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Chronic kidney disease and peripheral nerve function in the Health, Aging and Body Composition Study

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ABSTRACT

Background. Chronic kidney disease (CKD) is associated with poor mobility. Peripheral nerve function alterations play a significant role in low mobility. We tested the hypothesis that early CKD is associated with altered sensory, motor and autonomic nerve function.

Methods. Participants in the Health, Aging and Body Composition cohort who had kidney function measures in Year

3 (1999–2000) and nerve function measurements at Year 4 (2000–01) were analyzed ($n = 2290$). Sensory (vibration threshold, monofilament insensitivity to light and standard touch), motor [compound motor action potentials (CMAPs), nerve conduction velocities (NCVs)] and autonomic (heart rate response and recovery after a 400-m walk test) nerve function as well as participant characteristics were compared across cystatin C- and creatinine-based estimated glomerular filtration rate categorized as ≤ 60 (CKD) or >60 mL/min/1.73 m² (non-CKD).

The association between CKD and nerve function was examined with logistic regression adjusted for covariates.

Results. Participants with CKD ($n = 476$) were older (77 ± 3 versus 75 ± 3 years; $P < 0.05$) and had a higher prevalence of diabetes (20.6% versus 13.1%; $P < 0.001$). CKD was associated with higher odds for vibration detection threshold {odds ratio [OR] 1.7 [95% confidence interval (CI) 1.1–2.7]} and light touch insensitivity [OR 1.4 (95% CI 1.1–1.7)]. CMAPs and NCVs were not significantly different between CKD and non-CKD patients. In adjusted analyses, participants with CKD had higher odds of an abnormal heart rate response [OR 1.6 (95% CI 1.1–2.2)] and poor heart rate recovery [OR 1.5 (95% CI 1.1–2.0)].

Conclusions. CKD is associated with changes in sensory and autonomic nerve function, even after adjustment for demographics and comorbidities, including diabetes. Longitudinal studies in CKD are needed to determine the contribution of nerve impairments to clinically important outcomes.

Keywords: chronic kidney disease, peripheral nerve, motor, sensory

INTRODUCTION

Chronic kidney disease (CKD) affects >20 million Americans and is associated with an ‘accelerated aging’ phenotype [1]. Similar to aging, CKD is associated with increased falls, fractures, frailty and loss of mobility, the latter often assessed by gait speed [2, 3]. Decreased gait speed is common in patients with CKD, beginning with only minor loss of kidney function [4]. Loss of mobility is multifactorial in etiology, with poor bone health, sarcopenia, peripheral vascular disease and neuropathy all being likely contributors. In older adults, changes in motor and sensory peripheral nerve function are linked to decreased gait speed [5, 6] and endurance walking [7] and dysmobility [8, 9]. Alterations in sensory or motor peripheral nerve function are also related to decreases in muscle power [10], lower extremity strength [8] and skeletal muscle density [11], which may explain the link between peripheral nerve function and dysmobility in older adults.

In CKD, the prevalence of sensory or motor nerve impairments is not well characterized and it is uncertain if CKD is associated with peripheral nerve dysfunction, independent of diabetes, which is the leading cause of CKD. Diabetic polyneuropathy has a lifetime prevalence of ~50% and carries with it the risk of ulcers and falls [12, 13]. Proposed etiologies for peripheral neuropathy in diabetes include hyperglycemia, accumulation of advanced glycation end products (AGEs) and oxidative stress [14–17]. These metabolic derangements persist in diabetes even after patients develop CKD and probably continue to play a role in the development of peripheral nerve impairments. Even in CKD patients without diabetes, an accumulation of AGEs and oxidative stress occur [18]. Additionally, other uremic toxins accumulate, such as elevation in parathyroid hormone (PTH) [19, 20]. Structural and functional changes in axons have been demonstrated in advanced CKD [21]. Although most studies have evaluated advanced CKD, it is plausible that this pathophysiology begins in earlier stages of CKD, affecting peripheral nerve function. Therefore, in older community-dwelling individuals,

we tested whether measures of sensory, motor and autonomic nerve function are impaired in subjects with CKD [defined as an estimated glomerular filtration rate (eGFR) ≤ 60 mL/min/1.73 m²] compared with those with higher eGFR, even when adjusted for demographics and comorbidities.

MATERIALS AND METHODS

Study population

The Health, Aging and Body Composition (Health ABC) Study enrolled 3075 community-living older adults ages 70–79 years from two clinical sites in Memphis, TN and Pittsburgh, PA, USA, from April 1997 through June 1998. Participant eligibility included having no difficulty with performing activities of daily living that relate to mobility as well as the ability to walk 0.25 miles, walk up 10 steps, with no life-threatening cancers that require active therapy within 3 years prior to enrollment and plans to remain in the same geographic location for >3 years. Baseline evaluation included laboratory measurements, physical activity assessment, physiologic studies and a detailed history. Participants were followed for a period of 16 years. The study was approved by the Institutional Review Boards at the University of Tennessee Health Science Center and the University of Pittsburgh. This analysis was approved by the Institutional Review Board at the Indiana University School of Medicine, Indianapolis, IN, USA. Data from Year 3 (1999–2000) were used as baseline CKD because this is the closest year to the first available nerve function measurements at Year 4 (2000–01).

Measurements

Exposure variables. Kidney function at Year 3 (1999–2000) was evaluated using GFR estimated by the Chronic Kidney Disease Epidemiology Collaboration cystatin–creatinine (cys-cr) formula [22]. Blood samples were collected after overnight fasting. Creatinine was measured in a central laboratory on a Vitros 950 analyzer (Johnson & Johnson, New Brunswick, NJ, USA) using a colorimetric assay and calibrated to isotope-dilution mass spectrometry–traceable standards [23]. Cystatin C was analyzed on a BNII nephelometer (Dade Behring, Deerfield, IL, USA) using a particle-enhanced immunonephelometric assay [24]. CKD was defined as $\text{eGFR}_{\text{cys-cr}} \leq 60$ mL/min/1.73 m².

SOutcomes. Peripheral nerve function in the lower extremity was measured by a trained examiner as previously described [25, 26]. Year 4 nerve function measures were used for this analysis. For motor nerve function, compound motor action potential (CMAP) and nerve conduction velocity (NCV) were measured. Peroneal motor nerve conduction amplitude was measured in millivolts (mV) with stimulation at the popliteal fossa, fibular head and ankle using the NeuroMax 8 (XLTEK, Oakville, ON, Canada) and NCV was measured in meters per second (m/s).

Sensory nerve function was measured using the vibration detection threshold in microns (μm) on the bottom of the large toe with a VSA-3000 Vibratory Sensory Analyzer (Medoc, Ramat Yishai, Israel) and monofilament insensitivity, defined

as the inability to feel three of four touches at the dorsum of the large toe with a 10-gauge and a 1.4-gauge monofilament.

Clinically meaningful cut points of motor amplitude $<1\text{ mV}$, conduction velocity $<40\text{ m/s}$ [27] and vibration threshold $>130\mu\text{m}$ were used to define impairment, as previously described [8]. Self-reported symptoms attributable to peripheral neuropathy in the lower extremity of numbness or tingling and sudden stabbing or burning pains or aches in the preceding 12 months were collected.

Autonomic nerve function. Only participants who completed the long distance corridor walk (LDCW; 400-m walk) were included in these analyses [28]. The LDCW was performed with two traffic cones spaced 20 m apart. Participants walked 10 laps around the cones to complete 400 m. The testing began with a 2-min warm-up walk where the participant was asked to ‘cover as much ground as possible’ followed by the LDCW, where the participant was instructed to walk ‘as quickly as possible at a pace that can be maintained for 400 meters’ [28, 29]. Heart rate was recorded for each lap and blood pressure was measured at the end of the test. Resting heart rate was measured before the 400-m walk. Heart rate response was defined as the difference in heart rate at the end of a 400-m walk test and the resting heart rate measured before the 400-m walk. Heart rate recovery was the difference in heart rate immediately after exercise and the heart rate after a 2-min resting period. The heart rate measured was a single instantaneous value at each of the time points mentioned. Data were divided into tertiles and cutoffs for heart rate response were 37 and 50 bpm, whereas heart rate recovery tertile cutoffs were 13 and 21 bpm. Participants with a heart rate response in the first tertile were considered to have the poorest response while those with a heart rate increase >50 bpm were the reference group in logistic regression analysis. For heart rate recovery after a 2-min rest, participants in the >21 bpm range were considered the reference group while the group with <13 bpm change after the resting period were considered to have the poorest response.

Covariates. Demographic variables including age, sex, race and smoking status were determined by self-report. Body mass index was calculated in kg/m^2 . Diabetes was defined as the use of hypoglycemic agents, self-reported history, fasting plasma glucose level $>126\text{ mg/dL}$ or 2-h oral glucose tolerance test $>200\text{ mg/dL}$. Hypertension was defined as systolic blood pressure $>140\text{ mmHg}$, diastolic blood pressure $>90\text{ mmHg}$ or current use of antihypertensive medications and self-report of hypertension. Trained and certified clinical staff measured blood pressure from the right arm using conventional mercury sphygmomanometers. Current smoking habits at Year 3 were recorded. Physical activity, expressed in kcal/kg/week , was the total calories spent walking and climbing stairs at Year 4. Peripheral arterial disease was defined by an arm–ankle index <0.9 measured in the right and left lower extremities. A history of transient ischemic attack or stroke was defined as cerebrovascular disease and cardiovascular disease as history of coronary artery disease and/or congestive heart failure. Participants’ medications were recorded by study personnel and categorized by the Iowa Drug Information System into major therapeutic

groups. Serum vitamin B12 levels were measured at Year 3 using a competitive immunoassay (Bayer HealthCare, Pittsburgh, PA, USA) and levels $<260\text{ pg/mL}$ were considered ‘deficiency’ [30]. Intact PTH levels (N-tact PTH SP kit; DiaSorin, Saluggia, Italy) were measured at Year 2, as used in prior Health ABC publications [31, 32].

Statistical analyses

Participant characteristics in those with and without CKD were compared with a *t*-test or chi-squared test, as appropriate. A two-sided *P*-value <0.05 was considered statistically significant. Logistic regression analyses tested the association between CKD and nerve function. Factors were chosen on the basis of clinical relevance for initial exploratory analysis. Variables with a *P*-value <0.1 in univariate analysis were included in the multivariate model. Age, sex, race, diabetes status and physical activity were forced into the multivariable model while the other variables were included in a forward stepwise conditional fashion. In addition, for variables of heart rate response and heart rate recovery, beta blocker use was forced in the multivariable model. Overall model fit was assessed by a likelihood ratio test. A cross-validated Hosmer–Lemeshow chi-square statistic was used to assess for calibration. The specification and linearity of predictor variables were tested and found to be intact, with no significant correlation between variables. Binary logistic regression was used for variables of NCV, CMAP and vibration detection with two possible outcomes, whereas multinomial logistic regression was used for the ordinal variables of monofilament insensitivity, heart rate response and recovery with more than two possible outcomes. Analyses were repeated using eGFR (per each $10\text{ mL/min/1.73 m}^2$) as a continuous variable with continuous measures of motor and sensory nerve function. Given the nonlinear relationship between measures of sensory and motor nerve function and eGFR, we employed restrictive cubic splines to display these relationships using six predefined knots. The knots were used for eGFR at values of 15, 30, 45, 60, 90 and $120\text{ mL/min/1.73 m}^2$. The ‘postcubic spline package’ for Stata version 15.0 (StataCorp, College Station, TX, USA) was used to generate curves [33].

We conducted sensitivity analyses to confirm that findings were consistent in participants without diabetes. We also performed a sensitivity analysis where nerve function was compared in participants with $\text{eGFR} \leq 45\text{ mL/min/1.73 m}^2$ (CKD Stage 3b) and those with $\text{eGFR} > 45\text{ mL/min/1.73 m}^2$.

RESULTS

A total of 2359 participants (80.7%) had both creatinine and cystatin C measurements available to allow for calculation of eGFR at Year 3. Of these participants, 2290 who had at least one of the nerve function measurements available at Year 4 (2000–01) were included in the analyses. A total of 1453/2290 participants completed the LDCW.

The prevalence of CKD was 21% (476 participants) with no difference in sex or race between those with and without CKD. The mean eGFR was 48.5 ± 10.3 in participants with CKD. Participants with CKD were older (77 ± 3 versus 75 ± 3 years; $P < 0.05$) and had higher prevalence of diabetes (20.6% versus

13.1%; $P < 0.001$). Comorbidities, including hypertension (56.1% versus 39.9%), cardiovascular disease (31.9% versus 20.6%) and cerebrovascular disease (9.2% versus 6.2%) were higher in the CKD population. Other participant characteristics are as listed in Table 1.

Sensory nerve function

The prevalence of insensitivity to light touch (1.4-gauge monofilament testing) and standard touch (10-gauge monofilament testing) was higher in participants with CKD: 42% versus 36% and 11% versus 8%, respectively (both $P < 0.01$). The number of participants unable to feel the vibration at a preset threshold of 130 μm was significantly higher in participants with $\text{eGFR} \leq 60 \text{ mL/min/1.73 m}^2$ (8.5% versus 4.2%; $P < 0.001$). Although objectively measured peripheral nerve impairment was higher in the CKD population, no significant difference was found in the self-reported symptoms of numbness (30.6% versus 28.2%) or neuropathic pain (19.4% versus 16.4%) between groups (Table 2).

In the multivariable logistic regression model, CKD was associated with higher odds of impaired vibration detection threshold {odds ratio [OR] 1.7 [95% confidence interval (CI) 1.1–2.7]} (Table 3). The results remained significant in an analysis using eGFR as a continuous variable [OR 1.1 (95% CI 1.01–1.3), $P < 0.05$] (Supplementary data, Table S1). CKD was also associated with higher odds of light touch insensitivity [OR 1.4 (95% CI 1.1–1.7)] but not standard touch insensitivity (Table 3). Each 10 mL/min/1.73 m^2 lower eGFR was associated with higher odds of both light [OR 1.13 (95% CI 1.06–1.21)] and standard touch insensitivity [OR 1.12 (95% CI 1.01–1.25)] in fully adjusted models (Supplementary data, Table S1). Figure 1 shows the continuous relationship of vibration threshold with eGFR modeled as a restricted cubic spline. Lower eGFR was associated with an increasing vibration detection threshold (see Figure 1, top panel).

Motor nerve function

More participants with CKD had low CMAP (16.0% versus 10.2%; $P < 0.01$) as compared with those without CKD. Parameters of motor function (NCV and CMAP) were not significantly different for CKD versus non-CKD in multivariable regression analysis (Table 3). Each 10 mL/min/1.73 m^2 lower eGFR was associated with higher odds of reduced CMAP (Supplementary data, Table S1). Figure 1 (lower two panels) shows the relationship of eGFR to both CMAP and NCV expressed as continuous variables. As eGFR decreased below 60 mL/min/1.73 m^2 , lower eGFR was associated with lower CMAP and NCV values.

Autonomic variables

Heart rate response and recovery were significantly different in those with CKD versus non-CKD ($P < 0.05$). CKD participants had a significantly blunted increase in heart rate during exercise and significantly lower reduction in heart rate during the resting period (Table 2). In the model adjusted for beta blocker use and other covariates, participants with CKD had 1.6 times higher odds of having an abnormal heart rate response

Table 1. Description of all participants who had eGFR available at Year 3 ($n = 2290$)

Participant characteristics	eGFR at Year 3		P-value
	>60 (non-CKD) [$n = 1814$ (79.2%)]	≤ 60 (CKD) [$n = 476$ (20.8%)]	
Age (years), mean (SD)	75 (3)	77 (3)	<0.05
Male, %	47.0	49.6	0.32
Black, %	38.9	36.7	0.39
Active smoking at Year 3, %	7.2	7.5	0.91
Alcohol consumption (>1 drink/week), %	52.5	43.5	<0.05
BMI, mean (SD)	27.0 (4.8)	27.6 (4.8)	<0.05
Diabetes, %	13.1	20.6	<0.001
Hypertension, %	39.9	56.1	<0.001
Cardiovascular disease, %	20.6	31.9	<0.001
Cerebrovascular disease, %	6.2	9.2	<0.05
Peripheral vascular disease, %			
R<0.9, L<0.9	6.4, 7.4	11.1, 11.6	<0.001
eGFR _{cys-cr} , mean (SD)	79.9 (13.0)	48.5 (10.3)	<0.001
Deficient vitamin B12, %	15.8	13.9	0.29
Total physical activity (KWJ), mean (SD)	6.2 (18.4)	4.6 (10.3)	0.08

Table 2. Nerve function parameters in CKD and non-CKD

	Non-CKD	CKD	P-value
Sensory, n (%)			
Monofilament ($n = 2076$)			
Unable to detect 1.4 gauge	598 (35.9)	173 (42.2)	<0.05
Unable to detect 10 gauge	139 (8.3)	46 (11.2)	
Vibration detection threshold ($n = 2019$)	68 (4.2)	34 (8.5)	<0.001
Unable to detect vibration			
Numbness ($n = 2099$)	475 (28.2)	127 (30.6)	0.32
Stabbing pain ($n = 2106$)	277 (16.4)	81 (19.4)	0.15
Motor, n (%)			
CMAP <1 mV ($n = 1645$)	136 (10.2)	50 (16.0)	<0.05
NCV <40 m/s ($n = 1539$)	267 (21.2)	74 (26.4)	0.06
Autonomic function, n (%)			
Heart rate response	44.6 (14.5)	41.1 (16.2)	<0.05
Heart rate recovery	18.8 (10.7)	16.5 (10.1)	<0.05

(95% CI 1.1–2.2) as well as poor heart rate recovery [OR 1.5 (95% CI 1.1–2.0)] (Table 3). When eGFR was used as a continuous variable, each 10 mL/min/1.73 m^2 lower eGFR was associated with higher odds of third versus first tertile of heart response and recovery (Supplementary data, Table S1).

In a sensitivity analysis (Supplementary data, Table S2), we excluded participants with diabetes ($n = 1955$, 378 with CKD and 1577 non-CKD). Physical activity was significantly different between the two eGFR groups in analyses of those without diabetes. In fully adjusted analyses, CKD was associated with higher odds for light touch insensitivity [OR 1.4 (95% CI 1.1–1.8)] and slower heart rate recovery [OR 1.6 (95% CI 1.1–2.2)],

FIGURE 1: Restricted cubic spline showing relationship between (A) vibration detection threshold and eGFR, (B) CMAP and eGFR and (C) NCV and eGFR.

similar to findings in the main analysis above but not vibration detection [OR 1.6 (95% CI 1.0–2.8)] or heart rate response [OR 1.4 (95% CI 1.0–2.1)]. In a second sensitivity analysis, we compared participants with $\text{eGFR} \leq 45 \text{ mL/min/1.73 m}^2$ with those with $\text{eGFR} > 45 \text{ mL/min/1.73 m}^2$. Point prevalence of vibration, sensitivity to light and standard touch, CMAPs and autonomic nerve measures remained higher in those with $\text{eGFR} \leq 45 \text{ mL/min/1.73 m}^2$ versus those with $\text{eGFR} > 45 \text{ mL/min/1.73 m}^2$. The overall direction of relationships between nerve impairments and kidney function remained intact in logistic regression

analyses when comparing participants with $\text{eGFR} \leq 45 \text{ mL/min/1.73 m}^2$ with those with $\text{eGFR} > 45 \text{ mL/min/1.73 m}^2$.

DISCUSSION

Our findings are unique in that we show that age-related peripheral nerve impairments are more common in the setting of CKD. The present study demonstrates that subclinical sensory nerve impairments assessed by vibration sensitivity and monofilament testing were more prevalent in older community-dwelling adults with CKD than those without CKD. CKD remained associated with sensory impairments after adjusting for diabetes. Furthermore, lower values of continuous eGFR were associated with higher odds of monofilament insensitivity. Even in the nondiabetic CKD group sensitivity analysis, the monofilament insensitivity remained significant although the vibration detection threshold did not. Of interest, subjective symptoms of neuropathy such as numbness and pain were not different between those with CKD and without, despite differences in the prevalence of objective measures of monofilament insensitivity and vibration detection. This is consistent with data showing that older adults are asymptomatic for many age-related nerve impairments and hence symptoms may be poor indicators of underlying nerve deficits [34].

Previous studies have documented that dialysis-dependent CKD is associated with autonomic dysfunction and excess sympathetic activity [35]. In a study of 73 subjects with hypertensive CKD and a mean GFR of $40.7 \text{ mL/min/1.73 m}^2$, mean sympathetic nerve activity assessed by recording of efferent postganglionic sympathetic nerve activity to the skeletal muscle was increased in CKD compared with controls [36]. Heart rate recovery is a surrogate for autonomic nerve function and our findings in early CKD were consistent with this result. In the general population, a slower decrease in heart rate at 2 min after submaximal testing was associated with mortality [37]. The exercise testing methods used were different and hence we could not use the same cutoffs. Therefore we used tertiles to stratify heart rate recovery and defined the group with the least change (i.e. $< 13 \text{ bpm}$) as being abnormal. We found that CKD was associated with delayed heart rate recovery, which has been associated with higher rates of hospitalization in CKD [38]. In CKD requiring dialysis, heart rate variability by 24-h electrocardiographic monitoring, a measure of autonomic dysfunction, has prognostic value in predicting sudden cardiac death (SCD) [39]. This is important, as the incidence of SCD increases with the progression of CKD [40] and is the leading cause of cardiovascular death in patients on dialysis [41]. The role of autonomic nerve function changes and mortality in CKD merits further study.

In contrast to our findings in sensory and autonomic nerve function, we did not observe any differences in motor NCV or CMAP in participants with CKD versus those without CKD. This suggests that the pattern of nerve function changes associated with CKD are in the sensory and autonomic domain and less likely in the motor domain, at least in early CKD. The majority of our study population with $\text{GFR} \leq 60 \text{ mL/min/1.73 m}^2$ were in earlier stages of CKD (mean $\text{GFR} = 48.5 \pm 10.3 \text{ mL/min}$) and thus motor nerve impairments may occur only in

Table 3. Association of CKD with nerve function

Nerve function	Unadjusted model, OR (95% CI)		Adjusted model ^a , OR (95% CI)	
eGFR (mL/min/1.73 m ²)	≤60	>60	≤60	>60
Sensory				
Monofilament insensitivity				
1.4g	1.4 (1.1–1.8)	Ref	1.4 (1.1–1.7)	Ref
10g	1.6 (1.1–2.3)	Ref	1.2 (0.9–1.7)	Ref
Vibration detection threshold (<130 μm)	2.1 (1.4–3.3)	Ref	1.7 (1.1–2.7)	Ref
Motor				
Amplitude (CMAP <1 mV)	1.4 (1.0–2.0)	Ref	1.3 (0.9–1.9)	Ref
Velocity (NCV <40 m/s)	1.0 (0.8–1.4)	Ref	1.0 (0.7–1.3)	Ref
Autonomic				
Heart rate response ^c				
Ref >50 bpm				
Second tertile (37–50)	1.6 (1.2–2.3)	Ref	1.4 (1.0–2.0) ^b	Ref
Third tertile (<37)	1.6 (1.2–2.3)	Ref	1.6 (1.1–2.2) ^b	Ref
Heart rate recovery ^d				
Ref >21 bpm				
Second tertile (14–21)	1.2 (0.8–1.6)	Ref	1.1 (0.8–1.6) ^b	Ref
Third tertile (<13)	1.5 (1.1–2.0)	Ref	1.5 (1.1–2.0) ^b	Ref

^aAdjusted for demographics, comorbidities (diabetes mellitus, hypertension, coronary artery disease, peripheral vascular disease), lifestyle factors, pertinent labs (vitamin B12, serum PTH).

^bAdjusted for factors in note a as well as for beta blocker use.

^cHeart rate response = (heart rate at the end of a 400-m walk – heart rate at rest).

^dHeart rate recovery = (heart rate at the end of a 400-m walk – heart rate after 2 min rest).

more advanced CKD. The relationship between motor nerve function and CKD is important to investigate in future studies.

This study was not designed to investigate potential mechanisms for peripheral nerve impairments in early CKD. However, studies in patients undergoing dialysis depict anatomical changes such as increased cross-sectional area and hypoechoic areas that correlate with symptoms of clinical peripheral neuropathy [21]. Interestingly, even a single dialysis session leads to partial reversal of these anatomical changes [21] and changes in neurophysiological measures [42, 43]. Similarly, improvement in neuropathy was noted with improved kidney function after transplantation [44, 45], although this may not be true in all patients, as those receiving calcineurin inhibitor therapy remain at risk for developing neurotoxicity [46]. Electrolyte abnormalities such as hyperkalemia are postulated to lead to axonal membrane depolarization and nerve excitability [47]. Furthermore, a recent trial demonstrated that changes in nerve function in CKD that were attributed to neuropathy improved with dietary potassium restriction [48]. Nerve function also improves after parathyroidectomy in dialysis patients, indicating a potential role for PTH [49]. PTH levels are increased >30% for patients at GFRs between 40 and 49 mL/min/1.73 m² [20]. These studies suggest that accumulation of uremic toxins, secondary hyperparathyroidism and electrolyte derangements play a role in the pathophysiology of nerve impairments in CKD.

This study has several strengths and limitations. The size of the analysis population is an important strength. Another strength is that the Health ABC consists of community dwelling mobile adults and manifestations of disability or other end stage comorbidities were excluded, thus removing some potential confounders in our analyses of early CKD. In addition to

standardized measurements of nerve function, we also used validated measures of kidney function, the eGFR_{cys-cr} [22]. In the Health ABC Study, kidney function was measured at Year 3 and nerve measures at Year 4. Given that kidney function tends to decline over time, it is possible that eGFR may have decreased in some participants, allowing them to move from the >60 to the ≤60 mL/min/1.73 m² group from Year 3 to Year 4. The potential number of these participants is low since eGFR tends to be relatively stable over 1 year. Further, given the relationship we identified between kidney function and nerve function, greater impairments in nerve measures are most likely to occur with lower kidney function. Therefore any bias introduced due to the assessment of kidney function at Year 3 and nerve measures at Year 4 would, in all likelihood, reduce the magnitude of the observed association between them. Another important limitation of this analysis is the lack of albuminuria or proteinuria assessment at the same time point at the cystatin/creatinine assessments, precluding the use of albuminuria as a definition of CKD. Thus we may have misclassified CKD patients with albuminuria but eGFR >60 mL/min/1.73 m² as ‘non-CKD’. Our analysis is also limited by the methodology of the nerve function measures that were collected; for example, we were not able to comment on heat or cold sensitivity in CKD, which would have important clinical bearing, due to the lack of collection in the Health ABC cohort. Future studies will need to focus on more comprehensive testing of all nerve fiber types (both large and small) in CKD. We categorized participants based on cutoffs in the general population, which may not have the same clinical relevance in patients with CKD. Our findings may represent an earlier stage of neuropathy or a lack of relationship of objective testing with peripheral neuropathy symptoms may exist. In patients with diabetes, objective nerve function testing is often altered before clinical symptoms of

neuropathy [50]. It is unknown if the relationship between clinical symptoms and objective testing is similar in CKD.

In summary, in a cross-sectional analysis of community-dwelling older adults, $\text{GFR} \leq 60 \text{ mL/min/1.73 m}^2$ is associated with significant changes in nerve function parameters indicative of impaired sensory and autonomic function, even after adjustment for demographics and comorbidities, including diabetes. In older adults, peripheral nerve impairments contribute to reduced lower extremity muscle strength [25], gait dysfunction and reduced walking speed and endurance [7, 10]. Given the known loss of skeletal muscle strength and decreased gait speed in patients in CKD compared with age-matched controls [51], future studies will need to determine the contribution of these nerve impairments to these findings.

SUPPLEMENTARY DATA

Supplementary data are available at [ndt](http://ndt.oxfordjournals.org) online.

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AUTHORS' CONTRIBUTIONS

All authors have contributed to this manuscript and approved this submission.

CONFLICT OF INTEREST STATEMENT

None declared.

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