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Journal

Blood Pressure Monitoring, 21(2)

ISSN

1359-5237

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Publication Date

2016-04-01

DOI

10.1097/mbp.0000000000000168

Peer reviewed

Associations between cystatin C-based eGFR, ambulatory blood pressure parameters, and in-clinic versus ambulatory blood pressure agreement in older community-living adults

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Objectives **The objective of this study was to determine the relationship between chronic kidney disease [CKD; measured using cystatin C-based estimated glomerular filtration rate (eGFR)] and abnormal ambulatory blood pressure (including nocturnal dipping) in healthy older adults. Further, this study aimed to assess the agreement between clinic and ambulatory blood pressure monitoring.**

Methods **Serum cystatin C levels were measured to calculate eGFR. Participants underwent clinic and 24-h ambulatory blood pressure measurements. Multiple linear regression was performed to examine the association between reduced cystatin C-based eGFR (CKD_{cys}) and blood pressure parameters. Bland–Altman analysis was carried out to evaluate the agreement between clinic and ambulatory measurements.**

Results **The average age was 72 years. There were 60 individuals with CKD_{cys} (eGFR < 60 ml/min/1.73 m^2). Compared with those without CKD_{cys}, individuals with CKD_{cys} were older, more likely to have hypertension, and less likely to have normal dipping patterns. On multivariate analysis, the presence of CKD_{cys} was found to be significantly associated with a lower mean ambulatory diastolic blood pressure (− 2 mmHg, $P = 0.048$), but not with nocturnal dipping or other blood pressure parameters. Clinic systolic blood pressure (SBP) significantly overestimated the mean wake-time ambulatory SBP; the mean difference was 11 mmHg for those without CKD_{cys} (95% limits of agreement − 14 to 35 mmHg) and 14 mmHg for those with CKD_{cys} (95% limits of agreement − 13 to 41 mmHg); there was no statistically significant effect modification by CKD status.**

Conclusion **In older, seemingly healthy adults, mild CKD was associated with lower ambulatory diastolic blood pressure. The presence of CKD did not affect interpretation of clinic versus ambulatory blood pressure monitoring, although the accuracy of clinic SBP was poor.** ***Blood Press Monit*** **00:000–000**

Blood Pressure Monitoring 2015, **00**:000–000

Keywords: ambulatory blood pressure monitoring, chronic kidney disease, cystatin C, hypertension

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Received 8 July 2015 **Revised** 2 November 2015 **Accepted** 6 November 2015

Introduction

Ambulatory blood pressure monitoring (ABPM) provides data on the average blood pressure over 24 h, including wake and sleep values and diurnal patterns. It is considered by many to be the diagnostic standard against which other blood pressure modalities should be compared [1,2]. Individuals with confirmed out-of-office hypertension and those with less than 10% diurnal variation (nondippers) suffer increased morbidity and mortality [3,4]. A recent systematic review on the improved accuracy of hypertension diagnosis has confirmed that ABPM is more closely linked to cardiovascular disease outcomes than standard clinic blood pressure measurements, and the US Preventive Services Task Force has released a draft recommendation to use ABPM routinely in all patients with a positive screen for hypertension in clinic blood pressure measurements [5–7]. Whereas this change would vastly increase the frequency with which this measure is utilized and interpreted in clinical practice, populations with comorbid conditions including chronic kidney disease (CKD) were excluded from the data used in this analysis.

Those with CKD are more likely to have clinically apparent hypertension, either as a causative factor for CKD or as a consequence of longstanding CKD. Further, advanced CKD (stages IV and V) is associated with abnormal nocturnal dipping [8]. Although mild decrements in kidney function, as measured by cystatin C-based estimated glomerular filtration rate ($eGFR_{cys}$), have been associated with increased rates of hypertension [9], to our knowledge few studies have examined whether mild decrements in kidney function are associated with abnormal 24-h blood pressure patterns.

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Cystatin C-based eGFR is an important metric for these studies, because of its increased sensitivity at higher ranges of eGFR [10] and its utility in older adults, for whom creatinine may overestimate kidney function in the setting of lower muscle mass [11].

Furthermore, agreement between ABPM and clinic blood pressure measurements is variable and may differ in general populations [12], as well as in those with advanced CKD [13]; however, this question has not been examined closely among older adults, nor has it been investigated in the context of cystatin C-based eGFR measures. In older adults, cystatin C has the advantage of being less influenced by muscle mass or overall health status and serves as an early marker of decreased eGFR [10,14]. More work is needed, then, to understand the role ABPM plays in identifying hypertension among individuals with mild kidney disease.

In the present cross-sectional study, we examined the relationship between $eGFR_{cys}$ and ambulatory blood pressure parameters in a cohort of generally healthy, community-dwelling older adults in San Diego. We hypothesized that lower $eGFR_{cys}$ would be associated with abnormalities in blood pressure parameters, including nondipping and ambulatory hypertension, given the sodium and water retention seen in CKD and the known higher prevalence of nondipping in those with advanced CKD. We hypothesized that this association would be stronger on using $eGFR_{cys}$ than for kidney dysfunction as measured by creatinine ($eGFR_{cr}$). Finally, because the diagnosis of hypertension is overwhelmingly established based on clinic blood pressure measurement at present, we evaluated the agreement between ambulatory and clinic blood pressure measurements to determine the precision and accuracy of this approach in this population and tested whether it differed by $eGFR_{cys}$-based CKD status.

Methods

Study participants

Data were collected from a subset of participants originally enrolled in the San Diego Population Study (SDPS). A description of recruitment and study design for the original SDPS has been published previously [15]. In brief, SDPS is an ongoing observational study designed to examine the prevalence and incidence of chronic peripheral venous and arterial disease in a population of healthy, asymptomatic adults. Participants enrolled in the original 1994–1998 study ($n = 2408$) were current and former employees of the University of California, San Diego; 1103 returned for another visit between 2006 and 2011. We sent invitation letters to participants who had San Diego County addresses on file and had indicated willingness to be contacted for future studies ($N = 944$); 354 participants responded and agreed to participate in the current study between January 2012 and June 2013. Participants were at least 55 years of age, living independently, and able to provide their consent for the study. During a single study visit, we carried out relevant assessments including 24-h ABPM, measurement of kidney function using cystatin C, creatinine, and albuminuria, and assessment of physical and cognitive function. Participants were excluded from the current analysis if they lacked serum cystatin C measurements ($n = 6$) or did not undergo full 24-h ABPM ($n = 14$).

Kidney function

Serum specimens were collected from all participants at the time of the study visit. Serum creatinine was measured immediately at the University of California, San Diego Center for Advanced Laboratory Medicine, using a standard, calibrated creatinine assay. Serum specimens were subsequently stored at -70°C. Serum cystatin C was measured at the University of Minnesota Advanced Research and Diagnostic laboratory using a Gentian assay on a Roche COBAS 6000 analyzer. Glomerular filtration rates were estimated (eGFR) using the three recently developed CKD-EPI equations for creatinine, cystatin C, and the combination of the two [10]. Participants were categorized by the presence of CKD based on $eGFR_{cys}$ less than 60 ml/min/1.73 m^2 or $eGFR_{cr}$ less than 60 ml/min/1.73 m^2.

Covariates

Participant characteristics were obtained through a self-reported questionnaire and included information on age, sex, race, smoking and alcohol use, and medical conditions. Alcohol use was defined as current use; tobacco use was defined as current, former, or never. Personal history of hypertension was defined by self-report or by active use of an antihypertensive agent without an alternative indication. Diabetes was defined by self-report or through active use of insulin or hypoglycemic agents. Prevalent cardiovascular disease was defined as a history of myocardial infarction, congestive heart failure, stroke, or transient ischemic attack. Height and weight were measured during the study visit and were used to calculate BMI (reported in kg/m^2). An abnormal Epworth Sleepiness Score was defined as any score of 10 or higher or 24 possible points based on previous literature identifying such a score as predictive of excessive daytime sleepiness [16].

Blood pressure

Blood pressure was initially measured during the study visit by performing three seated measurements using an automated blood pressure cuff (Dynapulse, Vista, California, USA) after 5 min of seated rest. The average of these three measurements was used for analysis; the first measurement was not eliminated from the analysis as recent studies have found no statistically significant difference between this measurement and subsequent measurements [17]. ABPM was then initiated using a SpaceLabs 90217 monitor. The first ambulatory

measurement was obtained during the study visit to confirm proper cuff placement and machine accuracy. AQ6 Blood pressure was measured every 20 min while awake and every 60 min while asleep for a total duration of 24 h; measurement intervals were preprogrammed based on subject-anticipated sleep periods and sleep, and wake intervals were confirmed by in-person interviews on the morning after overnight monitoring. Daytime nap, if it occurred, was not considered as part of a sleep period. If there were discrepancies between the anticipated and actual sleep periods, analysis was carried out on the basis of self-reported sleep periods during in-person interviews after completion of overnight monitoring. Values collected during ambulatory monitoring were then averaged and reported as overall, wake, and sleep mean systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse pressure. Blood pressure values collected during the sleep period were compared with those collected during the wake period to calculate the percent change between the two, known as 'dipping', for both SBP and DBP. We considered 14 daytime and six nighttime readings to ABPM readings to be an adequate ABPM report. Blood pressure values were also used to calculate the ambulatory arterial stiffness index and the average real variability, reflecting arterial stiffness and reading-to-reading variability, respectively [18,19].

Statistical analysis

Baseline characteristics of participants were summarized by $eGFR_{cys}$ status. Differences between CKD statuses were determined using *t*-tests for continuous variables and χ^2-tests for categorical variables. Pearson's correlation coefficients were calculated for $eGFR_{cys}$ and $eGFR_{cr}$ versus clinic and ambulatory blood pressure measurements. Simple linear regression was performed to examine the relationship between $eGFR_{cys}$ and $eGFR_{cr}$ and various blood pressure measurements (clinic SBP, DBP, and pulse pressure, and mean ambulatory SBP, DBP, pulse pressure, and dipping). We chose covariates based on biological plausibility or statistical significance in univariate modeling. Staged multivariable linear regression was subsequently performed to account for (i) age and (ii) sex, race, BMI, history of hypertension treatment, diabetes, cardiovascular disease, smoking history, and abnormal Epworth score. We used stepwise regression to identify individual confounders, with particularly notable effects on the models. Similarly, we used linear regression to examine the associations of CKDcys and CKD_{cr} with in-clinic and ABPM metrics, with a parallel set of nested models. The prevalence of 'dippers', again defined as individuals with a diurnal variation of at least 10%, was calculated for 10-U incremental increases in $eGFR_{cys}$ and $eGFR_{cr}$ to ascertain prevalence rate ratios. This method was chosen given the relatively high percentage of nondipping in our cohort and the consequent concern that odds ratios would not accurately estimate relative risks.

We carried out sensitivity analyses testing for differences between those taking blood pressure medication and those who were not, as well as testing whether the presence of CKD, defined by both eGFR and the presence of microalbuminuria, was associated with dipping. We also considered whether albuminuria and $eGFR_{cys}$ might contribute separately to dipping behavior. To evaluate this, we explored linear models of systolic dipping, with albuminuria (expressed as log of the albumin/creatinine ratio) and eGFR included separately and then together, first in univariate analysis and then adjusted for demographic and clinical factors, as in our other models. We also examined associations between CKD_{cys} and nocturnal blood pressure as a linear outcome, as opposed to dipping percentage, as some studies have shown nocturnal blood pressure to be most important for cardiovascular outcomes. We also compared separate cystatin-based and creatinine-based CKD-EPI equations with the combined equation.

Finally, to examine the agreement between ABPM and in-clinic blood pressure measurement, we created Bland–Altman plots stratified by CKD status, from which the mean differences and 95% confidence intervals were identified. All analyses were carried out using SAS statistical software (release 9.3; SAS Institute Inc., Cary, North Carolina, USA); *P*-values less than 0.05 were considered significant.

Results

Baseline characteristics

There were 334 participants with a mean age of 72 ± 6 years from whom ambulatory blood pressure data and cystatin C measurements were collected; 225 (67%) were female (Table 1). Overall, the average $eGFR_{cys}$ was 78 ± 20; 60 participants (18%) were classified as having CKD by the cystatin C equation. Compared with participants without CKD_{cys}, those with CKD_{cys} were older, more likely to be female, and more likely to have hypertension and diabetes. On average, participants with CKD_{cys} had a higher BMI (29.9 vs. 26.7 kg/m^2). The mean in-clinic SBP and pulse pressure were significantly higher in those with CKD, but the mean in-clinic DBP was significantly lower. Similarly, the mean ambulatory pulse pressure was significantly higher in those with CKD, but the mean ambulatory DBP was significantly lower; the mean ambulatory SBP did not differ significantly between those with and those without CKD.

Those with CKD_{cys} had a slightly increased ambulatory arterial stiffness index, indicating increased stiffness, and more variable blood pressure than those who did not have CKD_{cys}. Albumin–creatinine ratios were relatively low in both groups.

Correlations

Correlation coefficients for eGFR and blood pressure measurements stratified by CKD status are provided in

Table 1 Characteristics of participants by CKD status

	No CKD[a]	CKD[a]	*P*-value
N	274	60	
Demographics			
Age	71 (6)	78 (7)	< 0.001
Female	177 (65)	48 (80)	0.02
Race			0.09
White	169 (62)	34 (57)	–
Black	30 (11)	13 (22)	–
Hispanic	37 (14)	10 (17)	–
Asian	29 (12)	2 (3)	–
Medical history			
Hypertension	124 (45)	45 (75)	< 0.001
Taking blood pressure medication (s)	136 (50)	47 (78)	0.002
Diabetes	25 (9)	12 (20)	0.02
Cardiovascular disease[b]	24 (9)	10 (17)	0.07
Family history of cardiovascular disease[b]	221 (81)	55 (92)	0.04
Alcohol use[c]	198 (73)	30 (50)	0.001
Tobacco use[c]	85 (31)	23 (38)	0.3
Measurements			
Estimated GFR (CKD-EPI cystatin)	85 (14)	47 (10)	< 0.001
Estimated GFR (CKD-EPI creatinine)	78 (13)	58 (16)	< 0.001
BMI (kg/m^2)	26.7 (4.9)	29.9 (6.6)	< 0.001
Mean in-clinic systolic blood pressure (mmHg)	140 (16)	145 (16)	0.02
Mean in-clinic diastolic blood pressure (mmHg)	76 (9)	71 (10)	0.002
Mean in-clinic pulse pressure (mmHg)	64 (12)	74 (14)	< 0.001
Mean 24-h systolic blood pressure (mmHg)	126 (12)	129 (14)	0.1
Mean 24-h diastolic blood pressure (mmHg)	74 (7)	69 (9)	< 0.001
Mean 24-h pulse pressure (mmHg)	53 (10)	61 (12)	< 0.001
Systolic dipping (%)	11 (7)	9 (10)	0.03
Dipper[d]	168 (61)	27 (45)	0.02
Abnormal Epworth Sleep Score	26 (9)	11 (18)	0.05
AASI	0.5 (0.13)	0.55 (0.15)	0.01
ARV	10.6 (2)	11.2 (1.9)	0.02
Urine microalbumin: creatinine (median) (mg/mmol)	18 (11, 34)	23 (11, 32)	0.3

Values are expressed as mean (SD) or *n* (%), unless otherwise stated.
AASI, Ambulatory Arterial Stiffness Index; ARV, average real variability; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure.
[a]CKD = eGFR < 60 ml/min using CKD-EPI cystatin.
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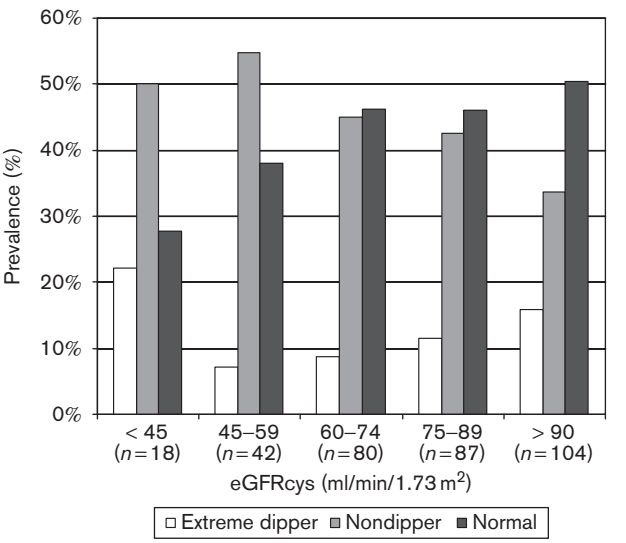
[b]History of myocardial infarction, heart failure or stroke***.
[c]History of any alcohol or tobacco use, respectively***.
[d]Diurnal variation in SBP ≥ 10%.

Fig. 1



Prevalence of dipping patterns across kidney function categories. $eGFR_{cys}$, estimated glomerular filtration rate cystatin.

Table 2. In participants without CKD_{cys}, $eGFR_{cys}$ was weakly correlated with systolic dipping but not with other ambulatory parameters or any clinic parameter. In participants with CKD_{cys}, $eGFR_{cys}$ was not correlated with systolic dipping, but it was moderately directly correlated with both the mean ambulatory DBP and the clinic DBP.

Associations between kidney function and blood pressure parameters

In unadjusted analysis, those with lower $eGFR_{cys}$ had a lower prevalence of normal dipping patterns (Fig. 1). Before adjustment, the presence of CKD_{cys}, but not CKD_{cr}, was associated with less dipping (per 1% point), a lower mean ambulatory DBP, and a higher mean ambulatory pulse pressure (Table 3a). Associations were also identified between the presence of CKD_{cys} and a higher

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Table 2 Pearson correlation coefficients (*P* for correlation) for eGFR and blood pressure by kidney function

	$eGFR_{cys}$	24 h systolic	24 h diastolic	Systolic dipping	Clinic systolic	Clinic diastolic
No CKD						
$eGFR_{cys}$	X	0.03 (0.6)	0.12 (0.05)	**0.12 (0.05)**	−0.0007 (0.9)	0.09 (0.14)
24-h systolic		X	0.54 (< 0.001)	−0.02 (0.8)	0.63 (< 0.001)	0.38 (< 0.001)
24-h diastolic			X	0.03 (0.6)	0.31 (< 0.001)	0.66 (< 0.001)
Systolic dipping				X	0.08 (0.2)	0.1 (0.1)
Clinic systolic					X	0.65 (< 0.001)
Clinic diastolic						X
CKD						
$eGFR_{cys}$	X	0.09 (0.5)	0.39 (0.002)	−0.02 (0.8)	0.08 (0.5)	0.38 (0.003)
24-h systolic		X	0.5 (< 0.001)	−0.18 (0.2)	0.6 (< 0.001)	0.28 (0.03)
24-h diastolic			X	−0.09 (0.5)	0.23 (0.07)	0.71 (< 0.001)
Systolic dipping				X	0.02 (0.9)	0.05 (0.7)
Clinic systolic					X	0.55 (< 0.001)
Clinic diastolic						X

CKD, chronic kidney disease; $eGFR_{cys}$, estimated glomerular filtration rate cystatin.

Table 3 (a) Association between GFR and blood pressure measurements for all participants, and (b) association between CKD_{cys} and blood pressure measurements by antihypertensive medication use

	Unadjusted			Age adjusted			Model 1[a]		
	β	95% CI	*P*-value	β	95% CI	*P*-value	β	95% CI	*P*-value
(a)									
Ambulatory blood pressure monitoring									
Systolic dipping (%)									
CKD_{cys} present	−3	−5 to −1	0.007	−2	−5 to 0	0.06	−1	−4 to 1	0.3
CKD_{cr} present	−2	−4 to 0	0.08	−1	−3 to 1	0.3	−1	−3 to 2	0.5
Mean 24-h DBP (mmHg)									
CKD_{cys} present	−5	−7 to −3	<0.001	−3	−5 to 0	0.02	−2	−5 to −0.02	0.05
CKD_{cr} present	−4	−6 to −2	<0.001	−2	−4 to 0	0.07	−2	−4 to 0	0.1
Mean 24-h SBP (mmHg)									
CKD_{cys} present	3	−1 to 6	0.1	2	−2 to 6	0.3	0	−4 to 4	0.99
CKD_{cr} present	−1	−5 to 2	0.5	−3	−6 to 1	0.2	−4	−7 to 0	0.069
Mean 24-h pulse pressure (mmHg)									
CKD_{cys} present	8	5–11	<0.001	5	2–8	0.003	2	−1 to 6	0.2
CKD_{cr} present	3	0 to 6	0.08	−1	−4 to 3	0.8	−2	−5 to 1	0.3
In-clinic measurements									
Mean clinic DBP (mmHg)									
CKD_{cys} present	−5	−7 to −2	0.001	−2	−5 to 1	0.2	−3	−6 to 0	0.06
CKD_{cr} present	−3	−6 to 0	0.03	−1	−4 to 2	0.5	−1	−4 to 2	0.5
Mean clinic SBP (mmHg)									
CKD_{cys} present	5	1–10	0.016	4	−2 to 8	0.2	0	−5 to 5	0.9
CKD_{cr} present	3	−1 to 8	0.16	1	−4 to 6	0.7	0	−5 to 5	0.9
(b)									
Ambulatory blood pressure monitoring									
Systolic dipping (%)									
CKD_{cys} present, med use −	−5	−9 to −1	0.02	−3	−8 to 1	0.2	−2	−8 to 2	0.2
CKD_{cys} present, med use +	−2	−5 to 0	0.08	−2	−5 to 1	0.1	−1	−4 to 2	0.4
Mean 24-h DBP (mmHg)									
CKD_{cys} present, med use −	−4	−8 to 1	0.09	−1	−5 to 3	0.7	−2	−7 to 2	0.3
CKD_{cys} present, med use +	−5	−8 to −3	<0.001	−3	−5 to 0	0.05	−2	−5 to 1	0.2
Mean 24-h SBP (mmHg)									
CKD_{cys} present, med use −	5	−2 to 13	0.2	4	−4 to 12	0.37	0	−8 to 7	0.9
CKD_{cys} present, med use +	1	−3 to 5	0.5	1	−3 to 6	0.66	0.35	−4 to 5	0.9
Mean 24-h pulse pressure (mmHg)									
CKD_{cys} present, med use −	9	3–15	0.004	5	−2 to 11	0.1	2	−4 to 8	0.6
CKD_{cys} present, med use +	7	3–10	<0.001	4	0–8	0.06	2	−2 to 6	0.2
In-clinic measurements									
Mean clinic DBP (mmHg)									
CKD_{cys} present, med use −	−3	−9 to 2	0.2	−2	−9 to 4	0.5	−5	−11 to 1	0.1
CKD_{cys} present, med use +	−5	−8 to −2	0.002	−1	−5 to 2	0.36	−1	−5 to 2	0.4
Mean clinic SBP (mmHg)									
CKD_{cys} present, med use −	7	−3 to 17	0.2	1	−9 to 12	0.8	−3	−13 to 7	0.6
CKD_{cys} present, med use +	4	−1 to 9	0.1	3	−2 to 9	0.3	2	−4 to 7	0.6

CI, confidence interval; CKD, chronic kidney disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure.
[a]Adjusted for age, sex, race, BMI and the presence of diabetes, cardiovascular disease, and smoking history.

mean clinic SBP and DBP. However, these effects were almost uniformly attenuated after full adjustment. In multivariate analysis, only an association between CKD_{cys} status and the mean ambulatory DBP remained (−2 mmHg, $P=0.048$). We performed stepwise regression and determined that age and BMI were the primary confounders responsible for the attenuating effects on the multiple blood pressure parameters.

Kidney function and normal dipping pattern prevalence

In the unadjusted model, the prevalence of a normal dipping pattern significantly increased for every 10 ml/min increment in either $eGFR_{cys}$ or $eGFR_{cr}$ (Table 4). This effect was attenuated to nonsignificance after adjustment for age and other confounders.

Table 4 Prevalence of normal dipping (>10%) as a function of eGFR

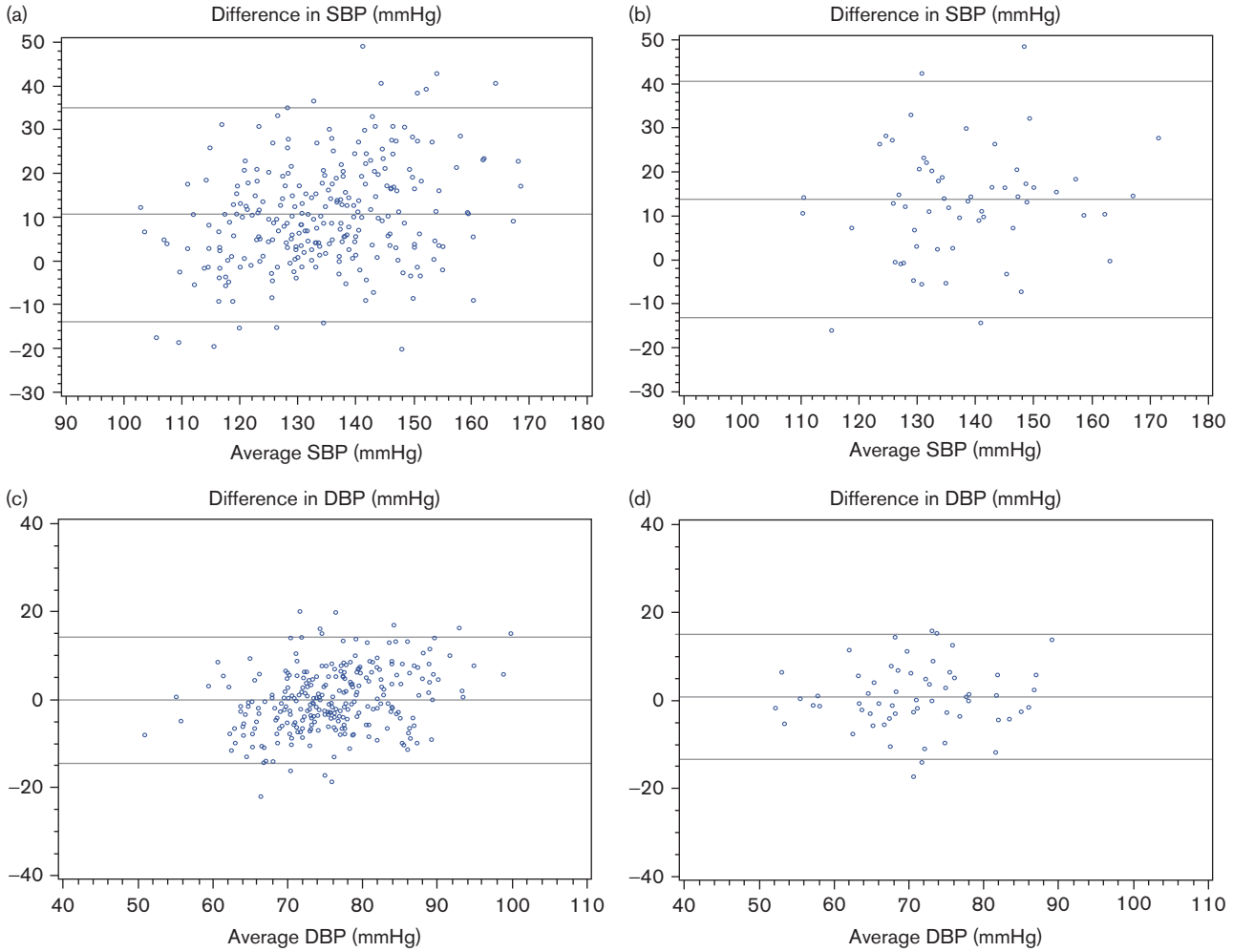
	Prevalence rate ratio	Confidence interval	*P*-value
eGFR by CKD-EPI cystatin equation (per 10 ml/min/1.73 m^2)			
Unadjusted	1.08	1.03–1.13	0.002
Age-adjusted	1.06	1.01–1.12	0.03
Model 1[a]	1.04	0.98–1.1	0.2
eGFR by CKD-EPI creatinine equation (per 10 ml/min/1.73 m^2)			
Unadjusted	1.09	1.03–1.17	0.006
Age-adjusted	1.07	1–1.15	0.07
Model 1[a]	1.06	0.99–1.14	0.09

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.
[a]Adjusted for age, sex, race, BMI and the presence of diabetes and cardiovascular disease as well as smoking history.

Agreement between ambulatory and clinic blood pressure

Regardless of CKD_{cys} status, clinic SBP significantly overestimated the mean wake-time ambulatory SBP

Fig. 2



(a) Ambulatory wake-time SBP versus clinic SBP – participants without CKD. The mean difference was 14 mmHg (95% limits of agreement −14 to 35 mmHg). (b). Ambulatory wake-time SBP versus clinic SBP – participants with CKD. Mean difference 14 mmHg (95% limits of agreement −13 to 41 mmHg). (c) Ambulatory wake-time DBP versus clinic DBP – participants without CKD. The mean difference was 0 mmHg (95% limits of agreement −14 to 14 mmHg). (d) Ambulatory wake-time DBP versus clinic DBP – participants with CKD. The mean difference was 1 mmHg (95% limits of agreement −14 to 15 mmHg). CKD, chronic kidney disease; DBP, diastolic blood pressure; SBP, systolic blood pressure.

(Fig. 2); the mean difference was 11 mmHg for those without CKD_{cys} (95% limits of agreement −14 to 35 mmHg) and 14 mmHg for those with CKD_{cys} (95% limits of agreement – 13 to 41 mmHg). In contrast, clinic DBP accurately estimated the mean wake-time ambulatory DBP in both groups; the mean difference was 0 mmHg for those without CKD_{cys} (95% limits of agreement – 14 to 14 mmHg) and 1 mmHg for those with CKD_{cys} (95% limits of agreement – 14 to 15 mmHg). We identified 67 individuals in our cohort (36 of whom were taking antihypertensive therapy) who met the criteria for white-coat hypertension, defined by the European Society of Hypertension [20] as a clinic blood pressure of 140/90 mmHg or higher and a 24-h ambulatory blood pressure less than 130/80 mmHg; the prevalence of white-coat hypertension did not differ by CKD_{cys} status.

Sensitivity analyses

To examine whether the utilization of antihypertensive medications affected the relationship between kidney function and blood pressure, we repeated linear regression and prevalence rate ratio analyses, comparing those on antihypertensive therapy with those who were not (Table 3b). No significant association existed for either antihypertensive therapy group between blood pressure and CKD_{cys} status.

We carried out a separate analysis that included the presence of microalbuminuria in the definition of CKD. The findings were similar to those obtained for the eGFR-based definition of CKD_{cys}, which did not include the presence or absence of microalbuminuria.

In analyses considering albuminuria and $eGFR_{cys}$ as separate factors, we found that, even in univariate models, the albumin/creatinine ratio had no association with systolic dipping [β-value for natural log of ACR, 0.62 (−0.41, 1.66), $P = 0.23$]. This remained the case in multivariate models, and adding ACR to a model with $eGFR_{cys}$ did not modify the β-coefficient for $eGFR_{cys}$ in unadjusted or adjusted models.

Sensitivity analysis was also carried out using the combined CKD-EPI equation for cystatin C and creatinine (CKD_{crcys}); results (not shown) were similar to those obtained using the cystatin-based equation.

Finally, we examined nocturnal blood pressure as a continuous variable rather than binary dipping or nondipping, with results again showing a statistically significant increase in nocturnal blood pressure that was attenuated by both age and BMI.

Discussion

CKD and hypertension are highly prevalent conditions that are frequently comorbid in older adults. In our study of community-dwelling older adults with predominantly mild CKD, we found that those with CKD had higher in-clinic SBPs but only modest correlations between kidney function and ambulatory blood pressure parameters. After adjusting for multiple covariates, only a lower mean ambulatory DBP was significantly associated with CKD status; nocturnal dipping was not greater in those with normal versus abnormal kidney function. Finally, clinic SBP – but not clinic DBP – was significantly higher in comparison with ambulatory wake-time monitoring, and this difference was not affected by CKD status.

The finding that individuals with CKD had a significantly lower 24-h mean DBP is consistent with previous work demonstrating associations between CKD and lower in-clinic DBP [21]. Importantly, our study was performed in relatively healthy older adults without major illness and, hence, it generalizes this finding outside a purely hypertensive population and to 24-h measures rather than in-clinic measures.

We found it to be somewhat surprising that CKD in this cohort was not independently associated with dipping status after adjustment for age and other confounders. This finding may be because of the mild degree of CKD in our cohort (average $eGFR_{cys}$ in those with CKD was 47 ml/min and only four had $eGFR_{cys}$ less than 30 ml/min/1.73 m^2). In cohorts with greater degrees of CKD, or end-stage renal disease, nondipping is common. Agarwal *et al.* [22] found a prevalence of nondipping of 75% among participants in a CKD clinic. It may be that only in more advanced disease are perturbations in blood pressure patterns observed.

We found that, after age adjustment, BMI was largely responsible for attenuating the relationship between CKD and abnormal blood pressure measurements, including dipping. One hypothesis to explain this observation may be that participants with higher BMI had both higher rates of CKD and subclinical obstructive sleep apnea (OSA). OSA is well established to be associated with nondipping [23,24]. The prevalence of abnormal Epworth Sleepiness Scores among participants at the time of enrollment was modestly higher among individuals classified as having CKD, although adjusting for these scores did not change the associations beyond the contribution from BMI. However, many OSA patients do not report daytime sleepiness [25,26], and the correlation between OSA severity and Epworth Sleepiness Score is weak at best [27], suggesting that OSA could still be a confounder in our study. Thus, further work is clearly needed.

We did not find an association between albuminuria, either when included as part of the CKD definition or when modeled alone, and systolic dipping; we believe that this may be because the levels of albuminuria in our cohort were very low. Although 25% of the cohort technically met the greater than 30 mg/g definition of microalbuminuria, 95% had microalbumin/creatinine ratios less than 70 mg/g, and only four individuals had macroalbuminuria, defined as ratios greater than 300 mg/g.

Compared with the mean ambulatory wake-time DBP, clinic DBP was a relatively accurate measurement, whereas clinic SBP significantly overestimated ambulatory wake-time SBP in comparison with ABPM findings. This observation did not differ by CKD status. Previous studies have described bias in in-clinic BP determinations, including white-coat hypertension [28] and the lack of a standardized approach to blood pressure measurement [29]. Our study shows this issue to be a problem both in those with and in those without CKD, as well as across the age range in our cohort. Bias in SBP and lack of precision in either SBP or DBP is more likely to lead to overtreatment based on in-clinic BP, as those who are labeled as 'hypertensive' are likely to receive medication. Our data add to the recognition that in-clinic SBP tends to overestimate out-of-office BP and demonstrate that this effect is independent of age or mild CKD. At least in this population, the use of ABPM, as may be recommended by USPHTF, would tend to decrease the number of individuals meeting the current criteria for hypertension treatment. AQ9

Our study has limitations. We do not have repeated measures of ABPM, nor do we have objective data on sleep or sleep quality. Moreover, our study was cross-sectional, which precluded the ability to study the longitudinal relationships between CKD and blood pressure. Despite these limitations, our study also has several strengths. First, our participants were extensively characterized with regard to clinic and ambulatory blood

pressure, kidney function, and medication use concurrently, which allowed exploration of the potential role of multiple covariates. To our knowledge, this is the first study to evaluate the relationship between kidney disease defined by cystatin C and ABPM in community-living older adults, and to examine the precision and accuracy of clinic versus ABPM in those with mild kidney disease defined by cystatin C. If ABPM comes into widespread clinical practice, as suggested by USPSTF, these insights will be important to inform clinical interpretation of ABPM in patients across the range of CKDs.

Conclusion

The presence of CKD was independently associated only with low ambulatory DBP and not with other blood pressure parameters, including dipping, in our cohort. Clinic DBP, but not SBP, was in agreement with wake-time ABPM, and this was similar irrespective of CKD. Nonetheless, both clinic parameters lacked precision. Further studies may help clarify the role of ABPM in older individuals, including the longitudinal relationship between low DBP, kidney function, and adverse outcomes.

Acknowledgements

This work was supported by NIH K23 DK091521 (DER).

Conflicts of interest

AQ10 None declared.

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