Title

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

Journal

Nephrology Dialysis Transplantation, 34(4)

Authors

Moorthi, Ranjani
Doshi, Simit
Fried, Linda
et al.

Publication Date

2019-04-01

DOI

10.1093/ndt/gfy102

Peer reviewed

21. McCarthy B, Casey D, Devane D *et al.* Pulmonary rehabilitation for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2015; (2): CD003793
22. Anderson L, Thompson DR, Oldridge N *et al.* Exercise-based cardiac rehabilitation for coronary heart disease. *Cochrane Database Syst Rev* 2016; 67: 1
23. Houchen-Wolloff L, Williams JE, Green RH *et al.* Survival following pulmonary rehabilitation in patients with COPD: the effect of program completion and change in incremental shuttle walking test distance. *J Chron Obstruct Pulmon Dis* 2017; 13: 37
24. Singh SJ, Morgan MD, Scott S *et al.* Development of a shuttle walking test of disability in patients with chronic airways obstruction. *Thorax* 1992; 47: 1019–1024
25. Singh SJ, Jones P, Evans R *et al.* Minimum clinically important improvement for the incremental shuttle walking test. *Thorax* 2008; 63: 775–777
26. MacLaughlin HL, Hall WL, Condry J *et al.* Participation in a structured weight loss program and all-cause mortality and cardiovascular morbidity in obese patients with chronic kidney disease. *J Ren Nutr* 2015; 25: 472–479
27. Sietsema KE, Hiatt WR, Esler A *et al.* Clinical and demographic predictors of exercise capacity in end-stage renal disease. *Am J Kidney Dis* 2002; 39: 76–85
28. Doherty P, Lewin R. The RAMIT trial, a pragmatic RCT of cardiac rehabilitation versus usual care: what does it tell us? *Heart* 2012; 98: 605–606
29. Wood D. Is cardiac rehabilitation fit for purpose in the NHS: maybe not. *Heart* 2012; 98: 607–608
30. West RR, Jones DA, Henderson AH. Rehabilitation after myocardial infarction trial (RAMIT): multi-centre randomised controlled trial of comprehensive cardiac rehabilitation in patients following acute myocardial infarction. *Heart* 2012; 98: 637–644
31. Hallan SI, Matsushita K, Sang Y *et al.* Age and association of kidney measures with mortality and end-stage renal disease. *JAMA* 2012; 308: 2349–2360
32. Palmer SC, Craig JC, Navaneethan SD *et al.* Benefits and harms of statin therapy for persons with chronic kidney disease: a systematic review and meta-analysis. *Ann Intern Med* 2012; 157: 263–275

Received: 6.6.2018; Editorial decision: 9.10.2018

Nephrol Dial Transplant (2019) 34: 625–632
doi: 10.1093/ndt/gfy102
Advance Access publication 10 May 2018

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

Ranjani N. Moorthi[1,*], Simit Doshi[1,*], Linda F. Fried[2,3,4], Sharon M. Moe[1,5], Mark J. Sarnak[6], Suzanne Satterfield[7], Ann V. Schwartz[8], Michael Shlipak[9], Brittney S. Lange-Maia[10], Tamara B. Harris[11], Anne B. Newman[12] and Elsa S. Strotmeyer[12]

[1]Department of Medicine, Division of Nephrology, Indiana University School of Medicine, Indianapolis, IN, USA, [2]Renal Section, VA Pittsburgh Healthcare System, Pittsburgh, Pennsylvania, USA, [3]Department of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania, USA, [4]Department of Epidemiology, University of Pittsburgh Graduate School of Public Health, Pittsburgh, PA, [5]Roudebush VA Medical Center, Indianapolis, IN, USA, [6]Department of Medicine, Division of Nephrology, Tufts Medical Center, Boston, MA, USA, [7]Department of Preventive Medicine, University of Tennessee Health Science Center, Memphis, TN, USA, [8]Department of Epidemiology and Biostatistics, University of California San Francisco, San Francisco, CA, USA, [9]Division of Nephrology, Department of Medicine, San Francisco VA Medical Center, San Francisco, CA; Kidney Health Research Collaborative, San Francisco VA Medical Center and University of California, San Francisco, CA, USA, [10]Department of Preventive Medicine and Center for Community Health Equity, Rush University Medical Center, Chicago, IL, USA, [11]Intramural Research Program, Laboratory of Epidemiology, and Population Sciences, National Institute on Aging, National Institutes of Health, Laboratory of Epidemiology, Demography, and Biometry, Bethesda, MD, USA and [12]Department of Epidemiology, University of Pittsburgh, Pittsburgh, PA, USA

*These authors contributed equally to this work
Correspondence and offprint requests to: Ranjani N. Moorthi; E-mail: rmoorthi@iu.edu

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 m^2 (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 m^2] 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 eGFRcys-cr ≤60 mL/min/1.73 m^2.

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 <1mV, conduction velocity <40m/s [27] and vibration threshold >130μm 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 mg/dL or 2-h oral glucose tolerance test >200 mg/dL. Hypertension was defined as systolic blood pressure >140 mmHg, diastolic blood pressure >90 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 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 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 mL/min/1.73 m^2. The 'postrcspline 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 eGFR ≤45 mL/min/1.73 m^2 (CKD Stage 3b) and those with eGFR >45 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 include 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 eGFR ≤60 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 (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)],

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
eGFRcys-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

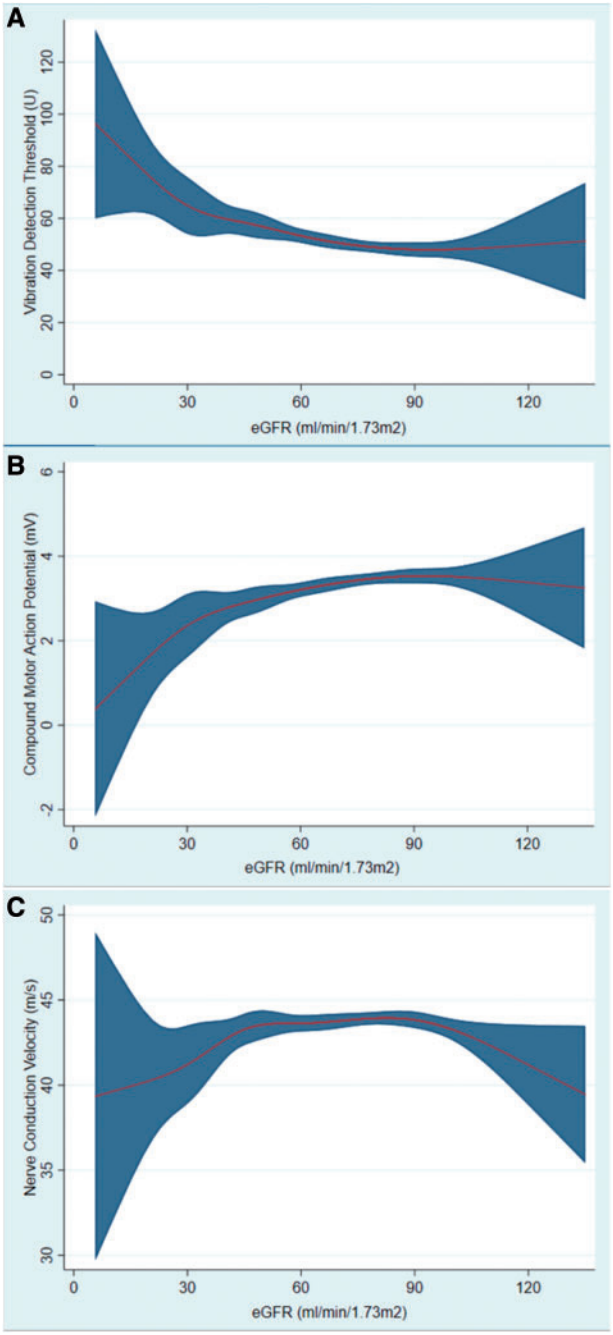

FIGURE 1: Restricted cubic spline showing relationship between (**A**) vibration detection threshold and eGFR, (**B**) CMAP and eGFR and (**C**) NCV and eGFR.

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 eGFR $\leq$45 mL/min/1.73 m^2 with those with eGFR >45 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 eGFR $\leq$45 mL/min/1.73 m^2 versus those with eGFR >45 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 eGFR $\leq$45 mL/min/1.73 m^2 with those with eGFR >45 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 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 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 GFR $\leq$60 mL/min/1.73 m^2 were in earlier stages of CKD (mean GFR = 48.5$\pm$ 10.3 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

[a]Adjusted for demographics, comorbidities (diabetes mellitus, hypertension, coronary artery disease, peripheral vascular disease), lifestyle factors, pertinent labs (vitamin B12, serum PTH).
[b]Adjusted for factors in note a as well as for beta blocker use.
[c]Heart rate response = (heart rate at the end of a 400-m walk – heart rate at rest).
[d]Heart 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 m^2 [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 eGFRcys-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 m^2 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 m^2 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, GFR $\leq$60 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 online.

FUNDING

This research was supported by the National Institute on Aging (NIA) contracts N01-AG-6-2101, N01-AG-6-2103, N01-AG-6-2106; NIA grant R01-AG028050 and National Institute of Nursing Research grant R01-NR012459. This research was funded in part by the Intramural Research Program of the National Institutes of Health, NIA. In addition, this work was supported by the K23 DK102824-01A1 Longitudinal Assessment of Skeletal Muscle Physiology in Dialysis Patients, Granting Agency: National Institute of Diabetes and Digestive and Kidney Diseases (author: R.N.M.) as well as the National Institutes of Aging funded grant the Aging Kidney: Chronic Injury, Impaired Functions and Clinical Outcomes (RO1 AG 027002).

AUTHORS' CONTRIBUTIONS

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

CONFLICT OF INTEREST STATEMENT

None declared.

REFERENCES

1. Kooman JP, Broers NJ, Usvyat L *et al.* Out of control: accelerated aging in uremia. *Nephrol Dial Transplant* 2013; 28: 48–54
2. Painter P, Roshanravan B. The association of physical activity and physical function with clinical outcomes in adults with chronic kidney disease. *Curr Opin Nephrol Hypertens* 2013; 22: 615–623
3. Roshanravan B, Robinson-Cohen C, Patel KV *et al.* Association between physical performance and all-cause mortality in CKD. *J Am Soc Nephrol* 2013; 24: 822–830
4. Roshanravan B, Khatri M, Robinson-Cohen C *et al.* A prospective study of frailty in nephrology-referred patients with CKD. *Am J Kidney Dis* 2012; 60: 912–921
5. McDermott MM, Guralnik JM, Albay M *et al.* Impairments of muscles and nerves associated with peripheral arterial disease and their relationship with lower extremity functioning: the InCHIANTI Study. *J Am Geriatr Soc* 2004; 52: 405–410
6. Deshpande N, Ferrucci L, Metter J *et al.* Association of lower limb cutaneous sensitivity with gait speed in the elderly: the Health ABC Study. *Am J Phys Med Rehabil* 2008; 87: 921–928
7. Lange-Maia BS, Newman AB, Cauley JA *et al.* Sensorimotor peripheral nerve function and the longitudinal relationship with endurance walking in the Health, Aging and Body Composition Study. *Arch Phys Med Rehabil* 2016; 97: 45–52
8. Ward RE, Boudreau RM, Caserotti P *et al.* Sensory and motor peripheral nerve function and incident mobility disability. *J Am Geriatr Soc* 2014; 62: 2273–2279
9. Ward RE, Caserotti P, Cauley JA *et al.* Mobility-related consequences of reduced lower-extremity peripheral nerve function with age: a systematic review. *Aging Dis* 2016; 7: 466–478
10. Ward RE, Boudreau RM, Caserotti P *et al.* Sensory and motor peripheral nerve function and longitudinal changes in quadriceps strength. *J Gerontol A Biol Sci Med Sci* 2015; 70: 464–470
11. Lauretani F, Bandinelli S, Bartali B *et al.* Axonal degeneration affects muscle density in older men and women. *Neurobiol Aging* 2006; 27: 1145–1154
12. Abbott CA, Carrington AL, Ashe H *et al.* The North-West Diabetes Foot Care Study: incidence of, and risk factors for, new diabetic foot ulceration in a community-based patient cohort. *Diabet Med* 2002; 19: 377–384
13. Timar B, Timar R, Gaită L *et al.* The impact of diabetic neuropathy on balance and on the risk of falls in patients with type 2 diabetes mellitus: a cross-sectional study. *PLoS One* 2016; 11: e0154654
14. Leroith D, Accili D. Mechanisms of disease: using genetically altered mice to study concepts of type 2 diabetes. *Nat Clin Pract Endocrinol Metab* 2008; 4: 164–172
15. Vinik AI, Strotmeyer ES, Nakave AA *et al.* Diabetic neuropathy in older adults. *Clin Geriatr Med* 2008; 24: 407–435
16. Roman-Pintos LM, Villegas-Rivera G, Rodriguez-Carrizalez AD *et al.* Diabetic polyneuropathy in type 2 diabetes mellitus: inflammation, oxidative stress, and mitochondrial function. *J Diabetes Res* 2016; 2016: 3425617
17. Shakeel M. Recent advances in understanding the role of oxidative stress in diabetic neuropathy. *Diabetes Metab Syndr* 2015; 9: 373–378
18. Ruiz S, Pergola PE, Zager RA *et al.* Targeting the transcription factor Nrf2 to ameliorate oxidative stress and inflammation in chronic kidney disease. *Kidney Int* 2013; 83: 1029–1041
19. Stenvinkel P, Carrero JJ, Axelsson J *et al.* Emerging biomarkers for evaluating cardiovascular risk in the chronic kidney disease patient: how do new pieces fit into the uremic puzzle? *Clin J Am Soc Nephrol* 2008; 3: 505–521
20. Isakova T, Wahl P, Vargas GS *et al.* Fibroblast growth factor 23 is elevated before parathyroid hormone and phosphate in chronic kidney disease. *Kidney Int* 2011; 79: 1370–1378
21. Borire AA, Arnold R, Pussell BA *et al.* Haemodialysis alters peripheral nerve morphology in end-stage kidney disease. *Clin Neurophysiol* 2017; 128: 281–286
22. Inker LA, Schmid CH, Tighiouart H *et al.* Estimating glomerular filtration rate from serum creatinine and cystatin C. *N Engl J Med* 2012; 367: 20–29
23. Kurella M, Chertow GM, Fried LF *et al.* Chronic kidney disease and cognitive impairment in the elderly: the health, aging, and body composition study. *J Am Soc Nephrol* 2005; 16: 2127–2133
24. Bibbins-Domingo K, Chertow GM, Fried LF *et al.* Renal function and heart failure risk in older black and white individuals: the Health, Aging, and Body Composition Study. *Arch Intern Med* 2006; 166: 1396–1402
25. Strotmeyer ES, de Rekeneire N, Schwartz AV *et al.* Sensory and motor peripheral nerve function and lower-extremity quadriceps strength: the Health, Aging and Body Composition Study. *J Am Geriatr Soc* 2009; 57: 2004–2010
26. Ward RE, Boudreau RM, Vinik AI *et al.* Reproducibility of peroneal motor nerve conduction measurement in older adults. *Clin Neurophysiol* 2013; 124: 603–609
27. Maser RE, Nielsen VK, Dorman JS *et al.* Measuring subclinical neuropathy: does it relate to clinical neuropathy? Pittsburgh epidemiology of diabetes complications study-V. *J Diabet Complications* 1991; 5: 6–12
28. Simonsick EM, Montgomery PS, Newman AB *et al.* Measuring fitness in healthy older adults: the Health ABC long distance corridor walk. *J Am Geriatr Soc* 2001; 49: 1544–1548
29. Lange-Maia BS, Strotmeyer ES, Harris TB *et al.* Physical activity and change in long distance corridor walk performance in the Health, Aging, and Body Composition Study. *J Am Geriatr Soc* 2015; 63: 1348–1354

30. Leishear K, Boudreau RM, Studenski SA *et al*. Relationship between vitamin B12 and sensory and motor peripheral nerve function in older adults. *J Am Geriatr Soc* 2012; 60: 1057–1063
31. Madero M, Wassel CL, Peralta CA *et al*. Markers of mineral metabolism are not associated with aortic pulse wave velocity in community-living elderly persons: the Health, Aging, and Body Composition Study. *Am J Hypertens* 2011; 24: 755–761
32. Isakova T, Cai X, Lee J *et al*. Associations of FGF23 with change in bone mineral density and fracture risk in older individuals. *J Bone Miner Res* 2016; 31: 742–748
33. Buis ML. POSTRCSPLINE: Stata module containing post-estimation commands for models using a restricted cubic spline [program], 2008. Statistical Software Components S456928, https://ideas.repec.org/c/boc/bocode/s456928.html
34. Gregg EW, Sorlie P, Paulose-Ram R *et al*. Prevalence of lower-extremity disease in the US adult population ≥40 years of age with and without diabetes: 1999-2000 National Health and Nutrition Examination Survey. *Diabetes Care* 2004; 27: 1591–1597
35. Chang YM, Shiao CC, Chang KC *et al*. Heart rate variability is an indicator for intradialytic hypotension among chronic hemodialysis patients. *Clin Exp Nephrol* 2016; 20: 650–659
36. Grassi G, Quarti-Trevano F, Seravalle G *et al*. Early sympathetic activation in the initial clinical stages of chronic renal failure. *Hypertension* 2011; 57: 846–851
37. Cole CR, Foody JM, Blackstone EH *et al*. Heart rate recovery after submaximal exercise testing as a predictor of mortality in a cardiovascularly healthy cohort. *Ann Intern Med* 2000; 132: 552–555
38. Brotman DJ, Bash LD, Qayyum R *et al*. Heart rate variability predicts ESRD and CKD-related hospitalization. *J Am Soc Nephrol* 2010; 21: 1560–1570
39. Fukuta H, Hayano J, Ishihara S *et al*. Prognostic value of heart rate variability in patients with end-stage renal disease on chronic haemodialysis. *Nephrol Dial Transplant* 2003; 18: 318–325
40. Green D, Roberts PR. Ventricular arrhythmias and sudden death in patients with chronic kidney disease. *J Ren Care* 2010; 36: 54–60
41. Green D, Ritchie JP, Abidin N *et al*. The association of ECG and echocardiographic abnormalities with sudden cardiac death in a dialysis patient cohort. *J Nephrol* 2014; 27: 81–86
42. Nielsen VK. The peripheral nerve function in chronic renal failure. VI. The relationship betweeen sensory and motor nerve conduction and kidney function, azotemia, age, sex, and clinical neuropathy. *Acta Med Scand* 1973; 194: 455–462
43. Lowitzsch K, Gohring U, Hecking E *et al*. Refractory period, sensory conduction velocity and visual evoked potentials before and after haemodialysis. *J Neurol Neurosurg Psychiatry* 1981; 44: 121–128
44. Bolton CF, Baltzan MA, Baltzan RB. Effects of renal transplantation on uremic neuropathy. A clinical and electrophysiologic study. *N Engl J Med* 1971; 284: 1170–1175
45. Bolton CF. Electrophysiologic changes in uremic neuropathy after successful renal transplantation. *Neurology* 1976; 26: 152–161
46. Arnold R, Pussell BA, Pianta TJ *et al*. Association between calcineurin inhibitor treatment and peripheral nerve dysfunction in renal transplant recipients. *Am J Transplant* 2013; 13: 2426–2432
47. Krishnan AV, Phoon RK, Pussell BA *et al*. Neuropathy, axonal Na^+/K^+ pump function and activity-dependent excitability changes in end-stage kidney disease. *Clin Neurophysiol* 2006; 117: 992–999
48. Arnold R, Pianta TJ, Pussell BA *et al*. Randomized, controlled trial of the effect of dietary potassium restriction on nerve function in CKD. *Clin J Am Soc Nephrol* 2017; 12: 1569–1577
49. Sprague SM, Moe SM. The case for routine parathyroid hormone monitoring. *Clin J Am Soc Nephrol* 2013; 8: 313–318
50. Tesfaye S, Boulton AJ, Dyck PJ *et al*. Diabetic neuropathies: update on definitions, diagnostic criteria, estimation of severity, and treatments. *Diabetes Care* 2010; 33: 2285–2293
51. Roshanravan B, Patel KV, Robinson-Cohen C *et al*. Creatinine clearance, walking speed, and muscle atrophy: a cohort study. *Am J Kidney Dis* 2015; 65: 737–747

Received: 1.1.2018; Editorial decision: 3.3.2018