of RAAS blockade using angiotensin-converting enzyme inhibitor or angiotensin receptor blockers on renal outcomes [21–24], although a subanalysis of the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) did not demonstrate a benefit of angiotensin-converting enzyme inhibition on renal outcomes [25].

Several prospective and retrospective studies [2–6] have evaluated renin as an explanatory variable on clinical outcomes, specifically the risk for myocardial infarction, stroke, and mortality, but not CKD risk. Alderman *et al.* [4] and Blumenfeld *et al.* [5] found that high PRA was associated with and led to greater rates of myocardial infarctions, whereas Brunner *et al.* [6] demonstrated greater rates of both stroke and myocardial infarctions. Recently, Muhlestein *et al.* [7] demonstrated that higher PRA was associated with greater rates of myocardial infarction, heart failure, and mortality. In contrast, Meade *et al.* [2], using a white male population, found no such relationship of PRA and cardiovascular outcomes. Parikh *et al.* [3] followed the Framingham offspring population and found that high renin patients had no increased risk for cardiovascular outcomes but did have higher rates of short-term mortality. A subanalysis on the Canadian population in the Heart Outcomes Prevention Evaluation study showed that the high PRA was a predictor of cardiovascular death and total mortality[12]. Within the heart failure population, a subanalysis of the valsartan heart failure trial (Val-HeFT) demonstrated that higher PRA was associated with greater mortality [9]. The study populations described above varied greatly in terms of sex distribution, minorities, and actual blood pressures at the beginning and during observation. The study by Meade *et al.*, which did not show higher myocardial infarctions with high PRA, had essentially a normotensive population but when a subanalysis was performed on patients with hypertension, there appeared to be a trend, although not statistically significant, toward greater myocardial infarction rates in higher PRA individuals [2,26]. Subsequent studies have described PRA and its link to worsened outcomes as part of posthoc analyses in large cardiac trials involving heart failure and ischemic heart disease patients [10,11]. Although an association was described in these studies, PRA was never the primary dependent variable studied and was more an afterthought evaluating the effects of neurohormones in general. The collective evaluations on PRA and cardiovascular outcomes as a whole have been not been consistent and the clinical question still remains to be conclusively determined.

To our knowledge, the relationship between PRA and prevalence of CKD has not been previously described. Earlier observations have evaluated PRA within end-stage renal disease populations [27,28] or within patients with existent CKD or acute kidney injury [29,30]. These studies, however, were small case series evaluating the relationship of PRA among patients with similar degrees of renal dysfunction. Evaluating PRA in renal disease raises some concerns about the validity of such a study, as renin is released from the juxtaglomerular apparatus (JGA) on the kidney and, thus, is a reflection of and dependent of the kidney. CKD can theoretically alter PRA in both ways. CKD may result in ischemia and

hypoperfusion to the JGA stimulating additional renin release. Conversely, as functional renal parenchyma declines with renal disease, this may lead to decreased renin production and secretion. The relatively small observations in ESRD or CKD populations describing PRA have shown that PRA levels are similar in CKD compared with normal populations [27–30], with the exception of those with extremely elevated and difficult-to-control hypertension. Regardless, the detrimental effects of high PRA and upregulated RAAS would make the kidney one of the organs more susceptible to vasculopathic injury resultant from RAAS overstimulation. Another potential mechanism is the actions of transforming growth factor-beta, which is a protein that causes cell growth and inflammation [31]. In non-CKD black individuals, transforming growth factor-beta 1 and PRA levels were shown to be positively associated [32].

Limitations

Our study should be qualified for its cross-sectional and retrospective observational nature. PRA and aldosterone are usually not routine laboratory tests and likely were ordered based upon clinical indications deemed as needed by clinicians managing these patients as likely workup for hypertension. Thus, our findings may not necessarily extend out to the remaining population of the KPSC or the general population. The effects of medication usage on PRA are somewhat underemphasized by our analyses. As a majority of antihypertensive medications affect PRA levels [33], our findings in medicated individuals may reflect how they were treated rather than the natural PRA modulation of RAAS activity. However, we attempted to minimize this confounding by categorizing medication usage based on how it affected PRA [34] and adjusted for them in the logistic regressions analysis. Although we report an association of higher PRA with increased OR for CKD, we cannot infer causality. PRA is reflective of RAAS activity and this pathway is assumed responsible if causality exists, but we are limited in describing any mechanism that may contribute to the associations that we found. Urine protein data were only available in a fraction of the population. Hypertension is likely to be an intermediary variable, as higher PRA may be associated with higher blood pressure and resultant renal damage. For our study analysis, blood pressure data were not available for the entire population at the time of PRA testing, although the diagnosis of hypertension was documented reliably. Our results enforce the biologic plausibility of the hypothesis that higher PRA individuals are more prone to CKD and that they may benefit from more aggressive RAAS blockade. These clinical and public health implications of our findings may prompt prospective interventional trials to determine causality to this end.

Proteinuria was assessed in a third of our cohort ($N=$ 3509) and, somewhat surprisingly, the rate of proteinuria was lower with higher PRA quartiles. However, hypertension or vascular ischemic renal disease is not generally associated with severe degrees of proteinuria. The mechanism that we hypothesize for higher CKD in our cohort is more associated with bland urine sediments and proteinuria may not be entirely reflective of that mechanism.

Strengths

Among the strengths of our study are its large population of individuals, which far exceeds any study evaluating renin to date. Our study population was ethnically diverse with ample representation of minorities including blacks, Hispanics, and Asians paralleling the distribution of the state of California. Although most of our patient population consisted of individuals with hypertension, our analysis also included over 1500 individuals without hypertension. The hypertensive individuals showed similar trends for CKD based on PRA compared with those without hypertension and the cohort as a whole.

In conclusion, in a large and ethnically diverse population of individuals in southern California with documented PRA levels, a greater OR for CKD was found in those with higher levels of PRA in a dose-dependent fashion. These associations may provide impetus for further evaluations and prospective studies assessing PRA and RAAS modulation as potential risk factors for CKD.

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Conflicts of interest

J.S., S.R., S.J., and K.K.-Z. have no disclosures or conflicts of interest relevant to this manuscript.

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