Correlates of physical functioning and performance across the spectrum of kidney function

ABSTRACT

The aim of this study was to determine the extent to which poor physical functioning, low participation in physical activity and muscle atrophy observed among patients on hemodialysis are evident in the earlier stages of chronic kidney disease (CKD). We enrolled adults in three groups: no CKD, stage 3-4 CKD, and hemodialysis. Outcomes measured were physical activity, muscle size, thigh muscle strength, physical performance, and self-reported physical function. Patients with CKD had muscle area intermediate between the no CKD and hemodialysis groups, but they had low levels of physical activity that were similar to the hemodialysis group. Physical activity and muscle size were significantly associated with all outcomes. Kidney function was not significantly associated with muscle strength or physical performance after adjustment for physical activity and muscle size. In conclusion, interventions aimed to increase muscle mass and energy expenditure might have an impact on improving physical function of CKD patients.

Keywords: physical activity, health related quality of life, chronic kidney disease, hemodialysis.

E. SEGURA-ORTÍ. PT, MSc, PhD.

Avda. Seminario s/n

46113 Moncada (Valencia) Spain

Phone 0034 961369000 Fax 0034 961395272

Department of Physiotherapy, Universidad CEU-Cardenal Herrera, Moncada, Valencia, Spain

esegura@uchceu.es

P. L. GORDON. RN, PhD.

505 Parnassus Ave, San Francisco, CA 94143, EE. UU.

Phone 00 1 415-476-9000

University California San Francisco, Division of Nephrology, Department of Medicine, San Francisco, California, United States

p.gordon@me.com

J. W. DOYLE. MS.

Nephrology Dept. VAMC-SF. 4150 Clement Street, San Francisco, CA 94121, EE. UU.

Phone 00 1 415 221-4810 Ext 2597 Fax 00 1 415 750-9358

Northern California Institute for Research and Education, Nephrology Section, San Francisco, California, United States

Julie.Doyle2@va.gov

K. L. JOHANSEN. MD.

505 Parnassus Ave, San Francisco, CA 94143, EE. UU.

Phone 00 1 415-476-9000

University California San Francisco, Medicine Department, San Francisco, California, United States

Kirsten.johansen@ucsf.edu

Corresponding author

E.Segura-Ortí

Avda. Seminario s/n

46113 Moncada (Valencia) Spain

Phone 0034 961369000 Fax 0034 961395272

esegura@uchceu.es

BIOGRAPHY

E.Segura-Ortí (PT, MSc, PhD) is a PT professor at the Universidad CEU-Cardenal Herrera

PL Gordon (RN, PhD) is RN. University California San Francisco

JW Doyle (MS) is researcher at the Northern California Institute for Research and Education

KL Johansen (MD) is Professor of Medicine at the University of California, San Francisco; Director of Dialysis at the San Francisco VA Medical Center.

INTRODUCTION

Physical dysfunction is well documented in patients receiving maintenance hemodialysis (Johansen, 2007; Painter, 2005), and there is increasing evidence that physical functioning is limited among patients at earlier stages of chronic kidney disease (CKD) as well. Several studies examining exercise capacity, physical performance, and self-reported physical functioning in patients with stage 3 and stage 4 CKD demonstrate lower levels of physical functioning in these patients when compared to normative data (Brodin, Ljungman, & Sunnerhagen, 2008; Gordon, Doyle, & Johansen, 2012; Padilla et al., 2008; Roshanravan et al., 2012). Further, several large cohort studies (Odden, Whooley, & Shlipak, 2004; Odden et al., 2006) show that limitations in exercise capacity and physical performance are evident as early as stage 2 CKD.

Similarly, although 75% or more of patients on maintenance hemodialysis exhibit some degree of wasting (Kalantar-Zadeh, Ikizler, Block, Avram, & Kopple, 2003), the advent and progression of changes in lean mass with the progression of CKD have not been thoroughly investigated. Leikis et al (Leikis et al., 2006) did not demonstrate a change in thigh muscle cross-sectional area by computed tomography over a two-year period in a group of seven patients whose mean creatinine clearance declined by 28%. A more recent study found an overall decline in thigh muscle cross-sectional area over two years among patients with CKD and ESRD but concluded that there was substantial variability in the course of muscle wasting in CKD (John, Sigrist, Taal, & McIntyre, 2013). The authors were unable to determine whether physical activity was a factor.

Loss of muscle mass has a grave impact on physical functioning, and both muscle wasting and poor functioning are related to poor outcomes and higher mortality

in this population (Avram, Mittman, Bonomini, Chattopadhyay, & Fein, 1995; Culp, Flanigan, Lowrie, Lew, & Zimmerman, 1996). Although the cause of muscle wasting in end stage renal disease is multifactorial, physical inactivity is known to be a major contributor to this muscle wasting and poor physical functioning (Clark, 2009; Park, Park, Shephard, & Aoyagi, 2010; Zamojska, Szklarek, Niewodniczy, & Nowicki, 2006) and poor physical functioning (Johansen, Chertow, da Silva, Carey, & Painter, 2001; Johansen et al., 2001).

Although patients on hemodialysis are significantly less physically active than age-matched healthy controls (Johansen et al., 2000), little is known about the physical activity levels of patients at earlier stages of CKD and the extent to which activity is associated with physical functioning and lean mass. Thus, little information is available regarding the rate of decline in physical functioning, muscle wasting and physical activity as CKD progresses, or the extent to which the decline is associated with the decline in GFR or other factors associated with the progression of CKD (Figure 1).

Therefore, the primary aim of this study was to determine the extent to which the poor physical functioning, low participation in physical activity and muscle atrophy observed among patients on hemodialysis are evident in the earlier stages of CKD and to investigate their correlation with kidney function. We further aimed to explore the independent associations of uremia, anemia, muscle area and low physical activity with functioning in this cohort. We hypothesized that although muscle size and physical activity would be important correlates of physical function and performance, kidney function would be associated with functioning independent of physical activity.

SUBJECTS AND METHODS

Design

The present study analyzed the association between kidney function, muscle size, physical activity and physical performance measures. We also performed multivariable linear regression analyses.

Physical activity was objectively measured by an accelerometer and through validated questionnaires to assess energy expenditure. Additionally, physical function was measured through a wide variety of physical performance tests to assess ability to perform activities of daily living.

Participants

Healthy volunteers 18 years of age and older without CKD (estimated glomerular filtration rate (GFR) ≥ 60 mL/min/1.73m^2 using the CKD-EPI equation (Levey et al., 1999), patients with stages 3a, 3b and 4 CKD, and patients with stage 5 CKD on hemodialysis were enrolled (Levin & Stevens, 2013). Potential participants were excluded if they had taken glucocorticoids for more than 14 days within the past 6 months; had any musculoskeletal condition that prevented muscle strength or functional testing; were unable to safely undergo MRI testing; or were unable to give informed consent. The Institutional Review Board approved all study procedures, and all patients provided written informed consent. The procedures followed were in accordance with the Helsinki Declaration of 1975, as revised in 2000.

Demographic, anthropometric, and laboratory data

Age, gender, race, and comorbid conditions were obtained by participant interview and review of medical records**.** The most recent laboratory reports of serum creatinine, albumin, hemoglobin and hematocrit, were obtained from the medical record. Height and weight were directly measured. Glomerular filtration rate (GFR) was estimated using the CKD-EPI equation (Levey et al., 1999) to classify patients according to CKD stages 0-4 by KDIGO guidelines (Levin & Stevens, 2013). Measures

of physical activity and of muscle size, strength and function were performed during a dedicated study visit on a midweek non-dialysis day for patients with ESRD and within a month of laboratory testing for non-dialysis participants.

Physical Activity Level

Physical activity was measured using a 3-dimensional accelerometer (RT3, Stayhealthy Inc., Monrovia, CA). Each participant wore the device mounted at the waistband for seven consecutive days. This instrument has shown validity and reliability in elderly population (Kochersberger, McConnell, Kuchibhatla, & Pieper, 1996; Matthews & Freedson, 1995). The data were expressed in arbitrary units and averaged over the seven days as the daily activity level (Johansen et al., 2000).

Physical Activity Questionnaires: Patients were asked to complete two questionnaires related to physical activity level that have been shown to be valid (Johansen et al., 2001). The Physical Activity Scale for the elderly (PASE) is designed to measure activity during the previous week based on participants' responses to a series of questions (Washburn, Smith, Jette, & Janney, 1993). The Human Activity Profile (HAP) (Fix & Daughton, 1986) is a scale designed to survey participation in common physical activities across a broad range of energy requirements. The adjusted activity score (AAS) (Fix & Daughton, 1986) was recorded.

Muscle Size

Knee-extensor (quadriceps) muscle size was measured using MRI because of their functional importance and because measurement variability is reduced by limiting the analysis to a large, well-defined muscle group (Johansen et al., 2003). Images of the entire thigh were acquired in a 1.5T Siemens Avanto MRI scanner with Total Imaging

Matrix technology. After obtaining a scout image, a series of T-1 weighted axial slices of the thigh were obtained from the iliac crest to the patella (Johansen et al., 2003). The single slice with the largest quadriceps muscle area and the two adjacent slices were selected for analysis. A customized software program written in IDL (Research Systems Inc., Boulder, CO) was used to quantify contractile and non-contractile components of the muscle as previously described (Johansen et al., 2003).

Muscle Strength

Isokinetic Strength: Strength of the knee extensor was assessed by isokinetic dynamometry, using the Cybex Extremity Testing Unit, a computerized dynamometer (Cybex/HUMAC 6000, Computer Sports Medicine Inc., Stoughton, MA) (Davies, 1984). Participants performed five repetitions at 90°/sec and 30 repetitions at 180°/sec, and the peak torque were recorded at each velocity.

Isometric Strength: Isometric strength or maximal voluntary contraction (MVC) of the knee extensor muscle group was measured at 60° extension using the isometric testing function of the Cybex Extremity Testing Unit. The best of five trials was recorded.

Physical Performance Tests

Participants performed the following standardized physical performance measures previously used in the CKD and ESRD populations (Johansen et al., 2001; Johansen et al., 2003; Johansen et al., 2006; Padilla et al., 2008; Segura-Orti, Kouidi, & Lison, 2009).

Gait Speed and stair climb: Participants were asked to walk a distance of 20 ft at a comfortable walking pace. Two trials were performed and the best time recorded. Patients were timed while climbing a single flight of stairs in a similar fashion.

The 6-Minute Walk: Participants were asked to walk back and forth along a 100 ft corridor, covering as much distance as possible during a 6-minute period. Participants were allowed to rest as necessary, although the clock was not stopped (ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories, 2002;). The final distance was recorded in meters. Reliability has been demonstrated in patients undergoing hemodialysis (Segura-Ortí & Martinez-Olmos, 2010).

Sit to Stand to Sit Tests: Participants were asked to sit in a chair of standard height, and then asked to stand up completely and sit back down five times with arms crossed over the chest. Time to complete five repetitions was recorded to the nearest hundredth of a second (Guralnik, Ferrucci, Simonsick, Salive, & Wallace, 1995). Reliability has been demonstrated in patients undergoing hemodialysis (Segura-Ortí & Martinez-Olmos, 2010).

Static Balance: Participants were asked to stand on one leg for as long as they could for up to 30 seconds. The score was recorded as the time in seconds until the participant needed to touch the examiner, put the other foot down, or move the foot on the floor to maintain balance (Nelson et al., 2004).

Self-reported functioning

Self-reported functioning was assessed using the Physical Function (PF) scale of the Medical Outcomes Study Short Form 36-item (SF-36) questionnaire (Ware, Kosinski, & Keller, 1994). Scores range from 0 to 100, with higher scores reflecting better physical functioning.

Statistical Analysis

The results are expressed as mean ± SD. We checked the normality of data distribution by the Kolomogorow–Smirnoff test, and non-normally distributed data were reported as median (interquartile range [IQR]) and logarithmically transformed before further analysis. Characteristics of individuals in the three study groups were compared using ANOVA or chi squared tests as appropriate. Because the CKD group was significantly older than the other two groups and because age is expected to be related to physical functioning and muscle size, we added age as a covariate for all comparisons among groups.

We used bivariate and multivariable linear regression analyses to determine the extent to which kidney function or the sequelae of impaired kidney function were associated with physical functioning and muscle size. For these analyses, the eGFR was treated as a linear variable. Covariates included in the multivariable linear regression analyses were age, muscle size (cross-sectional area), hemoglobin and physical activity. We used the AAS of the HAP as the physical activity variable because it was more related to physical function outcomes in bivariate analysis than the physical activity by accelerometry. We performed a forward stepwise regression. The results are expressed as standardized coefficients (per one SD for each variable), so that larger standardized coefficient means that the variable contributes more to the model. SPSS statistical program, version 15.0 for Windows (SPSS Inc., Chicago, IL, USA), was used for all analyses, and a two-sided $P<0.05$ was considered statistically significant.

RESULTS:

Study population

Seventy-nine eligible patients were approached, and 57 agreed to participate in the study, including 19 healthy controls, 22 patients with CKD (4 GFR category 3a, 7

GFR category 3b, 11 GFR category 4), and 16 patients with ESRD on hemodialysis (Table 1). The ethnicity of the final sample was as follows: 27 Caucasian, 21 African-American, 4 Hispanic, 3 Asian, 1 Native American and 1 Pacific Islander. Patients with CKD were older than participants on hemodialysis and those without CKD. Dialysis vintage for patients on hemodialysis was 38.5 months (median), minimum 5 months and maximum 139 months. Hemoglobin was significantly lower among both CKD and patients on maintenance hemodialysis than among controls, while patients on maintenance hemodialysis had significantly lower serum albumin concentration than both controls and CKD patients (Table 1).

Patients with CKD were similar to controls and better than patients on maintenance hemodialysis in isometric strength (MVC), static balance, and the physical function scale of the SF-36 ($p<0.05$ for all). Conversely, CKD patients were similar to patients on maintenance hemodialysis and significantly lower than controls in daily physical activity measured by accelerometer ($p<0.001$), physical activity by the adjusted activity score (AAS) of the HAP questionnaire ($p<0.05$), and distance covered in the 6MWT ($p<0.01$). Muscle area of the CKD group was intermediate between that of controls and patients with ESRD (Table 1).

Bivariate correlation results

Table 2 shows bivariate correlations between outcomes related to physical function and performance and potential predictors. As expected, muscle size and strength were correlated with each other, and muscle size also correlated with the 6-minute walking distance, static balance and stair climbing. Kidney function was correlated directly with physical activity ($r=0.53$, $p<0.01$ for accelerometry and $r=0.31$, $p<0.05$ for the AAS of the HAP), with muscle size ($r=0.55$, $p<0.01$) and strength

(r=0.47, p<0.01 for isometric strength), and with self-reported physical function (r=0.38, p<0.01) but not with most measures of physical performance (except static balance and 6 minute walk test, Table 2). Correlations between hemoglobin and functioning outcomes mirrored those for kidney function.

In addition, physical activity measured by accelerometry was associated with muscle size and strength, but somewhat surprisingly it was not correlated with most measures of physical performance except the 6-minute walk and static balance (Table 2). However, the AAS of the HAP questionnaire was correlated with all the physical performance measures.

Multivariable linear regression

Multivariable regression analyses were performed to evaluate the independent associations of kidney function with physical performance and functioning independent of physical activity, muscle size, and hemoglobin (Table 3). Physical activity or muscle size or both physical activity and muscle size were significantly associated with all outcomes. Hemoglobin was associated only with self-reported physical functioning. Kidney function was not significantly associated with either muscle strength or physical performance after adjustment for muscle area, physical activity or age.

DISCUSSION:

We found that physical activity was lower among patients with stage 3 or 4 CKD than among controls and was similar to that of patients with ESRD on maintenance hemodialysis. Contrary to our hypothesis, after adjusting for physical activity and other potential determinants of physical performance and functioning, none of the variables was independently related to kidney function. On the other hand, all

measures of muscle strength were independently related to muscle area even after adjustment for physical activity. Physical performance was less clearly related to muscle area, with only 6-minute walk distance and static balance showing a statistically significant association. The AAS of the HAP physical activity questionnaire was related to one of the measures of strength and all the physical performance measures. Hemoglobin was only associated with self-reported physical function. It is possible that muscle area and low physical activity may mediate the association between chronic kidney disease and low strength and poor physical performance.

Multivariable analyses showed that physical activity was associated with measures of physical performance and self-reported physical function. Muscle size and the AAS of the HAP physical activity questionnaire were associated with strength, with 6-minute walk distance, sit to stand to sit tests, and static balance, suggesting an important role of muscle area and physical activity on muscle function at any stage of kidney disease. Based on our results, anemia is not likely to be a mediator of this association, but we cannot rule out other factors such as vitamin D levels, acidosis, or unmeasured uremic toxins. Although our study was cross-sectional, inclusion of participants across the entire spectrum of kidney function yielded some interesting observations that might shed some light on the pathophysiology of poor physical functioning among patients with CKD. It was notable that the patients in this cohort with nondialysis-dependent CKD had activity levels that were as low as those of the patients on maintenance hemodialysis and less than half those of individuals with normal kidney function.

Putting our results into the context of prior studies, we found similar results regarding physical performance among the patients with CKD (Padilla et al., 2008), low levels of physical activity among the patients with ESRD (Johansen et al., 2001),

muscle size (Johansen et al., 2006) and meters covered during the 6-minute walking test (Cheema et al., 2007; Segura-Orti et al., 2009), but we found better sit to stand to sit and stair climbing results than previously reported data (Johansen et al., 2006)..

The direction of correlation between kidney function and physical activity and functioning was consistent across measures. These results are in agreement with those of Clyne *et al*. in which exercise capacity, measured as peak oxygen consumption was correlated with eGFR in a group of 58 patients with stage 4 and 5 CKD (Clyne, Jogestrand, Lins, & Pehrsson, 1994). Our results are also consistent with other studies in which cystatin C, a cysteine proteinase inhibitor that is freely filtered by the glomerulus, was used as a measure of kidney function that is independent of muscle mass. Lower kidney function was associated with worse physical function (400-m walk time, lower extremity performance, grip strength and knee extension strength) (Odden et al., 2006).

The independent associations we observed between muscle size and strength and between physical activity and physical performance tasks suggest that exercise programs might be beneficial for patients with CKD at any stage. Indeed, almost all exercise interventions, including aerobic or resistance training, have resulted in improvements in functioning among patients with CKD (Johansen & Painter, 2012) and ESRD (Johansen, 2007; Segura-Orti & Johansen, 2010). Interestingly, a randomized controlled trial of resistance exercise training, aerobic exercise training, or a combination of the two among clinically stable sedentary patients on maintenance hemodialysis (Johansen & Painter, 2012; Kopple et al., 2007) found that both types of exercise training induced a pattern of changes in gene transcription that would be likely to promote protein synthesis and reduce protein degradation (Kopple et al., 2007). More

studies are needed to determine which is the optimal intensity of aerobic and strength exercise training that lead to improvements.

The study findings have clinical implications in regard to nursing practice. Routine nursing care at any stage of kidney disease could include interventions such as exercise programs to increase muscle area and energy expenditure of patients. The aim would be to improve activities of daily living of CKD patients, such as walking capacity, balance and standing up from a chair, so as to improve health related quality of life.

It is important to interpret these results in light of the limitations of the study, particularly the modest sample size, cross-sectional design, and use of serum creatinine to estimate kidney function. A previous study showed that cystatin C was more strongly associated with physical performance than estimated glomerular filtration rate from creatinine. Whereas higher concentrations of cystatin C were significantly associated with poorer function, levels of eGFR (based on serum creatinine) were not consistently associated with physical function (Odden et al., 2006). The possibility that serum creatinine will overestimate GFR in the presence of muscle atrophy may have limited our power to detect associations between kidney function and measures of muscle and physical function. The patients in this study were mostly male and were younger than the average age of patients with CKD or undergoing hemodialysis (U.S. Renal Data System, 2009). In addition, their performance on the stair climbing and chair rising tasks was considerably better than that of a prior cohort of ESRD patients (Johansen et al., 2001). The cross-sectional design precludes determination of the direction of the association or causality of the observed associations between physical activity and function and between kidney function and physical function. We did not have direct measures of uremic toxins or of many other complications of CKD such as disordered

mineral metabolism or acidosis. Therefore, many potential mediators or confounders of the association between kidney function and physical functioning were not addressed.

In conclusion, we found that physical activity was extremely low even among CKD participants who had not reached ESRD. Muscle strength, sit to stand to sit time, balance and 6-minute walk distance were associated with muscle area and physical activity in multivariable analyses. These results suggest that reduced muscle area and low physical activity may affect physical functioning among patients with CKD.

Application section

The paper highlights the low physical activity level that already affects subjects suffering CKD even before reaching ESRD. Thus, nursing interventions to promote increased physical activity could be helpful in CKD disease patients. Low physical activity and muscle wasting may be important determinants of physical functioning among patients with CKD. It seems reasonable to promote interventions at the clinical setting aimed to increase muscle mass and physical activity and to analyze which is the impact on physical function of CKD patients. Longitudinal and interventional studies are needed to further define the factors causing poor physical functioning and to determine whether functioning can be improved or its decline prevented through exercise or other interventions.

NOTES

Acknowledgements

We are grateful to volunteers that participated in the study.

Declaration of Conflicting Interests' statement

The Authors declare that there is no conflict of interest

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

REFERENCES

ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. (2002). ATS statement: Guidelines for the six-minute walk test. *American Journal of Respiratory and Critical Care Medicine, 166*(1), 111-117.

Avram, M. M., Mittman, N., Bonomini, L., Chattopadhyay, J., & Fein, P. (1995). Markers for survival in dialysis: A seven-year prospective study. *American Journal of Kidney Diseases : The Official Journal of the National Kidney Foundation, 26*(1), 209-219.

Brodin, E., Ljungman, S., & Sunnerhagen, K. S. (2008). Rising from a chair: A simple screening test for physical function in predialysis patients. *Scandinavian Journal of Urology and Nephrology, 42*(3), 293-300. doi:10.1080/00365590701797556

Cheema, B., Abas, H., Smith, B., O'Sullivan, A., Chan, M., Patwardhan, A., . . . Singh, M. (2007). Progressive exercise for anabolism in kidney disease (PEAK): A randomized, controlled trial of resistance training during hemodialysis. *J Am Soc Nephrol, 18*(5), 1594-1601.

Clark, B. C. (2009). In vivo alterations in skeletal muscle form and function after disuse atrophy. *Medicine and Science in Sports and Exercise, 41*(10), 1869-1875. doi:10.1249/MSS.0b013e3181a645a6; 10.1249/MSS.0b013e3181a645a6

.

Clyne, N., Jogestrand, T., Lins, L. E., & Pehrsson, S. K. (1994). Progressive decline in renal function induces a gradual decrease in total hemoglobin and exercise capacity. *Nephron, 67*(3), 322-326.

Culp, K., Flanigan, M., Lowrie, E. G., Lew, N., & Zimmerman, B. (1996). Modeling mortality risk in hemodialysis patients using laboratory values as time-dependent covariates. *American Journal of Kidney Diseases : The Official Journal of the National Kidney Foundation, 28*(5), 741-746.

Davies, G. (1984). *Principles of isokinetic testing. A compendium of isokinetics in clinical usage.* Lacrosse, WI: Simon and Schuster.

Fix, A., & Daughton, D. (1986). *Human activity profile (HAP) manaul.* Odessa: Psychological Assessment Resources Inc.

Gordon, P. L., Doyle, J. W., & Johansen, K. L. (2012). Association of 1,25-dihydroxyvitamin D levels with physical performance and thigh muscle cross-sectional area in chronic kidney disease stage 3 and 4. *Journal of Renal Nutrition : The Official Journal of the Council on Renal Nutrition of the National Kidney Foundation, 22*(4), 423-433. doi:10.1053/j.jrn.2011.10.006; 10.1053/j.jrn.2011.10.006

Guralnik, J. M., Ferrucci, L., Simonsick, E. M., Salive, M. E., & Wallace, R. B. (1995). Lower-extremity function in persons over the age of 70 years as a predictor of subsequent disability. *The New England Journal of Medicine, 332*(9), 556-561.

Johansen, K. L. (2007). Exercise in the end-stage renal disease population. *Journal of the American Society of Nephrology : JASN, 18*(6), 1845-1854. doi:10.1681/ASN.2007010009

Johansen, K. L., Chertow, G. M., da Silva, M., Carey, S., & Painter, P. (2001). Determinants of physical performance in ambulatory patients on hemodialysis. *Kidney International, 60*(4), 1586-1591. doi:10.1046/j.1523-1755.2001.00972.x

Johansen, K. L., Chertow, G. M., Ng, A. V., Mulligan, K., Carey, S., Schoenfeld, P. Y., & Kent-Braun, J. A. (2000). Physical activity levels in patients on hemodialysis and healthy sedentary controls. *Kidney International, 57*(6), 2564-2570. doi:10.1046/j.1523-1755.2000.00116.x

Johansen, K. L., & Painter, P. (2012). Exercise in individuals with CKD. *American Journal of Kidney Diseases : The Official Journal of the National Kidney Foundation, 59*(1), 126-134. doi:10.1053/j.ajkd.2011.10.008; 10.1053/j.ajkd.2011.10.008

Johansen, K. L., Painter, P., Kent-Braun, J. A., Ng, A. V., Carey, S., Da Silva, M., & Chertow, G. M. (2001). Validation of questionnaires to estimate physical activity and functioning in end-stage renal disease. *Kidney International, 59*(3), 1121-1127. doi:10.1046/j.1523-1755.2001.0590031121.x

Johansen, K. L., Painter, P. L., Sakkas, G. K., Gordon, P., Doyle, J., & Shubert, T. (2006). Effects of resistance exercise training and nandrolone decanoate on body composition and muscle function among patients who receive hemodialysis: A randomized, controlled trial. *Journal of the American Society of Nephrology, 17*(8), 2307-2314.

Johansen, K. L., Shubert, T., Doyle, J., Soher, B., Sakkas, G. K., & Kent-Braun, J. A. (2003). Muscle atrophy in patients receiving hemodialysis: Effects on muscle strength, muscle quality, and physical function. *Kidney International, 63*(1), 291-297. doi:10.1046/j.1523-1755.2003.00704.x

John, S. G., Sigrist, M. K., Taal, M. W., & McIntyre, C. W. (2013). Natural history of skeletal muscle mass changes in chronic kidney disease stage 4 and 5 patients: An observational study. *PloS One, 8*(5), e65372. doi:10.1371/journal.pone.0065372; 10.1371/journal.pone.0065372

Kalantar-Zadeh, K., Ikizler, T. A., Block, G., Avram, M. M., & Kopple, J. D. (2003). Malnutrition-inflammation complex syndrome in dialysis patients: Causes and consequences. *American Journal of Kidney Diseases : The Official Journal of the National Kidney Foundation, 42*(5), 864-881.

Kochersberger, G., McConnell, E., Kuchibhatla, M. N., & Pieper, C. (1996). The reliability, validity, and stability of a measure of physical activity in the elderly. *Archives of Physical Medicine and Rehabilitation, 77*(8), 793-795.

Kopple, J. D., Wang, H., Casaburi, R., Fournier, M., Lewis, M. I., Taylor, W., & Storer, T. W. (2007). Exercise in maintenance hemodialysis patients induces transcriptional changes in genes favoring anabolic muscle. *Journal of the American Society of Nephrology : JASN, 18*(11), 2975-2986. doi:10.1681/ASN.2006070794

Leikis, M. J., McKenna, M. J., Petersen, A. C., Kent, A. B., Murphy, K. T., Leppik, J. A., . . . McMahon, L. P. (2006). Exercise performance falls over time in patients with chronic kidney disease despite maintenance of hemoglobin concentration.

Clinical Journal of the American Society of Nephrology : CJASN, 1(3), 488-495. doi:10.2215/CJN.01501005

Levey, A. S., Greene, T., Beck, G. J., Caggiula, A. W., Kusek, J. W., Hunsicker, L. G., & Klahr, S. (1999). Dietary protein restriction and the progression of chronic renal disease: What have all of the results of the MDRD study shown? modification of diet in renal disease study group. *Journal of the American Society of Nephrology : JASN, 10*(11), 2426-2439.

Levin, A., & Stevens, P. E. (2013). Chapter 1: Definition and classification of CKD. *Kidney International Supplements, 3*(1), 19-62. doi:10.1038/kisup.2012.64 [doi]

Matthews, C. E., & Freedson, P. S. (1995). Field trial of a three-dimensional activity monitor: Comparison with self report. *Medicine and Science in Sports and Exercise, 27*(7), 1071-1078.

Nelson, M. E., Layne, J. E., Bernstein, M. J., Nuernberger, A., Castaneda, C., Kaliton, D., . . . Fiatarone Singh, M. A. (2004). The effects of multidimensional home-based exercise on functional performance in elderly people. *The Journals of Gerontology.Series A, Biological Sciences and Medical Sciences, 59*(2), 154-160.

Odden, M. C., Chertow, G. M., Fried, L. F., Newman, A. B., Connelly, S., Angleman, S., . . . for the HABC Study. (2006). Cystatin C and measures of physical function in elderly adults: The health, aging, and body composition (HABC) study. *American Journal of Epidemiology, 164*(12), 1180-1189. doi:10.1093/aje/kwj333

Odden, M. C., Whooley, M. A., & Shlipak, M. G. (2004). Association of chronic kidney disease and anemia with physical capacity: The heart and soul study. *Journal of the*

American Society of Nephrology : JASN, 15(11), 2908-2915. doi:10.1097/01.ASN.0000143743.78092.E3

Padilla, J., Krasnoff, J., Da Silva, M., Hsu, C. Y., Frassetto, L., Johansen, K. L., & Painter, P. (2008). Physical functioning in patients with chronic kidney disease. *Journal of Nephrology, 21*(4), 550-559.

Painter, P. (2005). Physical functioning in end-stage renal disease patients: Update 2005. *Hemodialysis International.International Symposium on Home Hemodialysis, 9*(3), 218-235. doi:10.1111/j.1492-7535.2005.01136.x

Park, H., Park, S., Shephard, R. J., & Aoyagi, Y. (2010). Yearlong physical activity and sarcopenia in older adults: The nakanojo study. *European Journal of Applied Physiology, 109*(5), 953-961. doi:10.1007/s00421-010-1424-8; 10.1007/s00421-010-1424-8

Roshanravan, B., Khatri, M., Robinson-Cohen, C., Levin, G., Patel, K. V., de Boer, I. H., . . . Kestenbaum, B. (2012). A prospective study of frailty in nephrology-referred patients with CKD. *American Journal of Kidney Diseases : The Official Journal of the National Kidney Foundation, 60*(6), 912-921. doi:10.1053/j.ajkd.2012.05.017 [doi]

Segura-Orti, E., & Johansen, K. L. (2010). Exercise in end-stage renal disease. *Seminars in Dialysis, 23*(4), 422-430. doi:10.1111/j.1525-139X.2010.00766.x

Segura-Orti, E., Kouidi, E., & Lison, J. F. (2009). Effect of resistance exercise during hemodialysis on physical function and quality of life: Randomized controlled trial. *Clinical Nephrology, 71*(5), 527-537.

Segura-Orti, E., Martínez-Olmos F.J. (2011). Test-retest reliability and minimal detectable change scores for sit-to-stand-to-sit tests, the six-minute walk test, the one-leg heel-rise test, and handgrip strength in people undergoing hemodialysis. *Physical Therapy, 91*(8), 1244-1252

U.S. Renal Data System (Ed.). (2009). *USRDS 2009 annual data report: Atlas of chronic kidney disease and end-stage renal disease in the united states*. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases.

Ware, J., Kosinski, M., & Keller, S. (1994). *SF-36 physical and mental health summary scales: A user manual* (4th Edition ed.). Boston: The Health Institute, New England Medical Center.

Washburn, R. A., Smith, K. W., Jette, A. M., & Janney, C. A. (1993). The physical activity scale for the elderly (PASE): Development and evaluation. *Journal of Clinical Epidemiology, 46*(2), 153-162.

Zamojska, S., Szklarek, M., Niewodniczy, M., & Nowicki, M. (2006). Correlates of habitual physical activity in chronic haemodialysis patients. *Nephrology, Dialysis, Transplantation : Official Publication of the European Dialysis and Transplant Association - European Renal Association, 21*(5), 1323-1327. doi:10.1093/ndt/gfi323

Figure 1. Conceptual model of the association between kidney disease and physical function

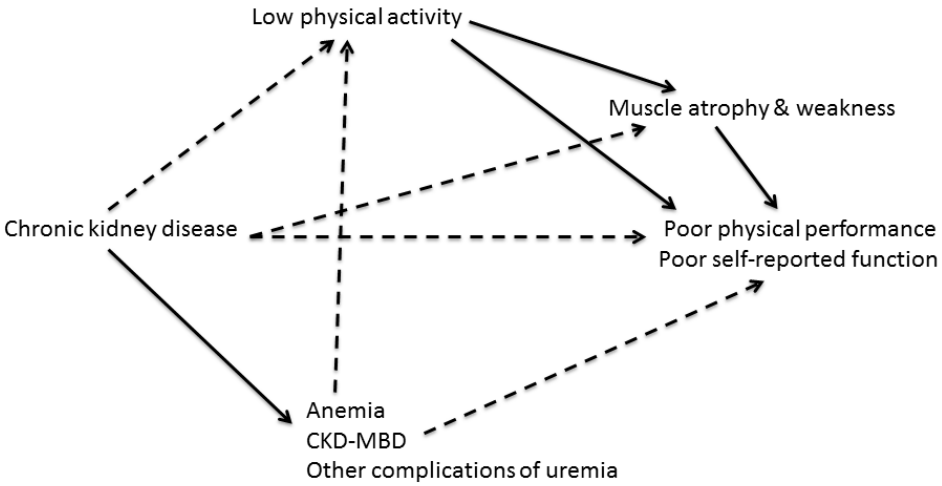

Table 1. Demographic and Physical function data

DEMOGRAPHIC AND CLINICAL VARIABLES	Control (n=19)	CKD (n=22)	Dialysis (n=16)	P
AGE (years)	53.2 ± 8.0	62.5 ± 10.1*	54.7 ± 7.2†	0.002
GENDER (%male/%female)	94.7%/5.3%	95.5%/4.5%	87.5%/12.5%	0.60
BODY MASS INDEX (Kg/m^2)	29.1 ± 5.7	32.9 ± 6.1	24.9 ± 5.7†	0.001
DIABETES MELLITUS (%Type 1/ %Type 2)	0%/5.3%	4.5%54.5%*	12.5%/12.5%	0.002
CURRENT SMOKING HABIT (%)	47.4%	27.3%	31.3%	0.42
HEMOGLOBIN (g/dL)	14.1 ± 1.6[b]	12.4 ± 1.6*	11.4 ± 1.2*	<0.001
CREATININE (mg/dL)	1.1 ± 0.1[a]	2.7 ± 1.2*	8.3 ± 2.9*†	<0.001
1/CREATININE	0.94 ± 0.11[a]	0.43 ± 0.14*	0.14 ± 0.07*†	<0.001
ESTIMATED GLOMERULAR FILTRATION RATE (ml/min per 1.73 m^2)	83.7 ± 12.9[a]	31.3 ± 14.5*	2 ± 0*†	<0.001
ALBUMIN (mg/dL)	3.9 ± 0.4[b]	3.8 ± 0.4	3.4 ± 0.4*†	0.005
OTHER VARIABLES				**P**
DAILY PHYSICAL ACTIVITY				
Accelerometer (Arbitrary Units)	212161.6 ± 139833.6	98737.3 ± 40191.3*[c]	98312.8 ± 47845.1*[f]	<0.001
PASE	143.5 ± 71.7	109.0 ± 75.1[d]	116.6 ± 82.9	0.34
HAP (Adjusted Activity Score)	71.7 ± 14.4	57.4 ± 16.7*[d]	58.7 ± 14.9*	0.01
MUSCLE SIZE (cm^2)	73.9 ± 16.4	62.3 ± 14.5*[e]	51.2 ± 13.9*[f]	<0.01
MUSCLE STRENGTH				
Isokinetic 90º/ s Peak Torque (Nm)	78.7 ± 31.1	64.0 ± 27.2[e]	57.1 ± 20.7[f]	0.16
Isokinetic 180º/ s Peak Torque (Nm)	53.6 ± 21.1[a]	46.7 ± 20.4[d]	38.9 ± 11.8[g]	0.06
Isometric MVC (N)	119.4 ± 42.9	106.1 ± 37.1[e]	83.5 ± 25.1*	0.05
20 FOOT WALK TEST (m/s)	1.3 ± 0.2	1.1 ± 0.3	1.3 ± 0.3	0.22
STAIR CLIMB TEST (stairs/s)	1.9 ± 0.3	1.5 ± 0.8	1.6 ± 0.5	0.07
SIX MINUTE WALK TEST (m)	534.5 ± 82.8	446.0 ± 102.0*	456.6 ± 87.7*[f]	0.02
SIT TO STAND TO SIT 5 REPETITIONS (s)	10.7 ± 2.8	12.6 ± 3.7[e]	12.2 ± 3.5[f]	0.32
STATIC BALANCE (s)	23.9 ± 8.6[b]	16.3 ± 11.4[e]	13.5 ± 10.1*[f]	0.02
SF 36 Physical Function Score	77.4 ± 21.0	60.5 ± 23.6[d]	55.3 ± 27.1*	0.01

Legend: HAP = Human Activity Profile; **MVC** = Maximal Voluntary Contraction; **PASE** = Physical Activity Scale for the Elderly;

Categorical variables are compared using Chi squared analysis and continuous variables by ANOVA/ANCOVA with post-hoc testing by Tukey or Games-Howell tests. All analyses of physical function variables are adjusted for age and BMI. Age and BMI were significant covariates for Creatinine (p=0.03), HAP (Adjusted Activity Score) (p=0.01),20 foot walk test (p=0.03), Six-minute walk test (p=0.08).
p values are overall ANOVA p-value.
* Significant vs. control group P<0.05
† Significant vs. CKD group P<0.05
[a] N=17; [b] N=18; [c] N=19; [d] N=20; [e] N=21; [f] N=15; [g] N=14
Unable to perform control group n=2 Isokinetic testing and n=1 Balance 1 leg test
Unable to perform CKD group n=1 MRI, n=3 Accelerometer, n=3 Isokinetic testing, n=1 Sit to Stand to Sit test, n=1 Balance 1 leg test, n=2 PASE, n=2 SF-36
Unable to perform MHD group n=1 MRI, n=1 Accelerometer, n=1 Isokinetic testing, n=1 Sit to Stand to Sit test, n=1 Six-minute walk test, n=1 Balance 1 leg test

Table 2. Univariate Correlations between Age, Body Mass Index, 1/creatinine, Hemoglobin and physical activity, and Related Variables

Variable	Age	eGFR	Hb	Muscle Size	Accelerometry (Arbitrary Units)	HAP (AAS)
Age (Years)	--					
eGFR (ml/min per 1.73 m^2)	-0.08	--				
Hemoglobin (g/dL)	0.05	0.70**	--			
Muscle Size (cm^2)	-0.33*	0.55**	0.37**	--		
PA/ day (Arbitrary units)	-0.08	0.53**	0.34*	0.64***	--	
HAP (AAS)	-0.09	0.31*	0.22	0.27	0.27	--
Isokinetic 90º/s Peak Torque (Nm)	-0.28*	0.36**	0.33*	0.65***	0.43**	0.49***
Isokinetic 180º/sec Peak Torque (Nm)	-0.30*	0.35*	0.31*	0.72***	0.44**	0.34*
Isometric strength MVC (N)	-0.21	0.47**	0.47***	0.74***	0.51***	0.36**
Stair climb (steps/s)	-0.08	0.26	0.25	0.31*	0.24	0.58***
20 foot walk test (m/s)	-0.19	0.04	0.05	-0.06	0.12	0.46***
6 Minute Walk Test (m)	-0.26	0.30*	0.04	0.46***	0.41**	0.62***
STS 5 (repetitions)	-0.33*	-0.16	-0.21	-0.23	-0.12	-0.44**
Static Balance (s)	-0.26	0.40**	-0.30*	0.43**	0.29*	0.41**
SF 36 Physical Function	-0.02	0.38**	0.46**	0.22	0.17	0.57***

Data are presented as r value in Spearman's correlation test
* $p<0.05$; ** $p<0.01$; *** $p<0.001$
Legend: AAS = Adjusted Activity Score; **BMI** = Body Mass Index; eGFR = Estimated glomerular filtration rate; **HAP** = Human Activity Profile; **Hgb** = Hemoglobin; **MVC** = Maximal Voluntary Contraction; **PA** = Physical activity; **STS**= Sit to stand to Sit test

Table 3. Multiple regression analyses

Dependent Variable	Standardized Coefficient, per one SD					Model	
	eGFR	Hgb	Age	Muscle area	HAP (AAS)	Adjusted R^2	p-value
Isokinetic 90º/s PT (Nm)	-0.13	-	-	0.59***	0.35**	0.55	<0.001
Isokinetic 180º/s PT (Nm)	0.05	-	-0.21*	0.70***	-	0.59	<0.001
Isometric MVC (N)	0.06	-	-	0.75***	-	0.56	<0.001
6 minute walk test (m)	0.04	-	-	0.28*	0.58***	0.48	<0.001
STS 5 (s)	-0.07	-	0.27*	-	-0.49***	0.29	<0.001
Static Balance (s)	0.06	-	-	0.36**	0.40**	0.34	<0.001
SF 36 Physical Function	0.07	0.28*	-	-	0.51**	0.39	<0.001

LEGEND: eGFR = Estimated glomerular filtration rate; **Hgb** = Hemoglobin; **MVC** = Maximal Voluntary Contraction; **PA** = Physical Activity; **PF** = Physical Function; **PT** = Peak Torque; **STS** = Sit to Stand to Sit Test
* $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$