Physical Performance in Adults with Chronic Kidney Disease

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Abstract

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Background and Purpose. Chronic kidney disease (CKD) and dialysis dependent end stage renal disease (ESRD-D) are associated with reduced physical performance and functional mobility, though associated factors are not well understood. The overarching purpose of this dissertation is to explore questions related to physical performance in CKD /ESRD-D with 3 studies. "The Relationship of Fatigue with Physical Performance and Mobility Disability in Chronic Kidney Disease" aimed to examine the association of fatigue with physical performance and mobility disability in adults with CKD (stages 2-4). "Reliability of Physical Performance and Instrumented Measures in Adults with Kidney Disease" aimed to assesses the reliability of physical and inertial sensor measurement units (IMUs) in adults with CKD and ESRD-D and compare differences between these groups. "The Acute Effects of Dialysis on Physical Performance in Adults with Hemodialysis Dependent End Stage Renal Disease" aimed to examine differences in physical performance that occur immediately after a dialysis session and assess the association of dialysis-related factors to observed change.

Methods. To assess relationships between physical performance, fatigue, and mobility disability, a cross-sectional study of 293 adults with CKD (stages 2-4) was conducted. Physical performance measures included the short physical performance battery (SBBP), Five Times Sit to Stand (FSTS), gait speed, 6 Minute Walk Test (6MWT) and handgrip strength (HGS). Fatigue was assessed with the SF-36 Energy-Fatigue-Vitality Subscale (SF-EF). Regression analysis was conducted to assess the relationship of fatigue to each physical performance measure controlling for age, BMI, and CKD-related factors. Logistic regression, controlling for age, BMI, and CKD-related factors, assessed the relationship of fatigue and mobility disability (defined by the inability to walk ¼ mile and/or climb 1 flight of 10 steps) based on established cut-points on the SPPB, gait speed and FSTS.

Test-retest reliability was assessed 1-week apart in a group of 21 CKD (n=11) and ESRD-D (n=10) patients on standard physical performance measures (SPPB, gait speed, FSTS, 2-Minute Walk Test (2MWT), quadricep strength (QS), and GS) and on inertial measurement unit (IMU) measures of gait (stride length and gait speed), turns (turn duration, number of steps in turn, and turn velocity), sit-stand duration, and postural sway (root mean squared, pathlength, velocity, jerkiness). Intraclass correlation coefficients were assessed for reliability and differences between CKD and ESRD-D groups were assessed with paired *t*-tests.

To assess the immediate effects of hemodialysis, standard physical performance measures (SPPB, gait speed, FSTS, 2MWT, QS, GS), the IMU measures previously described, and a fatigue numeric rating were collected immediately pre and post a hemodialysis session in 11 adults with ESRD-D. Paired *t*-tests were used to assess differences in physical performance pre-post dialysis and Pearson correlations were examined to assess the relationship between pre-post HD changes in physical performance, post-dialysis fatigue rating (PDF) and dialysis-related

variables (Kt/V, pre-post HD weight change, # of months on HD, and intradialytic hemodynamic instability (HI)).

Results. Fatigue was significantly associated with FSTS and gait speed and contributed to 2.1% and 3.1% of the variance in FSTS and gait speed, respectively. This relationship remained even after adjusting for covariates. Mobility disability was not associated with fatigue.

Good-excellent test-retest reliability was demonstrated in the following standard physical performance measures: SPPB (ICC = .91), FSTS (ICC = .95), gait speed (ICC = .89), 2MWT (ICC = .94), NSB (ICC = .81), QS (ICC_{right} = .94 and ICC_{left} =.90), GS (ICC = .96). Good reliability was found for the following IMU measures: steps in turn (ICC=.75), FSTS sit-stand duration (ICC=.87), postural sway PATH (ICC=.77_{usual} and .85_{narrow}), and sway JERK (ICC_{narrow}=.70). No differences were found between groups on physical performance measures.

Statistically significant differences from pre-post HD were found on quadricep strength dynamometry (t (10) = 3.35, p <.01). There were significant positive correlations between HI and post-dialysis fatigue (PDF) (r = 0.72), indicating that PDF was associated with increased HI. There was a significant positive correlation between FSTS and HI instability (*r = 0.63)* indicating that poorer performance on the FSTS was related to increased HI.

Conclusions

This dissertation identified a relationship between fatigue and physical performance in those with CKD, a set of clinically reliable physical performance measures for use with CKD/ESRD-D, and evidence that strength may decline immediately following a hemodialysis session. Future research directions include detection of the direction of causal relationships between fatigue and physical performance, development of a psychometrically strong composite

physical performance outcome measure for CKD/ESRD, and identification of pathophysiological mechanisms related to strength decline following dialysis.

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Chapter 1

Literature Review

Introduction

Chronic kidney disease (CKD) is a public health problem and affects 15% (>30 million) US adults.[1] Risk for development of kidney disease is linked to a host of genetic, geographic, and clinical factors. Kidney disease results in poor physical performance and fatigue that affects mobility essential for maintaining functional independence and quality of life.[2] Independent of age, comorbidities, or vascular events, those with CKD and end-stage renal disease (ESRD) have poor quality of life and decreased physical function compared to healthy individuals.[3-6] For all-age CKD, an increase of 19.6% in disability reported life years were reported from 2005-2015 and an increased proportion of those with CKD are spending their lives in ill health and disability.[5,7] Research is needed on physical performance in adults with CKD/ESRD to better understand physical performance in relation to mobility disability. CKD is asymptomatic in its early stages and symptoms do not generally develop until later stages of the disease when associated complications arise. Kidney disease occurs when the kidneys are damaged to the point that they are no longer able to filter blood. CKD is characterized by many physiologic features that are related to aging and has been suggested to be a disease of "premature aging".[8] With inadequate filtering of the blood by the kidneys, toxins can build up and negatively affect the body's other systems. The kidneys also play a pivotal role in maintaining the body's fluid and hormonal balances. Thus, CKD is also associated with disorders of fluid and electrolyte balance (volume overload, hyperkalemia, metabolic acidosis, hyperphosphatemia), abnormalities related to hormonal or systemic dysfunction (e.g., anorexia, anemia, malnutrition, hyperlipidemia, neuropathy), toxicity of drugs excreted by the kidneys, malnutrition, cardiovascular disease (CVD) and increased inflammatory processes evidenced by higher levels of inflammatory biomarkers.[9]

The two most common causes of CKD are hypertension (HTN) and diabetes (DM). Other potential causes of CKD are glomerulonephritis, polycystic kidney disease, lupus, urinary tract obstructions or chronic infections.[10] It is estimated that 1 in 3 people with CKD has DM and that 1 in 5 adults with HTN have CKD[1]. HTN and DM occur co-morbidly in 53.4% of the U.S. CKD population, with the combinations of CKD/HTN and CKD/HTN/DM being more prevalent than the combination of CKD/DM.[11] Comorbidities associated with HTN and DM, as contribute to the overall disease burden, leading to poorer functional outcomes, including physical performance.[11]

Kidney disease is traditionally classified into 5 categories of decreasing kidney function based on an estimated glomerular filtration rate (eGFR) which is most frequently estimated from the serum concentration of creatinine (an endogenous filtration marker), age, sex, and race (Table 1). CKD is diagnosed through simple blood tests that assess the amount of creatinine (a waste product of muscle metabolism that is filtered by the kidneys) and a urine test that checks for protein (albumin) in the urine A newer system incorporates both eGFR and albuminuria which has 6 categories of decreasing eGFR and three categories of kidney damage measured by levels of albuminuria; resulting in 18 categories of kidney disease and 4 prognostic risk categories. [9,10] It is generally accepted, no matter the classification system, that an eGFR below 60 mL/min per 1.73m^2 that persists for > 3 months (no matter the cause) is considered kidney disease. A GFR of < 15 mL/min per 1.73m^2 is considered kidney failure, is termed end stage renal disease (ESRD) and requires renal replacement therapy (dialysis or transplant) for survival.[9,12] Medicare continues to use the traditional, more simplistic 5 stage system that considers only the eGFR categories resulting in categorization to 5 states of kidney disease, with ESRD being Stage 5.[9] This more simplistic system remains pervasive, even in the current

literature, so when referring to stage of disease, this dissertation will use the 1-5 staging terminology and definitions (Table 1).

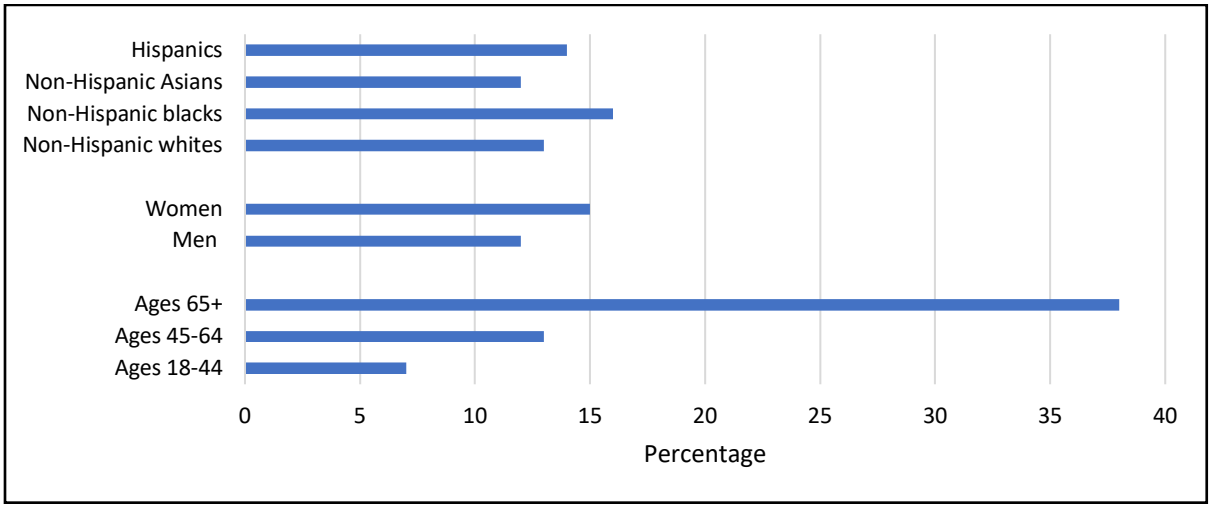
Table 1. Kidney Disease Classification by Estimated Glomerular Filtration Rate

Stage	GFR (mL/min/1.73m^2)	Clinical Terms
1	≥90	Normal or high
2	60-89	Mildly decreased
3	a: 45-59 b: 30-44	a: Mildly-moderately decreased b: Moderately-severely decreased
4	15-29	Severely decreased
5	<15	Kidney failure (add D if treated by dialysis)

CKD Demographics, Morbidity, and Mortality

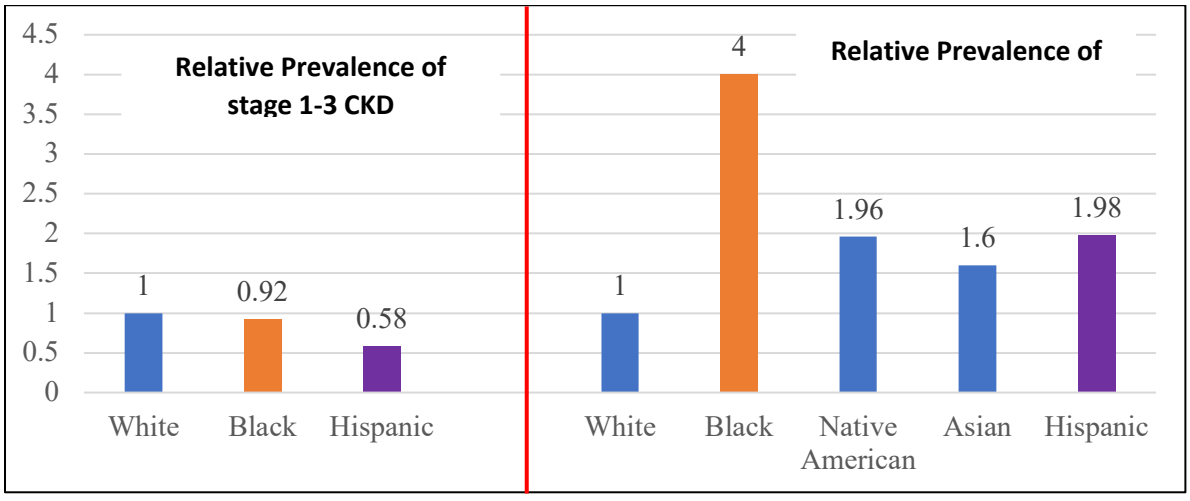
In 2019, chronic kidney disease (CKD) accounted for over 120 billion dollars in total U.S. Medicare spending, and represented 33.8% of total Medicare fee-for-service spending.[13] CKD is more common in older adults (>65 years old) and women, non-Hispanic blacks and Hispanics (Figure 1).[1] The mean age of the population is increasing as is the percentage of people over the age of 65 who have ESRD.[14] Rising rates of CKD in the U.S. have stabilized, but internationally the prevalence of ESRD is still increasing at the staggering rate of 5-7% per year. This rise has been attributed to population aging, higher international rates of diabetes mellitus (DM) and hypertension (HTN), and a generalized slower recognition and diagnosis of advancing CKD. [7,15]

Figure 1. Percentage of CKD among US adults 18 Years or older by age, sex, and ethnicity[1]



In the US, there is a significantly higher prevalence of ESRD in non-white minority groups despite similar rates of CKD (Figure 2). The progression of disease in non-white minorities has been associated with poorer access to primary healthcare, delayed diagnosis, and lack of early care of CKD. Higher rates of the HTN and DM in minority groups that are associated with increased socio-economic stress, food insecurity, and poverty have also been suggested to be a contributing factor.[16]

Figure 2. U.S. Prevalence of CKD and ESRD by Race/Ethnicity[17]



The Global Burden of Disease study reports that in 2015, CKD was associated with 1.2 million deaths; half of which were attributed to cardiovascular death. Independent associations have been found between kidney function (measured by eGFR) and risk of death, cardiovascular events, and hospitalization. Adjusted hazard ratios for mortality in ESRD have been reported at 5.9 (95% CI, 5.4-6.5).[18]

CKD/ESRD Within a Disability Framework

Healthy People 2020, the national health initiative released by the U.S. Department of Health and Human Services, identifies important objectives to reach the vision of "a society in which all people live long and healthy lives" and these objectives pertain to those with CKD.[19]

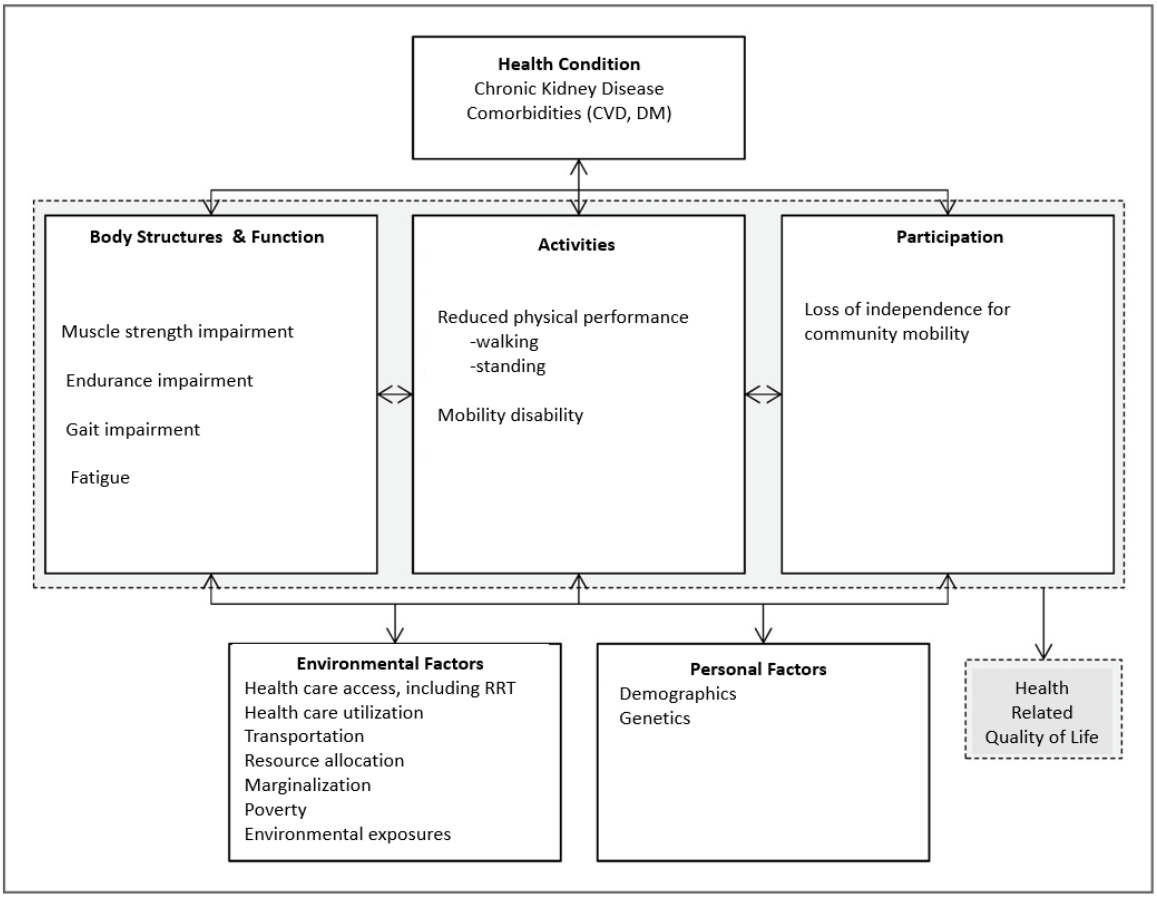
- Increase the proportion of those with renal disease who report confidence in managing their condition
- Reduce the proportion of adults with renal disease who have moderate to severe functional limitations
- Increase the proportion of those with ESRD and reduced physical or cognitive function who engage in light, moderate, or vigorous leisure time activities
- Increase the proportion of health care providers with specialization in CKD
- Reduce the proportion of noninstitutionalized people with ESRD and disability who have an unmet need for long-term services and supports
- Reduce the rate of falls among those with ESRD

The International Classification of Function (ICF) is a biopsychosocial framework that allows for modeling of relationships between factors that contribute to the experience of disability.[20] In 2001, the World Health Organization published the ICF as a framework for classifying functioning and disability's relationship to health conditions with the notion that

having some form of disability in one's lifetime is a universal human experience.[20] The purpose for its development was to standardize descriptions and measurements of health's relationship with disability for construction of a broader and more relevant picture of an individual outside of their medical diagnosis (a biopsychosocial approach). The ICF framework is meant to aid decision making at both the individual and population level for service provision, policy development, economic analysis, and research and is particularly useful for complex diseases such as CKD.

The ICF is organized in two main subdivisions: human functioning/disability and contextual factors. CKD is modeled using the ICF in Figure 2. The human functioning/disability subdivision has three domains of human function which are classified based on body (biological), individual, and societal perspectives, and each component of this subdivision is labeled body functions and structures, activities, and participation, respectively. Dysfunction at one or more of these levels is considered *disability.* The contextual factors are subdivided is into environmental and personal factors. An example of CKD modeled with the ICF is presented in Figure 3.

Figure 3. CKD modeled with the ICF



Painter et al. utilizes components of this model to review and describe the functioning and disability sub-division of the ICF in those with CKD. Resultant recommendations from this review were that assessment of parameters in the functioning and disability subdivision is crucial, noting that lower levels of physical functioning are present in CKD and known to be predictive of poor outcomes.[21,22] This model is useful in studying physical performance and its relationship to the effects of CKD/ESRD's on body structure and functions and their relationships to reduced physical performance and mobility disability.

Effects of CKD/ESRD on Function

Physical function is defined as one's ability to carry out activities that require physical actions, ranging from self-care (activities of daily living (ADLs)) to more complex activities that require a combination of skills.[23] Physical function is usually measured objectively with physical performance tests such as timed short ambulation, stair climbing and sit-to-stand tasks. Physical performance is reduced in those with CKD/ESRD.[21] The ability to ambulate independently is critical for independence and loss of independent ambulation can be used as a marker for loss of mobility. The term "mobility disability", is defined by 1) the inability to walk > 1/4 mile (400m) and/or 2) the inability to climb 1 flight (10 steps) of stairs).[24-26] In older adults, mobility disability is a risk factor for loss of community independence, disability, mortality, and poorer quality of life (QOL).[25,27]CKD-associated declines in physical performance have been reported and include decreased muscle performance, exercise tolerance, cardiac capacity, postural stability, and functional mobility[28,29]

Muscle Performance

In CKD, loss of muscle mass is associated with an increased risk for death..[30] Sarcopenia is defined by the International Classification of Diseases, 10th Revision (ICD-10) as the loss of muscle tissue and function due to aging, chronic disease, low protein energy intake and physical inactivity. Critical for many functions of the body, loss of skeletal muscle mass and quality can result in weakness, reduced mobility, and poor exercise tolerance.[31] The CKD-associated uremic state is associated with both protein energy wasting and multiple metabolic derangements that contribute to sarcopenia.[32-35] Cross sectional studies have documented inconsistent associations of muscle mass loss with inflammation (C-reactive protein), bicarbonate, and albumin indicating

high inflammatory levels, systemic acidosis, and poor nutritional status.[36] Currently, clinical biomarkers of sarcopenia have not been effectively validated in CKD and relationships with patient-centered outcomes such as disability and quality of life are poorly understood.[37]

Decreased strength can lead to inactivity and cause further loss of muscle mass. It is unknown which of these is the initiating factor for loss of strength in renal disease.[32] Handgrip strength (HGS) , a useful clinical tool to measure muscle function, has been reported to be below the 50th percentile in over half of adults on HD with ESRD.[38] In a large CKD cohort, isometric quadricep endurance was significantly associated with persistent severe lower extremity limitation which was defined as having difficulty walking ¼ mile or climbing 10 steps without resting.[39] A 2 year longitudinal study of 32 stage 4-5 CKD and 56 dialysis patients demonstrated that over 1 year loss of muscle mass was much higher in those who were not on dialysis, and that this muscle mass decline was not continuous, suggesting that muscle wasting may be at peak levels just prior to dialysis initiation.[40] Screening for muscle wasting earlier in the disease process may hold promise for introducing interventions prior to patient's displaying signs of decreased mobility. Currently, there is some evidence that use of anabolic steroids and nandrolone decanoate can decrease CKD-induced muscle wasting in dialysis patients, but stronger evidence points to resistive exercise interventions' effectiveness in arresting or reversing sarcopenia.[32,37]

Exercise Tolerance and Endurance

As previously stated, significant prevalence of cardiovascular disease (CVD) is found in CKD and CVD is the leading cause of death in those with stage 5 CKD. Decreasing eGFR is independently associated with an increased risk of cardiovascular events and adjusted hazard

ratios for cardiovascular events in stage 5 CKD have been reported at 3.4 (95% CI, 3.1-3.8).[41,42] CVD contributes to poor exercise tolerance and decreased physical activity. In sedentary patients with eGFR of <47 ml/min/1.73m^2, Vo_{2peak} was ~55% of age predicted values and this reduction in exercise capacity was associated with poor performance on maximal gait speed and sit to stand tests, indicating day-to-day activities were affected even earlier in the disease process.[4] Peak exercise capacity, measured by metabolic equivalent tasks (METs), has been shown to be reduced in those with a eGFR <60 mL/min per 1.73m^2, and declines with disease progression. The Heart and Soul Study found that when compared to age-matched controls, those with CKD were found to have lower exercise capacity (5.5 METs vs. 7.9 METs, p <0.001).[43] In this study both eGFR and anemia were independent predictors of exercise capacity and when presenting together, these effects were additive. Changes in cardiac capacity are due to decreased left ventricular ejection fractions and decreased left ventricular end-systolic volumes[44] CVD parameters are generally better in those treated with kidney transplant when compared to peritoneal or hemodialysis (HD), and HD initiation has been shown to increase CVD.[44,45]

Fatigue

The most bothersome symptom reported by those with CKD in all stages is fatigue.[46-48] Fatigue has been identified by the International Standardized Outcomes in Nephrology (SONG) Initiative as a core outcome that is critically important to both patient and health professionals and is recommended to be reported across trials.[48] Fatigue, defined as "extreme and persistent tiredness, weakness – mental, physical, or both" has been reported in as many as 70-90% of patients with CKD and has been attributed to sarcopenia, high BMI, poor nutritional status, anemia, disruptions in acid/base balance, poor sleep, depression and systemic inflammation.[49,50]

In a small sample (n=112) of those with CKD, regardless of receiving dialysis, those reporting higher levels of fatigue also reported participating in fewer daily activities.[51] In the HD population, fatigue rates have ranged from 42%-89% and has been related to factors such as ultrafiltration, diffusion, osmotic disequilibrium, changes in blood pressure, higher levels of tumor necrosis factor, poor nutritional status, poor sleep, and a more sedentary lifestyle.[49,52] Post-dialysis fatigue is known to be pervasive and has been linked to increased dependence for activities of daily living (ADL's) and increased dependence in ADLs.[53,54]

In older adults, data suggests that self-reported fatigue is a long-term risk factor for poor mobility and limitations in performing instrumental activities of daily living (IADLs).[53] Regardless of comorbidities, older persons who report high levels of fatigue, have been found to have less handgrip strength, slower gait speeds, and poor lower extremity function.[49] Currently the relationships between self-reported fatigue and mobility impairment in those with CKD/ESRD are not well understood. If similar relationships exist between fatigue and poor physical function in CKD, fatigue may be a useful indicator of the need for intervention earlier in the disease process.

Postural Control and Balance

Postural stability is the ability to maintain center of pressure relative to a person's base of support, either with movement (such as walking), or in a fixed position. Postural instability during quiet standing has been reported in CKD and found associated with physical and cognitive function, as well as decreasing renal function.[55] Blake et al. found 39% poorer postural stability in a group of HD patients compared to healthy controls.[56] Similarly, Shin et al. compared the effect of a dual task on static postural control between those on HD and healthy

controls and found significantly more postural sway in the HD group.[57] In older adults, balance performance is known to predict persistent lower extremity impairment, death, and hospitalization.[58] Relationships of postural instability and poor outcomes are not well understood for those with CKD/ESRD.

Functional Mobility

Physical function is defined as one's ability to carry out activities that require physical actions, ranging from self-care (activities of daily living (ADLs)) to more complex activities that require a combination of skills.[23] Physical function is usually measured objectively with physical performance tests such as timed short ambulation, stair climbing and sit-to-stand tasks. Physical performance is reduced in those with CKD/ESRD.[21] For example, in pre-dialysis patients, the odds of being able to stand from a chair unassisted is 1.5 times higher for every 1 mL/min per 1.73m^2 drop in eGFR.[59] Lower eGFR was associated with lower global gait scores in 7 different gait domains (rhythm, phases, variability, pace, tandem, turning, base of support) as well as gait speed (-.09, 95% CI: 0.14-0.03 & -1.55, 95% CI: -2.43—0.67, respectively) in a study of 1430 patients.48. This same study revealed that lower gait scores are related to a history of falling.[60] Physical function limitations have been found to develop in earlier stages of chronic kidney disease (mean eGFR = 50, mL/min/1.73m^2) with physical performance being reduced in about 70% of these patients; suggesting a potential window for initiation of screening and prevention.[61]

Effects of CKD/ESRD on Activity and Participation

Reduced physical activity has been reported in those with CKD/ESRD.[3,5,21] The Heart and Soul Study found that when compared to age-matched controls, those with CKD were found

to have significantly lower self-reported physical activity (PA) (67.6% vs. 74.9%, *p< 0.001)* and lower exercise capacity (EC) (5.5 METs vs. 7.9 METs, p <0.001).[43] Sedentary behavior in CKD is associated with worse physical performance on the composite Short Physical Performance Battery (SPPB) and is found to be increased in those with CKD who are more frail.[62] In HD patients, less physical activity (<4,000 steps) had an increased risk of death (HR=2.37, CI=1.22-4.60). Consistent with the Heart and Soul study, a study of 280 patients that compared those with CKD and HD to controls using actigraphy to assess PA levels reported that those with CKD rested more and were significantly less active.[63]

As with aging, those with CKD are at similar risk to increased risk of falls, loss of independence, and increased hospitalizations. Those over 65 years old with a eGFR <45 mL/min/1.73m^2 have a threefold odds of declining function on activities of daily living and are at a greater risk for developing frailty and loss of independence.[64]

Prospective studied have shown that with initiation of dialysis, a marked decreased in functional status has been found. In a nursing home cohort of newly initiated dialysis patients, at 1 year only 13% maintained their pre-dialysis functional status measured by the Minimum Data-Set for Activities of Daily Living.[65] In study of 97, >80 year old, community-dwelling HD patients, 78% were functionally independent at dialysis initiation. After 1 year this dropped to 23% and after 6 months, more than 30% needed to have assistance and/or changes to their living situation; indicating rapid onset of disability following dialysis initiation.[66]

Statement of the Problem

Few studies have examined the relationship between fatigue and physical performance in CKD. Considering that increased fatigue and decreased physical performance can have negative effects on quality of life, understanding these relationships is needed to inform potential interventions. In older adults, mobility disability is a risk factor for loss of community independence, disability, mortality, and poorer quality of life (QOL).[8,21,67] Decline in physical performance, including decreased gait speed, strength, and cardiovascular endurance, has been reported in CKD, but these relationships with disability are not well understood. [24,26] Early identification of risk for mobility disability in adults with CKD will facilitate improved preservation of independent living, an important public health goal. A clearer understanding of physical performance around the dialysis session, as well as which dialysis factors impact physical performance is needed to guide recommendations around rehabilitation in ESRD-D.

Research Aims

This dissertation is comprised of 3 papers whose aims are described below.

I. "The Relationship of Self-perceived Fatigue with Physical Performance and Mobility Disability in Chronic Kidney Disease"
    i. Examine the association of fatigue with measures of physical performance in the domains of strength, endurance, and functional composite performance
    ii. To determine if there is an independent association between fatigue and mobility disability in CKD

II. "Reliability of Physical Performance and Instrumented Measures in Adults with Kidney Disease"

i. Examine the test-retest reliability of standard and instrumented measures of physical performance in adults with CKD and ESRD-D

ii. Describe differences in balance, gait, and lower extremity strength between adults with CKD (stages 2-4) and those with dialysis dependent ESRD

III. "The Acute Effects of Dialysis on Physical Performance in Adults with Hemodialysis Dependent End Stage Renal Disease"

i. Examine changes in physical performance on measures of gait, balance, endurance, and muscle performance that occur within 20 minutes following a HD session

ii. Determine whether pre-post HD differences in physical performance are correlated with variables related to a HD exposure

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Chapter 2

The Relationship of Fatigue with Physical Performance and Mobility Disability in Chronic Kidney Disease

Abstract

Background: Fatigue and poor physical performance is common and associated with poor outcomes in those with dialysis dependent end-stage renal disease (ESRD). Little is known about fatigue in chronic kidney disease (CKD) nor its relationship to physical performance. Mobility disability is "when impairments in mobility restrict the ability of individuals to move about in their natural environment in order to carry out activities essential to daily life". The relationships between fatigue and mobility disability have not been described in CKD. This study aimed to examine the association of fatigue with physical performance and mobility disability.

Methods. Cross-sectional data from a sample of 293 Seattle-area men and women (mean age = 53.8±13.9 years) with non-dialysis dependent CKD was analyzed. Fatigue was assessed with the Energy/Fatigue Subscale of the SF-36 (SF-EF) and high fatigue was defined as one standard deviation below the standardized population mean. Objective measures of physical performance were the Short Physical Performance Battery (SPPB), Five Times Sit to Stand (FSTS), gait speed, 6-Minute Walk Test (6MWT) and dominant handgrip strength (HGS). Linear regression analysis assessed the relationship between fatigue and physical performance and then controlled for age, BMI, and CKD-related factors. Dichotomous variables were created for mobility disability (defined by the inability to independently walk ¼ mile or climb 1 flight of stairs) using established physical performance cut-points on the SPPB, gait speed, and FSTS. Logistic regression analysis assessed the relationship between fatigue and mobility disability and then controlled for age, BMI, and CKD-related factors.

Results. Thirty-nine percent of the sample reported having high fatigue. Physical performance was below age-expected norms on the gait speed, FSTS, and 6MWT. Fatigue was significantly

associated with FSTS and gait speed and contributed to 2.1% and 3.1% of the variance in FSTS and gait speed, respectively. This relationship remained even after adjusting for covariates. Mobility disability was present in up to 51% of the sample though not found to be significantly associated with fatigue.

Conclusions. Based on these findings, it is possible that fatigue may play a role in poor lower extremity physical performance. Mobility disability was present in over half of the study participants. The high prevalence of mobility disability suggests that clinicians should consider CKD a risk factor for mobility disability and screen these patients for functional impairment. The causal link between fatigue and lower extremity function should be further investigated to understand and treat mobility disability in this population.

Background and Purpose

High fatigue and poor physical performance are known to occur in chronic kidney disease (CKD). [1-6] Decreased muscle mass and strength, termed sarcopenia, are known consequences of aging and this loss is accelerated in those with CKD.[4-6] CKD is an increasing global public health problem evidenced by increasing rates of prevalence, morbidity and mortality.[7] In 2016, the overall prevalence of CKD in the United States was approximately 14% (30 million Americans) and accounted for $114 billion dollars in Medicare fee-for-service spending.[8] CKD is defined as abnormalities of kidney structure and function that have been present for > 3 months, with a glomerular filtration rate (GFR) of < 60 mL/min per 1.73m^2.[9] Kidney disease ranges from mild to severe and can be described by 5 distinct stages based on the GFR. [10] GFR is considered the best estimate of kidney function and is calculated by age, gender, race, body size, and blood creatinine. Stage 1 kidney disease is defined by normal kidney function and a GFR of ≥ 90 mL/min per 1.73m^2, stage 2 kidney disease is defined as mild loss of kidney function with a GFR of 60-89 mL/min per 1.73m^2, stage 3 is defined mild to severe loss of kidney function with a GFR of 30-59 mL/min per 1.73m^2, stage 4 is defined by severe loss of kidney function with a GFR of 29-15 mL/min per 1.73m^2, and stage 5 is considered end-stage renal disease (ESRD) and defined by kidney failure with a GFR of < 15 mL/min per 1.73m^2. Those with ESRD require renal replacement therapy (transplant or dialysis) to survive. [11,12] Little is known about the relationships between poor physical performance, fatigue, and disability in those with stage 2-4 CKD.

Fatigue, defined as extreme and persistent tiredness, weakness – mental, physical, or both is the most frequently reported symptom in mid-late stages of chronic kidney disease (CKD).[13-15] The prevalence of fatigue in those with stages 4-5 CKD has been reported at 70-90% while the

prevalence of fatigue in adults during earlier stages of the disease is generally under-reported.[16] Studies of those in late stages (stage 4-5) of CKD report that fatigue is associated with aspects of disability, including increased risk for dependence on others, decreased physical activity and poorer quality of life. [16-18] Fatigue has also been shown to contribute to an increased risk for mortality in those with stages 2-5 CKD and independently associated with progression to ESRD, death, or hospitalization in those with CKD.[18] Over the first year of dialysis, fatigue (assessed with the SF-36 energy/fatigue subscale) was found to be associated with an increased risk of death (hazard ratio = 1.4) after controlling for dialysis type, demographics, creatinine, inflammation, anti-depressant use, and body mass index (BMI).[19]

Numerous factors have been related to perpetuating clinically significant fatigue in adults with CKD, including anemia, malnutrition, physical inactivity, systemic inflammation, poor sleep, poor emotional status, and increased age. [20-22] To this date, only some of these factors (i.e., anemia and inflammation) are at the forefront of clinical management, while others such as activity modifications and exercise to reduce functional impairments are not widely utilized.[23] Facilitation of effective disablement management in CKD requires a better understanding of the potential perpetuating factors related to fatigue, an important patient-centered outcome.

Decreased physical performance is also known to be prevalent, even in early stages of CKD, and linked to higher rates of morbidity, hospitalization, mortality, and disability.[24] Performance-based measures are used to test physiologic capacity to perform specific functional activities. Examples of physiologic capacities required to complete functional activities are flexibility, muscle strength, balance, coordination, and body-system endurance. For example, a common physical performance measure that requires physiologic capacity of lower extremity strength, power and body system endurance is the sit-to-stand test which requires one to perform

multiple sit-to-stand repetitions as quickly as possible without upper extremity assistance. In pre-dialysis patients, the odds of being able to stand one time from a chair unassisted were found to be 1.5 times higher for every 1 mL/min per 1.73m2 drop in eGFR, evidence to a decline in lower extremity functional strength early in the disease process.[25]

Gait speed, another common physical performance measure, is dependent on many physiologic capacities. Gait speed is a reliable measure assessed with timed short distance walks of distances generally between 4-10 meters at usual or fast paces.[26] Gait speed has been termed the "sixth functional vital sign" due to its predictive capabilities of clinical outcomes in aging adults and those with cognitive decline.[27] In CKD, a 0.1 m/s decrement in gait speed was found associated with a 26% higher risk of death when adjusting for covariates.[28] In a study of 1430 participants, lower GFR was associated with lower global gait scores in 7 different gait domains (rhythm, phases, variability, pace, tandem, turning, base of support) as well as gait speed.[29] Lower gait speeds in adults > 60 years old are associated with multiple disability outcomes including higher fall rates (>0.7 m/s), cognitive decline (>1.0 m/s), increased independence in self-care (>0.7 m/s), limited community ambulation (>1.3 m/s), and mortality (>0.7 m/s) .[27,30]

The 6-minute walk test (6MWT) is a test that assesses endurance and functional mobility by having a patient walk at a fast pace as far as they can for 6 minutes. It also can be used to estimate submaximal cardiac capacity.[31] A randomized controlled trial (n=107) evaluating the effect of exercise interventions in adults with CKD (stages 3-4) found that at baseline, the participants had 60-65% of healthy predicted physical function on both the 6MWT and the sit to stand test. This study found that the exercise intervention group improved both physical performance, fatigue, and overall quality of life.[32]

In healthy older adults, studies have reported significant relationships between self-perceived fatigue, functional disability, and physical performance, suggesting an inverse relationship between fatigue and physical performance.[33,34] For example, older persons who report increased fatigue have been found to have decreased grip strength and slower gait speeds, even after adjusting for comorbidity.[35] CKD has been described as a process of "premature aging" that occurs due to multiple mechanisms that contribute to cellular senescence though toxic alterations to body's internal environment.[4] One can hypothesize that similar relationships between fatigue and physical performance exist in adults with CKD, however, research is lacking in this area.

Retaining the ability to be mobile is essential to quality of life and preservation of independence.[36] Rates of disability, mortality, and morbidity are higher in older adults who lose mobility.[37,38] In the U.S. in order for a person to safely cross the street at a traffic light they need to be able to ambulate at .74-1.06 m/s, with faster speeds required for cities with larger populations.[39] Walking distances required for community ambulation have been reported for different U.S. environments and examples include supermarket (107-696 m), doctors office (39-206 m), restaurants (28-119 m), drugstores (50m).[40] Mobility disability is a risk factor for loss of community independence, disability, mortality, and poorer quality of life (QOL).[4-6] Mobility disability happens when impairments in mobility restrict the ability of individuals to move about in their natural environment in order to carry out activities essential to daily life".[41] Mobility disability has been defined as 1) the inability to walk > 1/4 mile (400m) unassisted and/or 2) the inability to climb 1 flight (10 steps) of stairs unassisted).[36,42-44] Gait speed, walking distance, and the ability to ambulate in multiple environments has been established as predictors of mobility disability.[41] Cut points that are predictive of mobility disability are not established for CKD, but

have been established on the following physical performance measures in the geriatric literature: gait speed (≤1.0 m/s), Five Times Sit to Stand (≥10 sec), and the Short Physical Performance Battery (score ≤10).[30,42,44-46] Early identification of mobility disability in adults with mild-moderate CKD will facilitate improved preservation of independent living.

The aims of this study were: 1) to examine the association of fatigue and measures of physical performance in the domains of strength, endurance, and functional composite performance, and 2) to determine if there is an association between self-perceived fatigue and mobility disability in adults with CKD. The hypotheses are that higher fatigue will be associated with poorer physical performance and that higher fatigue will be associated with mobility disability.

Methods

Study Design, Setting, and Participants

A cross-sectional study was conducted using baseline data from the Seattle Kidney Study (SKS), a longitudinal observational study of CKD patients. Participants with CKD were recruited from the Seattle Kidney Study between 2004 and 2007 from University of Washington affiliated hospitals and nephrology clinics. [47] General inclusion criteria for the SKS were > 18 years old and CKD of any stage (defined as a eGFR by serum creatinine equation based CKD-EPI equation of >90 mL/min/1.73 m^2 or the presence of urine albumin-creatinine ratio of >30mg/g from a 12 hour urine collection) that did not require dialysis. Exclusion criteria included kidney transplantation, dementia, institutionalization, expected to start renal replacement therapy or leave the area within 3 months, participation in a clinical trial, non-English speaking, or inability to undergo the informed consent process. All SKS participants

underwent written informed consent prior to participation. The University of Washington and Veterans Affairs Puget Sound Health Care System review boards provided approval for the SKS. The baseline visit data was used for this analysis. For this study, inclusion criteria were completion of both the SF-36 questionnaire and physical function testing.

Demographic and Clinical Data

Age, gender, race, work status, prevalent disease, smoking, and use of assistive device information was obtained via patient questionnaire. At the baseline study visit, study coordinators collected blood pressure, serum, plasma, and a 12-hour urine sample and lab values for factors previously found to be associated with both fatigue and physical performance were examined.[19,21,48] These values included albumin (nutritional indicator), C-reactive protein (inflammatory marker), bicarbonate (metabolic indicator), hemoglobin, and GFR which was estimated was estimated by the 2012 CKD EPI equation.

Health and Activity Measures

Sleep status was derived from the sleep subscale of the Kidney Disease Quality of Questionnaire which is scored from 0-100 with lower scores indicating worse overall sleep.[49] Exercise frequency was assessed by the question "During the past one month, how often did you exercise?" with responses options being never, < 1x/week, 1x/week, 2-3x/week, and >3x/week. Use of an assistive device was defined as use of any device type, regardless of frequency.

Fatigue Measures

Participants completed the Medical Outcomes Study 36-Item Short-Form Health Survey version 2 (SF-36).[50] The SF-36 is a widely used measure of health and wellbeing and contains a

4-item vitality/energy level/fatigue subscale (SF-EF) that was used to assess self-perceived fatigue. SF-EF scores range from 0-100 with higher scores indicating better vitality and less fatigue. The scores are standardized such that a mean score of 50 and a standard deviation of 10 represents the distribution of the US general population.[51] The SF-EF has been found sensitive to treatment effects in randomized trials in chronic diseases such as anemia, CHF, hypertension, prostate disease, COPD, AIDS, and CKD.[52,53] The SF-EF has been found to have internal consistency (Cronbach's alpha = 0.82) and test-retest reliability (ICC = 0.64) in those with CKD.[54] Change scores on the SF-EF have been found significantly associated with frequency of going out of the home (OR = 1.03, CI= 1.01-1.05, $p<0.001$), an indicator of social participation.[53] Decrements of 5-points on the SF-EF scale are associated with negative outcomes including job loss, hospitalization, and mortality in those with diseases known to cause fatigue, including CKD.[52] A decrement of 5 points on the SF-EF is considered the minimally important difference in those whose scores fall below the average.[52]

Emotional Health

The Mental Component Summary (MCS) is derived from eight scale scores of the SF-36 and is used as a measure of emotional status with lower scores indicating more emotional problems affecting quality of life.[50] The MCS scores are standardized like the SF-EF with a mean score being 50 and a standard deviation of 10 for a score range of 1-100 with higher scores indicating better emotional status.

Physical Performance Measures

Short Physical Performance Battery (SPPB). The SPPB is a composite measure of functional mobility consisting of balance tests, gait speed, and the Five Times Sit to Stand Test.[55] The sum

SPPB score ranges from 0 (worst performance) to 12 (best performance). In older community dwelling adults, scores of ≤10 have been found to be predictive of mobility disability.[56] Excellent reliability of the SPPB has been reported in a small group of adults undergoing hemodialysis (ICC = 0.94, CI = 0.91-0.97).[57]

Gait Speed. Gait speed was calculated using the 4-meter course of the SPPB. Participants were asked to walk at a usual pace from a static standing start and walk past tape that was placed at the 4-meter mark. A stopwatch started timing at the initiation of the walk and stopped when the first foot completely crossed the 4-meter line. The fastest of two trials was used to calculate gait speed in gait speed meters/second. A gait speed of <1.0 m/sec is an established cut-point for mobility disability in older adults (mean age 74.2).[44]

The Five Times Sit to Stand Test (FSTS). The FSTS, a component of the SPPB, is an independent measure of lower extremity strength, power, and muscular endurance. Participants complete 5 sit -to-stand repetitions (without using their arms) from a standard height chair (18") as quickly as they can. High test-retest reliability of the FSTS (ICC = 0.95, 95% CI = .89-.97) is reported in older adult females and validity was demonstrated via a strong correlation to the Timed Up and Go (r=0.64, $p < .05$). [58] The FSTS has a predictive cut-point of ≥10 seconds for mobility disability in community dwelling older adults.[45] The minimum clinically important differences on the FSTS in adults on hemodialysis participating in an exercise intervention was reported as -4.2 seconds.[57]

Six Minute Walk Test (6MWT). The 6MWT assesses the endurance, functional ambulation, and submaximal body-system endurance.[31,59] The instructions of this test are to "walk and cover as much distance as you safely can in 6 minutes" and allows for rest if needed. The walking test

was performed in a marked indoor corridor. Excellent test-retest reliability of the 6MWT (ICC=.94, 95% CI: .92-.99) has been established in adults with dialysis dependent ESRD.[60]

Handgrip strength (HGS). Dominant HGS was measured over 3 consecutive trials using a Takei handheld dynamometer (Takei Scientific Instruments Co., Ltd, Tokyo, Japan) positioned with the arm at side and elbow flexed to 90 degrees. The maximum of 3 trials was used for this analysis. Test-retest reliability has been established for GS in those undergoing hemodialysis (ICC =.95, 95% CI = .88-.99).[60] Handgrip strength predictive of mobility disability in adults over the age of 55 have been established at <37 kg in men and <21 kg in women regardless of BMI.[61]

Statistical Analysis

Statistical tests were performed using SPSS Version 26.0 and were conducted at the nominal significance level of $p < 0.05$. Complete case analysis was used, and extreme outliers (defined as >3 times the interquartile range) were assessed and excluded from analysis. Descriptive statistics were generated and reported as mean (standard deviation) for continuous variables and percentages for categorical variables. Means were compared to available normative data. Standard multiple linear regressions were performed to estimate the association of fatigue and the dependent physical performance variables of gait speed, FSTS, 6MWT, and GS. Second models were then generated controlling for the following co-variates: age, emotion, sleep, number of medications, exercise frequency, body mass index (BMI), hemoglobin (Hgb), albumin (Alb), CO_2, C-reactive protein (CRP) and eGFR. Preliminary analyses were performed to ensure there was no violation of the assumptions of normality, linearity, multilinearity, or heteroscedasticity. Visual inspection of plots of residuals vs. standardized values revealed

homoscedasticity. Assumptions of normality were met, as assessed by Q-Q plots. There was no evidence of multicollinearity, as assessed by tolerance values greater than 0.1.

To assess the relationship between fatigue and mobility disability, dichotomous variables for physical performance were calculated using previous cut-points for mobility disability on gait speed (≤0.1 m/s), FSTS (≥10 seconds), and an SPPB (≤10). Unadjusted logistic regression models were then generated to assess the relationship between fatigue and mobility disability, followed by models that controlled for age, sleep, number of medications, exercise frequency, BMI, Hgb, Alb, CRP and eGFR. Linearity of the continuous variables with respect to the logit of the dependent variable was assessed via the Box-Tidwell procedure. A Bonferroni correction was applied using all 19 terms in the model resulting and a statistical significance being accepted when $p < 0.05$[62] Based on this assessment, all continuous variables were found to be linearly related to the logit of the dependent variable. There were 2 and 1 standardized residuals in the gait-speed model and the FSTS model (respectively) with values of 2.55 which were kept in both analyses as they were non-influential.

Results

A complete case analysis of 293 records was conducted using SPSS Version 26.0. The Six Minute Walk Test was introduced later in the study which resulted in only 248 participants included in the analysis for this variable.

Demographic Characteristics

The mean age of the sample was 53.8 (13.9) and 51.5% female. The race distribution was as follows: Caucasian (56.7%), Black (22.9%), Asian/Pacific Islander (10.2%), Hispanic (6.1%) and Other (10%). Only 30.3% reported being employed in some capacity. 83% reported

having hypertension (HTN), 37% had diabetes and 24% had a cardiovascular disease indicator. Demographic data is reported in Table 1.

Table 1. Demographic Characteristics

(n=293)	Missing (n)	%/Mean (SD)
Age (years)		53.8 (13.9)
Gender (% female)		51.5%
Race		
Caucasian		56.7%
Black		22.9%
Asian/Pacific Islander		10.2%
Hispanic		6.1%
Other		10.0%
Marital Status	3	
Married		34.8%
Never Married		33.4%
Widowed		6.5%
Divorced		24.2%
Work Status	5	
Full-time		19.8%
Part-time		11.3%
Unemployed		33.4%
Retired		33.4%
On Disability		3.0%
Prevalent Disease		
Hypertension		87.0%
Diabetes		36.5%
Any CAD		24.2%
Current smoking	2	19.5%
Use of Assistive Device		9.9%

SD= standard deviation; CAD= coronary artery disease

Fatigue and Clinical Covariates

Descriptive characteristics of fatigue and clinical covariates are presented in Table 2. The mean eGFR was 52 ml/min per 1.73m^2 (27.1) which indicates most of the sample was in stages 2-4 of CKD. The mean SF-EF score was 48.81 (22.35), slightly below the standardized mean of

50 indicating that this this sample was slightly more fatigued than established norms for non-institutionalized U.S. community dwelling adults (aged 18-94).[63] A little less than half of the sample (40%) were considered high fatigue, defined by being 1 standard deviation below the mean on the SF-EF. The mean number of medications was 7.69 (3.5) indicating a high rate of health-related problems. The mean score on the SF-36 MCS was 69.28 (20.43), considered to be above the population mean of 50 for emotional and mental wellness related to quality of life.[63] Available normative lab values derived from the American Board of Internal Medicine (ABIM) are presented for reference in Table 2.[64] The mean BMI of the sample was 30.28 kg/m^2 which is considered above the accepted cut-point for obesity (≥30 kg/m^2).[65] The sample had abnormally high CRP values indicating this group had clinically significant inflammation.[66]

Table 2. Descriptive Statistics for Fatigue and Clinical Covariates

(n=293)	Missing (N)	%/Mean (SD)	Normative Values
Fatigue			
SF-36 EF (0-100)		48.81 (22.35)	
Clinical Covariates			
Exercise (times/week)	4		
Never		17.4%	
≤1 day/week		31.0%	
2-3 days/week		26.6%	
>3 days/week		23.2%	
Number of Medications	8	7.69 (3.5)	
SF-36 MCS (0-100)		69.28 (20.43)	40-60
BMI (kg/m^2)		30.28 (7.3)	≥18.5-24.9
eGFR (ml/min per 1.73m^2)	1	52.08 (27.1)	>90
Hemoglobin (g/dl)	11	12.70 (1.9)	12-17.5
CRP (mg/dl)	1	3.47 (6.8)	<1
Albumin (mg/dl)	1	3.71 (0.6)	3.5-5.5
Creatinine (IU/L)	1	1.83 (1.1)	0.5-2.8
Bicarbonate (mmol/L)	1	23.35 (3.7)	23-.38

SD = standard deviation, SF-EF= SF-36 short form energy fatigue scale, n/a = not available, SF-36 MCS= SF- 36 Mental Component Score., BMI=body mass index, eGFR= estimated glomerular filtration rate, CRP=C-reactive protein

Physical Performance

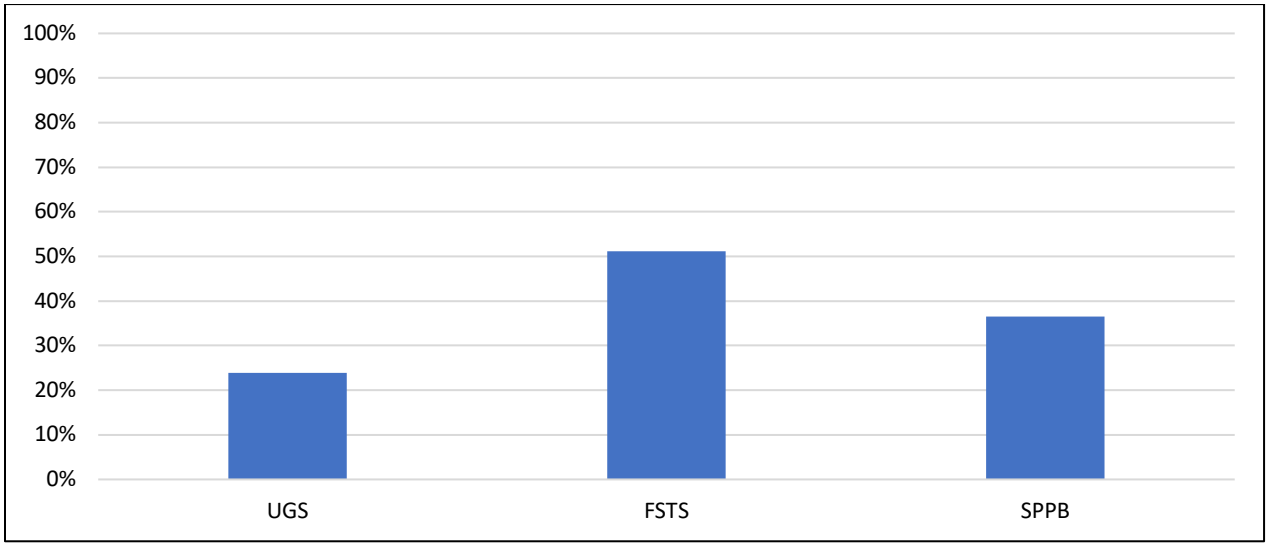
Physical performance mean values and frequency of mobility disability based on established cut points on physical performance measures is presented in Table 3. The presence of mobility disability varied based on the test. The largest mobility disability rate (51.2%) was found using the FSTS cut point of ≥ 10 seconds, followed by the SPPB total score cut point of <10 (36.5%), and the cut point of ≤.1 m/s for usual gait speed (23.9%) indicating that 24 -51% of the sample was at risk for mobility disability based on these predictive physical performance tests (Figure 1).

Table 3. Descriptive Statistics for Physical Performance and Mobility Disability

N= 293	Missing (N)	Mean (SD)
Physical Performance		
SPPB		10.54 (1.9)
Gait speed (m/sec)		0.96 (0.2)
FSTS (sec)		11.26 (5.2)
6MWT (meters)	48	418.46 (87.5)
HGS (kg)		32.88 (11.1)
Mobility Disability		
Gait speed ≤1.0 m/s		70 (23.9%)
FSTS ≥10 seconds		150 (51.2%)
SPPB <10		107 (36.5%)

SD = standard deviation, SPPB= Short Physical Performance Battery, FSTS= Five Times Sit to Stand, 6MWT= 6-Minute Walk Test, HGS= hand grip strength, SF-EF= SF-36 Energy/Fatigue Score, SF-36 MCS= short form 36 Mental Component Score.

Figure 1. Percentage of Sample Below Cut Points indicating Risk for Mobility Disability



FSTS= Five Times Sit to Stand, SPPB= Short Physical Performance Battery, UGS=usual gait speed

Relationships Between Fatigue and Physical Performance

Gait speed. One case was identified as an outlier and excluded for the analysis of gait speed. The unadjusted model (Model 1) demonstrated a statistically significant association between fatigue with gait speed($F(1,291)=9.238$, $p<.05$), $R^2 = .031$. According to this model, a 5-point decrease in SF-EF score was associated with a .01 m/s decrease in gait speed. The adjusted model (Model 2) showed a statistically significant association remained between fatigue and gait speed ($F(12,252) = 5.339$, $p<.001$), $R^2 = .203$, indicating that less fatigue (more energy) was associated with faster gait speed. A 5-unit decrease in EF-36 (more fatigue) was associated with a .01 m/s (CI = -.30 - .00) decrease in gait speed, even when holding all other variables constant. According to Model 2, SF-EF, age, BMI and Alb were all significant predictors of gait speed and this model explained 20% of the variance in gait speed. Regression coefficients and standard errors for this model can be found in Table 4.

Table 4. Multiple Regression results for gait speed

Gait Speed	β	95% CI for *B*		SE β	*B*	R^2	ΔR^2
		LL	UL				
Model 1						0.031	0.027**
Constant	0.868***	0.81	0.93	.03			
SF-EF	0.002**	0.00	0.00	.01	0.18**		
Model 2						0.203	0.165***
Constant	1.029	0.71	1.35	0.16			
SF-EF	0.002*	0.00	0.00	0.00	0.17*		
Age	-0.005***	-0.01	-0.00	-0.01	-0.28***		
SF-36 MCS	0.001	-0.00	0.00	0.00	0.08		
Sleep Score	0.000	-0.00	0.00	0.00	-0.04		
Number of Medications	-0.000	-0.01	0.01	0.00	0.00		
Exercise Frequency	0.008	0-.01	0.03	0.01	-0.18		
BMI	-0.005*	-0.01	-0.00	0.00	-0.17*		
Hemoglobin (g/dl)	0.008	-0.01	0.02	0.01	0.06		
Albumin (g/dL)	0.044*	0.00	0.08	0.02	0.13*		
CO_2 (mg/L)	-0.003	-0.01	0.00	0.01	-0.06		
C-Reactive Protein (mg/L)	-0.002	0-.01	0.00	0.00	-0.05		
eGFR	0.000	-0.00	0.00	0.04	0.04		

Model = "Enter" method in SPSS Statistics; β = unstandardized regression limit; SE β = limit; SE β = standard error of the coefficient; β = standardized coefficient; R2 = coefficient of determination; ΔR2 = adjusted R2; CI = confidence interval; LL = lower limit; UL = upper limit; SF-EF = SF-36 Energy Fatigue Vitality Scale, SF-36 MCS = SF-36 mental component summary, BMI = body mass index, eGFR = estimated glomerular filtration rate, 6MWT=Six Minute Walk Test; * p < .05. **p <.01. *** p <.001.

FSTS. Model 3, the unadjusted model of SF-EF and gait speed, demonstrated a statistically significant relationship between fatigue and five times sit to stand duration ($F(1,291) = 4.332$, $p<.05$), $R^2 = .015$. According to this model, a 5-point decrease in SF-EF score (more fatigue) was associated with a .056 second increase in FTSTS (longer duration). The adjusted model (Model 4) was a statistically significant model for the association of fatigue with FTSTS duration ($F(12,252)=7.613$, $p<.001$), $R^2 = .266$. According to Model 4, a 5-point decrease in SF-

EF scores was associated with a .165 second increase in sit to stand time, holding all variables constant. SF-EF, age, sleep, exercise frequency, BMI, and Alb were all significant ($p<.05$) predictors of FSTS in Model 4, and this model 27% of the variance of FSTS. Regression coefficients and standard errors for these models can be found in Table 5.

Table 5. Multiple Regression results for five times sit to stand duration

FSTS	β	95% CI for β		SE β	*B*	R^2	ΔR^2
		LL	UL				
Model 3						0.021*	0.01*
Constant	12.629	11.21	14.05	0.72			
SF-EF	-0.028*	-0.06	-0.00	0.01	-0.12		
Model 4						0.266	0.231***
Constant	6.845***	-0.09	13.78				
SF-EF	-0.033*	-0.06	-0.00	0.02	-0.14*		
Age	0.108***	-0.06	0.15	0.02	0.30***		
SF-36 MCS	-0.099	-0.04	0.02	0.02	-0.04		
Sleep Score	0.037*	0.01	0.07	0.02	0.15*		
Number of Medications	0.137	-0.03	0.30	0.09	0.10		
Exercise Frequency	-0.447*	-0.86	-0.03	0.21	-0.12*		
BMI	0.171***	0.09	0.25	0.04	0.24***		
Hemoglobin (g/dl)	-0.012	-0.32	0.34	0.17	0.00		
Albumin (g/dL)	-1.014*	-1.88	-0.15	0.44	-0.13*		
CO_2 (mg/L)	-0.089	0-.25	0.07	0.08	-0.06		
C-Reactive Protein (mg/L)	0.006	-0.08	0.09	0.04	-0.01		
eGFR	-0.007	-0.03	0.02	0.01	-0.04		

Model = "Enter" method in SPSS Statistics; β = unstandardized regression limit; SE β = limit; SE β = standard error of the coefficient; β = standardized coefficient; R2 = coefficient of determination; ΔR2 = adjusted R2; CI = confidence interval; LL = lower limit; UL = upper limit; * p < .05. **p <.01. *** p <.001. FSTS= Five Times Sit to Stand, SF-EF = SF-36 Energy Fatigue Vitality Scale, SF-36 MCS = SF-36 mental component summary, BMI = body mass index, eGFR = estimated glomerular filtration rate

6MWT. Model 5, the unadjusted model of SF-EF and 6MWT, was statistically significant (F (1,228) = 4.810, *p<.05)*, R^2 = .02 and a 5-unit increase in SF-EF is associated with 2.82 (CI = .3-5.35) meter increase in 6MWT. The adjusted model (Model 6) showed that a statistically significant association between fatigue and 6MWT remained (F (10, 218) = 6.116,

p<.001), R^2 = .219. According to Model 6, a 5-unit increase in EF-36 is associated with a 1.67 (CI = -.5 – 4.6) meter increase in 6MWT, holding all other variables constant. Age, exercise frequency, BMI, and hemoglobin were all significant predictors according to model 6, and this model explained 23% of the variance in the 6MWT. Regression coefficients and standard errors for this model can be found in Table 6.

Table 6. Multiple Regression results for 6-minute walk distance

6MWT	β	95% CI for β		SE β	*B*	R^2	ΔR^2
		LL	UL				
Model 5						0.021	0.012*
Constant	389.58***	361.45	417.72	14.28			
SF-EF	0.564*	.057	1.07	0.26	0.14		
Model 6						0.232	0.190***
Constant	337.18***	205.05	469.32				
SF-EF	0.334	-0.25	0.92	0.30	0.09		
Age	-1.740***	-2.60	-0.89	0.44***	-0.27		
SF-36 MCS	-0.032	-0.62	0.56	0.30	-0.01		
Sleep Score	-0.019	-0.64	0.60	0.31	-0.01		
Number of Medications	-0.633	-3.79	2.52	1.60	-0.03		
Exercise Frequency	13.364**	5.50	21.23	4.00**	0.20		
BMI	-2.390**	-4.08	-0.70	0.86**	-0.18		
Hemoglobin (g/dl)	11.204**	4.80	17.61	3.25**	0.24		
Albumin (g/dL)	9.109	-7.11	25.32	8.23	0.07		
CO_2 (mmol/L)	0.683	-2.36	3.72	1.54	0.03		
C-Reactive Protein (mg/L)	1.117	-0.42	2.66	0.78	0.09		
eGFR	-0.111	-0.54	0.32	0.22	-0.04		

Note. Model = "Enter" method in SPSS Statistics; β = unstandardized regression limit; SE β = limit; SE β = standard error of the coefficient; β = standardized coefficient; R2 = coefficient of determination; ΔR2 = adjusted R2; CI = confidence interval; LL = lower limit; UL = upper limit; * p < .05. **p <.01. *** p <.001. SF-EF = SF-36 Energy Fatigue Vitality Scale, SF-36 MCS = SF-36 mental component summary, BMI = body mass index, eGFR = estimated glomerular filtration rate

HGS. One extreme outlier was identified for HGS and was omitted from this analysis. Model 7, the unadjusted model of SF-EF and HGS, did not demonstrate a statistically significant associated. After adjusting for covariates (Model 8), the relationship between SF-EF and HGS

continued to be insignificant, though the model was significant (F (12,264) = 7.097, *p<.001*), R^2 = .253. Age, Hgb, Alb, CRP, and eGFR were all significant predictors of HGS based on Model 2 and explained 25% of the variance in HGS. SF-EF was not associated with HGS in either model. Regression coefficients and standard errors for this model can be found in Table 7.

Table 7. Multiple Regression results for grip strength (kg)

HGS	β	95% CI for β		SE *B*	*B*	R^2	ΔR^2
		LL	UL				
Model 7						0.000	-0.004
Constant	32.64	29.38	35.85				
SF-EF	0.008	-0.052	0.068	.030	.016		
Model 8						0.253	0.217***
Constant	13.520***	-1.45	28.49	7.60			
SF-EF	0.021	-0.05	0.09	0.03	0.043		
Age	-0.181***	-0.28	-0.08	0.05	-0.23		
SF-36 MCS	-0.022	-0.52	0.59	0.30	-0.01		
Sleep Score	-0.001	-0.07	0.07	0.04	-0.01		
Number of Medications	-0.310	-0.70	0.03	0.19	-0.11		
Exercise Frequency	-0.458	-1.41	0.39	0.46	-0.08		
BMI	0.022	-0.19	0.18	0.09	0.00		
Hemoglobin (g/dl)	2.160***	1.58	2.99	0.36	0.40		
Albumin (g/dL)	0.021***	-1.99	1.79	0.96	0.00		
CO_2 (mmol/L)	0.460	-2.26	3.62	1.51	0.03		
C-Reactive Protein (mg/L)	0.280**	0.66	5.60	1.25	0.17		
eGFR	-0.121***	-0.17	-0.06	0.03	-0.28		

Model = "Enter" method in SPSS Statistics; β = unstandardized regression limit; SE β = limit; SE β = standard error of the coefficient; β = standardized coefficient; R2 = coefficient of determination; ΔR2 = adjusted R2; CI = confidence interval; LL = lower limit; UL = upper limit; * p < .05. **p <.01. *** p <.001. HGS= handgrip strength, SF-EF = SF-36 Energy Fatigue Vitality Scale, SF-36 MCS = SF-36 mental component summary, BMI = body mass index, eGFR = estimated glomerular filtration rate

Fatigue and Mobility Disability

The logistic regression model using the SPPB cut point of <10 for mobility disability was statistically significant X^2 (12) = 62.21. This model explained 30% (Nagelkerke R^2) of the variance in mobility disability based on SPPB score. Increasing age and higher BMI was associated with

an increased likelihood of having mobility disability. Of the 12 predictor variables, four were statistically significant: age, exercise frequency, BMI, and Alb. Based on this model, a 5-point decrease in SF-EF score was associated with 2% decrease in the odds of having mobility disability based on the SPPB time cut point. (as shown in Table 8).

Table 8. Logistic regression predicting mobility disability based on SPPB cut point

	β	Standard Error	Wald	*df*	*p*	OR	95% CI for OR	
							Lower	Upper
SF-36 Vitality Scale Score	-0.018	0.01	6.63	1	.06	0.98	0.96	1.00
Age	0.080***	0.02	24.42	1	.00***	1.00	0.99	1.02
Sleep Score	0.005	0.01	0.35	1	.55	1.08	1.05	1.12
SF-36 MCS	-0.007	0.01	0.61	1	.44	1.00	1.00	1.01
Number of Medications	-0.034	.05	0.53	1	.47	0.97	0.88	1.06
Exercise Frequency	-0.273*	0.12	5.36	1	.02*	0.76	0.60	0.95
BMI	0.066**	0.02	8.65	1	.00**	1.07	1.02	1.11
Hemoglobin (g/dl)	-0.005	0.10	0.00	1	.96	0.99	0.82	1.19
Albumin (g/dL)	-0.571*	0.25	5.37	1	.02*	0.55	0.34	0.89
CO_2	0.003	0.05	0.01	1	.95	0.95	0.90	0.98
C-Reactive Protein (mg/L)	0.006	0.02	0.08	1	0.78	1.01	0.97	1.05
eGFR	-0.008	0.01	0.83	1	0.36	0.99	0.98	1.01

Note. d*f* = degrees of freedom; OR = odds ratio; CI = confidence interval. * p < .05. **p <.01. *** p <.001. SF-EF = SF-36 Energy Fatigue Vitality Scale (5-point increments), SF-36 MCS = SF-36 mental component summary, BMI = body mass index, eGFR = estimated glomerular filtration rate

The logistic regression model using the gait speed cut point for mobility disability was statistically significant X^2 (12) = 50.04, p <.001. The model explained 26% (Nagelkerke R^2) of the variance in mobility disability defined by gait speed. Of the 12 predictor variables, only three were statistically significant: age, BMI, and eGFR. According to this model, a 5-point decrease in SF-EF was associated with 0.99 times higher odds of having mobility disability defined by a ≤ 1.0 m/s gait speed (as shown in Table 9).

Table 9. Logistic regression predicting mobility disability based on gait speed cut-point

	B	Standard Error	Wald	*df*	*p*	OR	95% CI for OR	
							Lower	Upper
SF-EF	-0.015	0.09	2.71	1	0.100	0.99	0.97	1.00
Age	-0.047*	0.02	9.86	1	0.002*	1.05	1.05	1.08
Sleep Score	-0.001	0.01	0.00	1	0.955	1.00	1.00	1.02
SF-36 MCS	-0.007	0.01	0.61	1	0.436	1.00	1.00	1.01
Number of Medications	-0.001	0.05	0.00	1	0.986	1.00	0.91	1.10
Exercise Frequency	-0.177	0.12	2.32	1	0.128	.837	0.67	1.05
BMI	0.070*	0.02	9.75	1	0.002*	1.07	1.03	1.12
Hemoglobin (g/dl)	0.081	0.10	0.71	1	0.400	1.08	0.90	1.31
Albumin (g/dL)	-0.251	0.25	1.02	1	0.312	0.78	0.48	1.27
CO_2	0.041	0.03	0.74	1	0.389	0.94	0.87	1.02
C-Reactive Protein (mg/L)	0.015	0.02	0.50	1	0.479	1.02	0.97	1.06
eGFR	-0.023*	0.01	6.41	1	0.035*	.98	0.96	1.00

Note. d*f* = degrees of freedom; OR = odds ratio; CI = confidence interval. * p < .05. **p <.01. *** p <.001. SF-EF = SF-36 Energy Fatigue Vitality Scale (5-point increments), SF-36 MCS = SF-36 mental component summary, BMI = body mass index, eGFR = estimated glomerular filtration rate

The logistic regression model using the FSTS cut point for mobility disability was statistically significant X^2 (12) = 67.296. There were 2 and 1 standardized residuals in the gait-speed model and the FSTS model (respectively) with values of 2.55 which were kept in both analyses as they were non-influential. This model explained 30% (Nagelkerke R^2) of the variance in mobility disability based on FSTS time. Of the 12 predictor variables, only three were statistically significant: age, sleep scores, and BMI (as shown in Table 8). Increasing age and higher BMI, and poorer sleep was associated with an increased likelihood of having mobility disability based on FSTS duration. Based on this model, a 5-point decrease in SF-EF score was associated with 0.99 times increase in mobility disability based on the ≥10 second FSTS cut point.

Table 9. Logistic regression predicting mobility disability based on FSTS cut point

	B	Standard Error	Wald	*df*	*p*	Odds Ratio	95% CI for Odds Ratio	
							Lower	Upper
SF-EF	-0.014	0.00	2.93	1	0.09	0.99	0.97	1.00
Age	0.053***	0.01	17.91	1	<0.001** *	1.06	1.03	1.08
Sleep Score	0.017*	0.01	4.20	1	0.04*	1.02	1.00	1.04
SF-36 MCS	-0.002	0.01	0.05	1	0.82	0.98	0.98	1.01
Number of Medications	0.011	0.04	0.07	1	0.80	1.01	0.93	1.01
Exercise Frequency	-0.207	0.11	3.80	1	0.05	.81	0.66	1.00
BMI	0.078***	0.02	12.72	1	<0.001** *	1.08	1.04	1.13
Hemoglobin (g/dl)	0.006	0.08	0.01	1	0.94	1.01	0.86	1.18
Albumin (g/dL)	-0.282	0.23	1.56	1	0.21	0.75	0.49	1.17
CO_2	-0.061	0.04	2.29	1	0.13	0.94	0.87	1.00
C-Reactive Protein (mg/L)	-0.012	0.02	0.28	1	0.60	0.98	0.94	1.03
eGFR	-0.008	0.01	1.64	1	0.20	0.99	0.98	1.00

Note. d*f* = degrees of freedom; OR = odds ratio; CI = confidence interval. * p < .05. **p <.01. *** p <.001. SF-EF = SF-36 Energy Fatigue Vitality Scale (5-point increments), SF-36 MCS = SF-36 mental component summary, BMI = body mass index, eGFR = estimated glomerular filtration rate

Discussion

The present study analyzed self-perceived fatigue and its association with physical performance and mobility disability in adults with CKD. Independent relationships were observed between self-perceived fatigue and physical performance assessed by FSTS and gait speed, and these relationships remained significant even after controlling for age, BMI and CKD-related factors. This study identified a high prevalence (24-51%) of mobility disability in adults with CKD. Although fatigue was not independently associated with mobility disability, other factors including eGFR, gait speed, and sleep were significantly associated with mobility disability. The results of this study highlight the potential role of fatigue in physical

performance. Further clinical research is needed to identify early physical decline and treatment to prevent mobility disability in adults with CKD.

Higher than average fatigue was present in over half of this sample and fatigue was associated with slower gait speed and slower ability to rise 5 times from a chair. In older adults, self-perceived fatigue and peak-torque production of the lower extremity on isokinetic testing have been reported to be related.[67] This study found that maximal grip strength was not associated with fatigue, and although frequently used as a proxy for whole-body strength, may not be as strongly related to fatigue compared to measures of lower extremity function. Despite the sample performing below expected norms on the 6MWT, it was not significantly associated with fatigue. This finding was surprising considering that gait speed and fatigue were related. More research is needed to better understand the relationships between fatigue and differing domains (strength, endurance, power) of muscle performance.

Although significant, the relationships between fatigue and lower extremity physical function were small with fatigue explaining only 2-3% of the variance in the unadjusted models. The four-item SF-EF may not adequately capture all aspects of fatigue. Ashberg operationalized the definition of fatigue and distinguishes three forms: physiological, objective, and self-perceived.[68] This construct identifies physiologic fatigue as an inability of the muscle to generate work, strength, or power. Objective fatigue is described as modified performance on a task and may be influenced by the type of activity or work that is required. Self-perceived fatigue is understood as a conscious, unpleasant symptom that effects the whole body and can be influenced by both intrinsic and extrinsic factors. Contextualizing fatigue as a multidimensional, multifactorial phenomenon helps to explain why physical performance measures may not be similarly associated with the self-reported experiences on the unidimensional SF-EF fatigue

measure. Despite being the most common measure of fatigue in the CKD literature, the SF-EF has been criticized, namely for not adequately capturing the entirety a patient's fatigue experience. Future research should consider using a multi-dimensional measure such as the NIH toolbox PROMIS-Fatigue measure that was designed to isolate this latent construct.[69]

Self-perceived fatigue explained only a small portion of the variance and this study revealed consistent significant relationships between physical performance and several factors other than fatigue. As expected, those with increased age had significantly poorer performance on all the lower extremity functional tasks and was associated with mobility disability. BMI was associated with poorer lower extremity physical function on all tests. These findings are consistent with reports that older adults (>65 years) with a BMI of ≥30kg/m^2 have worse altogether ambulatory performance and studies in CKD that suggest a higher BMI is associated with frailty and poorer physical performance.[70,71] It has been suggested that those with CKD have higher fat mass compared to muscle mass (both contributing to overall BMI) and that body composition is frequently altered in CKD due to muscle wasting.[71] Although there has been some evidence that higher BMI is protective in dialysis dependent CKD whether this is the case in earlier stages of the disease has yet to be determined. Lower albumin levels were also associated with lower gait speed and decreased FSTS time. These findings support prior research that inadequate nutrient intake contributes to loss of muscle strength, mass, and poorer function in CKD.[72]

As previously noted, CKD has been described as "premature aging" and these results support that this description is accurate from a mobility perspective. For example, 4-meter usual gait speed norms have been published for healthy, community dwelling elderly between the ages of 70-79 as being between .99 m/s (women) and 1.07 m/s (men) while normative data for those in their 50's and 60's are above 1 m/s.[73] This sample had a mean gait speed of 0.96 (±.02), indicating

that although much younger, they were walking at speeds more consistent with the elderly. The 6MWT revealed similar reduced functioning. This sample had a mean 6MWT of 418 m, significantly lower than what would be expected when compared to published age-associated norms (538-572 m for those who are between 60-69).[74] The average dominant HGS for this sample was below the aforementioned cut-points that are predictive of mobility disability. These results show that those who are younger (mean age = 53.8 years, SD = 13.9) and in Stages 2-5 CKD are displaying the functional ability of those who are > 70 years old. Age-related muscle atrophy and CKD-related muscle atrophy have been described as similar and due to metabolic and structural changes associated with both aging and CKD.[75,76] This may explain the similarities in decreased lower extremity physical performance and higher than normal fatigue found in this relatively young study sample.

Risk for mobility disability was identified in 51 % of adults with CKD despite the sample being much younger (mean age=54) compared to the samples in which the mobility-disability construct was established (>70 years). These results support findings reported by Seidel et al. in a study of 84 people (mean age 64.5, SD 13.5) with pre-dialysis (stage 3-5) CKD that found overall disability was indeed experienced earlier in the disease process and was related to physical components of quality of life.[77] Seidel et al. used the Late Life Function and Disability Instrument to assess disability while the current study used the mobility disability construct, both established in the geriatric population. Considering that younger, middle-aged cohorts may experience disability differently than older adults, using geriatric instruments and cut points possibly underestimate their actual experienced level of disability. Sensitive screening and informed interventions for disablement in those with CKD are needed.

Limitations

The cross-sectional nature of this study limits its ability to determine causation or assess temporal relationships. For example, slower gait speed may cause fatigue, but fatigue may also cause slower gait speeds. As previously mentioned, the multidimensional aspects of fatigue, such as severity, impact, quality, frequency, and duration, may not have been adequately captured by the SF-EF and use of a multidimensional scale may have yielded different results. This study also did not adequately represent older individuals who are more prone to CKD, impaired physical performance, and fatigue.

Conclusions

The findings of this study suggest that, in adults with CKD, fatigue may play a role in reduced lower extremity physical performance. Independent associations observed between self-perceived fatigue and lower extremity physical performance, remained significant after controlling for age, BMI and CKD-related factors. Furthermore, there was a high prevalence (up to 51%) of mobility disability in this relatively young cohort. Although fatigue was not independently associated with mobility disability, other factors including eGFR, gait speed, and sleep were significantly associated with mobility disability. Identifying pre-dialysis CKD as a risk factor for mobility disability is important for clinicians who encounter this common diagnosis. Further research is needed to better understand the causal influence of fatigue on physical performance and vice versa in adults with CKD.

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Chapter 3

Reliability of Physical Performance and Instrumented Measures in Adults with Kidney Disease

Abstract

Background: Chronic kidney disease (CKD) and hemodialysis (HD) dependent end stage renal disease (ESRD-D) is common and associated with reduced physical function and quality of life. Reliability of physical performance measures in adults with CKD and ESRD-D are not widely established. Instrumented physical function testing using wearable inertial measurement units (IMUs) may provide additional sensitive measures of mobility in adults with CKD and ESRD-D. The purpose of this study was to (1) examine the test-retest reliability of traditional and instrumented physical performance measures; (2) describe differences in physical performance between adults with CKD and ESRD-D.

Methods: Twenty-one adults (11 CKD, 10 ESRD-D) completed a physical performance assessment consisting of a battery of standard and instrumented physical performance measures at baseline and 1 week. Standard measures included the Short Physical Performance Battery (SPPB), gait speed, Five Times Sit-to-Stand (FSTS), 2-Minute Walk Test (2MWT), and quadricep (QS) and grip (GS) strength dynamometry. Instrumented measures included parameters of gait (step length and gait speed), turns (turn duration, number of steps in turn, and turn velocity), sit-stand duration, postural sway root mean squared (RMS), pathlength (PATH), velocity, and jerkiness (JERK). Test-retest reliability was assessed with intraclass correlation coefficients (ICC) and differences in CKD versus ESRD-D physical performance were assessed with paired t-tests.

Results: Good-excellent test-retest reliability was demonstrated in the traditional physical performance measures: SPPB (ICC = .91), FSTS (ICC = .95), gait speed (ICC = .89), 2MWT (ICC = .94), NSB (ICC = .81), QS (ICC_{right} = .94 and ICC_{left} =.90), GS (ICC = .96). Moderate

reliability was demonstrated in following instrumented gait and turn parameters: stride length (ICC_{left}= .53 and ICC_{right} = .52), gait speed (ICC_{left}=.67, ICC_{right}=.68), turn velocity (ICC=.60), turn duration (ICC=.62) and good reliability was found for 'steps in turn' (ICC=.75). Good reliability was demonstrated in the instrumented FSTS sit-stand duration (ICC=.87), postural sway PATH (ICC=.77_{usual} and .85_{narrow}), and sway JERK (ICC_{narrow}=.70) . Moderate reliability was demonstrated in the following instrumented sway parameters: VELOCITY (ICC_{usual}= .62 and ICC_{narrow}=.62) and JERK (ICC_{narrow}= .60) and RMS (ICCusual=.63 and ICCnarrow= .67). No differences were found between groups on physical performance measures.

Conclusions: In adults with CKD and ESRD-D, good to excellent clinically acceptable test-retest reliability was demonstrated in all of the standard physical performance tests. The instrumented parameters of number of steps in turn, sit-stand duration, and the sway PATH showed good, clinically acceptable test-retest reliability. No differences were found in physical performance between the groups with CKD and ESRD-D, potentially due to the groups not being age-matched and small sample size. These results indicate that this battery of standard physical performance measures and the instrumented measures of sway PATH, number of steps in turn, and sit to stand duration are considered clinically reliable for use with this population.

Background and Purpose

Adults with chronic kidney disease (CKD) and end stage renal disease (ESRD) are known to have reduced physical function and poor quality of life quality of life.[1,2] The burden of CKD includes a high prevalence of co-morbidities, sensory deficits, deconditioning, and decreased muscle mass which has striking similarities to aging.[3-7] These factors have been suggested to contribute to a decline in physical performance. Preliminary studies report that adults with pre-HD CKD also display poorer physical performance and reduced quality of life putting them in a stage of "pre-disablement".[8-10] In those with dialysis dependent ESRD (ESRD-D), this decline in physical performance contributes to a higher prevalence of falls, loss of independence, hospitalizations, and frailty.[8,11-13] Adults with ESRD-D fall at a rate of 1.18-1.60 falls/year, compared to community-dwelling older-adult fall rates of 0.6-0.8 falls/year and data supports that repeated falls result in serious consequences including fractures, institutionalization, and mortality.[14,15] In CKD, poor physical functioning reduces quality of life and the ability to conduct activities of daily living (ADLs).[16] The pathological mechanisms of this decline are yet to be fully understood but are clearly multifactorial. Skeletal muscle wasting, inflammation, endothelial dysfunction, anemia, and inactivity have all been associated with these reductions.[17-19] Clinically useful, sensitive, and reliable objective markers of physical performance are needed to better evaluate functional impairment in adults with CKD and ESRD-D to quantify normal and pathological physical performance, plan rehabilitation strategies, and assess the effectiveness of interventions.

Physical performance outcomes are generally understudied compared to surrogate outcomes (death, mortality, hospitalizations) in CKD and ESRD.[20] Meaningful interpretation of

the available physical performance-related outcomes in CKD is challenged by heterogeneity of measurement coupled with a lack of psychometric evidence supporting the use of the measures specific to the population.[20,21] The effects of HD on physical performance are also not well known, though current literature reflects poorer physical performance in those with ESRD-D, this assumption is biased by a lack of supporting evidence for the people in earlier stage of the disease. Research in other populations, such as older adults, reports reliability of standard physical performance tests, including the Short Physical Performance Battery (SPPB), usual gait speed, 2-Minute Walk Test (2MWT), Five Times Sit to Stand (FSTS), and lower extremity strength dynamometry but the psychometric strengths of these tests are not well established in renal disease.[22-27]

Gait disturbances are a proposed mechanism for increased falls and those with worse kidney function have demonstrated slower gait speeds and abnormal global gait characteristics.[28] Balance and postural stability have been shown to be reduced in ESRD-D and suggested to contribute to increased falls.[29] Very few publications report outcomes related to balance and postural stability in non-HD CKD leading to sparse evidence of its impact on function.[14] A preliminary study in adults with ESRD-D (n=113) reports impairments to coordination and balance contribute more to social isolation and poor quality of life than muscle strength deficits.[30] In non-HD CKD, worse physical and cognitive function was related to postural instability and declining renal function in women.[31]

Considering the high level of disability in the renal disease population, sensitive and reliable measures of physical performance are needed. Instrumentation of physical performance with wearable inertial measurement units (IMUs) presents an opportunity to better understand functional abilities across stages of adult CKD. IMUs have gyroscopes and accelerometers to

detect ‘micro-level’ objective components of complex functional activities outside of a lab-based environment. IMUs allow for portable assessment of multiple characteristics of functional movement including temporal, spatial, acceleration, angular velocity, positional and angular characteristics. These can provide sensitive supplementation to characteristics derived from traditional physical performance measures. Gait parameters assessed with IMUs were found to outperform traditional physical performance tests in predicting fall occurrence and have also been found capable of identifying fall risk factors in older adults.[32,33] In those with vestibular disorders, IMU postural sway parameters were able to classify fallers from non-fallers.[34] IMUs have also been found to provide sensitive evaluation of motor impairment in Parkinson’s disease (PD).[35] In fascioscapulohumeral dystrophy, IMU gait parameters of stride length, stride velocity, and trunk range of motion were sensitive to disease progression over an average of 20 months.[35,36]

The purpose of this study is twofold: (1) to examine test-retest reliability of standard and instrumented measures of physical performance in adults with CKD and ESRD-D and (2) to describe differences in balance, gait and strength between adults with CKD versus ESRD-D. The hypotheses are that standard and inertial sensor measures of physical performance will show good-excellent reliability in this sample of adults with CKD and ESRD-D and that adults with ESRD-D will show poorer physical performance compared to those not on HD.

Methods

Study Design, Setting, and Participants

A prospective test-retest study design was used, and data was collected at baseline and at one week. Adults with kidney disease (11 CKD; 10 ESRD-D) were recruited from greater Seattle area HD centers and clinics between March 2019 and January 2020. Inclusion criteria

was the following for the group with ESRD-D: 1) >3 months of standard 4-hour HD sessions 2) undergoing at least thrice weekly HD sessions. Inclusion criteria for the group with CKD group was: 1) an eGFR < 60 ml/min/1.73m^2. Exclusion criteria for both groups were the following: 1)a severe cardiopulmonary diagnosis; 2) a dementia diagnosis; 3) lack of English fluency; 4) inability to ambulate 100' independently (use of an assistive device was acceptable). Data collection sessions were conducted at Seattle area Northwest Kidney Centers as well as the University of Washington Amplifying Movement and Performance Lab. Data collection occurred just prior to the mid-week HD day (meaning they had dialyzed 2 days prior) for the ESRD-D group. This ensured findings were not influenced by the weekly 2-day break in HD. This study was funded by the American Academy of Acute Care Physical Therapy Research Grant and the Walter C. and Anita C. Stolov Research Award. Study approval was granted by the University of Washington Institutional Review Board and participants completed an informed consent process.

Clinical Covariates

Medical history and demographics were obtained via questionnaires and the lab values were obtained thru available medical records. Exercise frequency was asked with the question "On average, how many times per week do you exercise?" Prevalent heart disease was defined as prevalence or history of any coronary artery disease, congestive heart failure, or arrythmia. Sensation was measured using a Semmes Weinstein monofilament using the classic procedure to test for the absence of protective sensation and loss of sensation was defined as having >2 points/10 of sensory loss on one foot.[37]

Standard Physical Performance Measures

Short Physical Performance Battery (SPPB). The SPPB is a combined test that assesses physical function in 3 domains: balance, lower extremity power, and gait speed. Balance is assessed by standing in place for 10 seconds in 3 progressively more difficult conditions, lower extremity strength is assessed using a Five Times Sit-to-Stand Test, and gait speed is assessed with a 4-meter 'usual pace' timed walk. Scores for each component are added up and a summary score from 0-12 is created.[38] Excellent reliability of the SPPB has been reported in a small group of adults on HD (ICC = 0.94, CI = 0.91-0.97).[39] In community dwelling older adults a SPPB score of ≤10 is predictive of increased risk for mobility disability.[40] The mean normative score for healthy community-dwelling older adults (mean age = 74.1, SD = 5.7) has been reported as 10.1.[41] Ceiling effects have been observed for the SPPB in higher functioning populations including community-dwelling older adults and those with COPD.[42,43]

Five Times Sit-to-Stand (FSTS): The FSTS is a functional test that requires a patient stand as quickly as they can 5 times from a standard height (18") chair without the use of their arms. The FSTS duration is an indicator of lower extremity strength, power, and overall endurance. High test-retest reliability of the stopwatch FSTS (ICC = 0.95) is reported in older adult females with CKD.[24] Validity has been demonstrated via a strong correlation to the Timed Up and Go ($r=0.64$, $p < .05$). The FSTS has a predictive cut-point of ≥10 seconds for developing mobility disability in community dwelling older adults, but cut-points are currently unknown for CKD.[40]

Usual Gait Speed. Gait speed was calculated using a 4-meter course. Participants were asked to walk at a usual pace from a static standing start and walk past tape that was placed at the 4-meter mark. A stopwatch started timing at the initiation of the walk and stopped when the first foot completely crossed the 4-meter line. The fastest of two trials was used to calculate gait speed in meters/second. A gait speed of <1.0 m/sec is an established cut-point for mobility disability in

older adults (mean age 74.2).[44] *2-Minute Walk Test (2MWT).* The 2MWT test assesses the distance in meters that a patient can ambulate when instructed to cover as much distance as they over two minutes. A 7-meter course marked by 2 pieces of tape was used and participants were instructed to perform laps by turning after both feet crossed the course markers. Test-retest reliability has been established in a population-based sample of US adults (ICC = .82, 95% CI = .76-.87) and aged-matched norms are available.[45]

Ninety Second Balance Test (NSB). The NSB assesses static balance by asking a person to stand in progressively challenging balance positions (semi-tandem, tandem, and single leg) for 30 seconds. Participants were asked to stand 2-feet from a wall and maintain balance in each position while maintaining their gaze on a piece of tape that was placed at their eye level. The total time that they maintained balance in each position was summed for a total NSB time. The NSBT has been used in the geriatric literature as a predictor of mobility disability (in this case defined by a gait speed of <1m/sec) with those having a NSB time of <53 seconds being at higher risk for mobility disability.[46]

*Quadricep and Grip Strength Dynamometr*y. Quadricep strength (QS) was measured using a Lafayette Instruments handheld dynamometer (HHD) (model 01163; Lafayette Instrument Company, Lafayette, Ind., USA). The HHD was programmed to measure peak force in kilograms during a 5-second isometric muscle contraction. The pad of the HHD was placed at the anterior lower leg between the lateral and medial malleolus. Participants were positioned in supported sitting with their knee at 90º of knee flexion. Participants were asked to exert maximum force against the dynamometer. Three trials on each leg were conducted. The maximum strength obtained for each side was used for this analysis. HHD of QS has been

reported to be valid in the community dwelling elderly with strong correlations with the gold standard Biodex isometric measurements ($r = 0.91$, $p = < 0.0001$).[47]

Maximum handgrip strength (HGS) was measured using a Jaymar™ handheld dynameter and the maximum of 3 trials was used. Suitable reliability of HGS using isometric dynamometry strength has been reported over multiple time points for a duration of 24 weeks (ICC: >0.60) in a group of 257 older (mean age = >75 years), malnourished, sarcopenic adults. (23). Handgrip strength cut points for mobility disability are established for both men (33 kg) and women (37 kg) regardless of BMI.[48]

Instrumented Physical Performance Measures

Instrumented testing of physical performance was conducted using the APDM Mobility Lab System™ (APDM, Inc, Portland, OR**).** The APDM consists of six small IMUs, called "Opals" that are placed on the participants' wrists, lumbar region, sternum, and feet. These contain tri-axial accelerometers, gyroscopes, and magnetometers which record data that is transmitted wirelessly and processed by the APDM Mobility Lab™ software. To my knowledge, the APDM system has not been used to assess physical performance in CKD, but studies support the use of inertial sensor technology in adults with other chronic health conditions with known mobility deficits including neuropathy, PD, and multiple sclerosis.[49]

Gait. A 28-meter segment (the 2nd and 3rd laps) of 2MWT was manually cut for the instrumented fast gait and turning parameters. This smaller segment was used to eliminate the effects of acceleration and deceleration that occur at the beginning of test and to limit the effects of fatigue due to sustained fast walking. The APDM Mobility Lab™ software can distinguish straight line gait from turns and provides separate analysis for each. Instrumented measures of gait included:

gait speed (meter/sec) and stride length (meters) which are collected by the IMUs that are placed on each foot. These parameters APDM have been found to excellent reliability (ICC > 0.93) in able-bodied adults and be sensitive to mobility decline in PD.[50,51] Age associated normalized values are available for these spatiotemporal gait parameters.[52] The Mobility Lab™ software uses the lumbar and bilateral foot IMU's to generate turning parameters. The same 2-lap segment of fast gait speed was used to gather instrumented turning data of 4 complete 180 degree turns. Instrumented turning parameters were the following: turn duration (sec), number of steps in turn, and peak velocity of the turn (degrees/sec). APDM turn duration and peak velocity have been found to have excellent agreement with motion capture measures (ICC = 0.96-0.98) in cognitively impaired older adults.[53]

Sit-to-stand duration. The APDM analyzed the total average duration (sec) of the sit-to-stand segment of the FSTS.

Postural Sway. Data for instrumented postural sway was collected in 2 static stance positions (1) usual base; (2) narrow base. The participant was instructed to stand unsupported at a distance 2 feet from a wall with their arms at their sides. A piece of tape was placed at the participant's eye level and they were asked to fix their gaze straight ahead on the tape. A plastic wedge was placed between the participant's feet to ensure consistent positioning for a usual base and for the narrow base the participant placed the medial aspects of their feet together. The following sway parameters were collected: root mean square (m/sec^2) (RMS) of acceleration time series, total length of sway acceleration trajectory (m/s^2)(PATH) and sway jerkiness (m^2/s^2) (JERK), and sway acceleration velocity (m/s) (VELOCITY). PATH and JERK were found to have concurrent validity to gold standard force-plate center of pressure for measures of postural sway in cognitively impaired older adults.[54] In PD PATH and RMS were found highly correlated with

force plate measures (*r*= .73 and .74, respectively*)*.[55] Test-retest reliability of these measures has been reported as good to excellent in PD for RMS (ICC = 0.83), PATH (ICC = 0.81), and JERK (ICC = 0.86), with JERK and PATH being the most reliable.[55] Excellent reliability for VELOCITY has been reported in adults with vestibular disorders (ICC=0.82).[34]

Statistical Analysis

Intraclass correlation coefficients (ICC) estimates and their 95% confidence intervals (CI) were calculated using absolute agreement with a two-way random effect mixed model. The ICCs were interpreted using the following conventional approach: values of < 0.00-0.10 indicate poor reliability, values between 0.10-0.39 indicate weak reliability, values between 0.40-0.69 indicate moderate reliability, values between 0.70-0.89 indicated strong reliability, and values > 0.90 indicated excellent reliability.[56] ICCs of 0.75 or greater are considered to have adequate reliability for clinical measures in rehabilitation.[57] Full case analysis was used and if there was missing data from either visit 1 or 2 it was not included in the reliability analysis. Extreme outliers (defined as >3 times the interquartile range) were identified and if present for either visit, the case was eliminated from the analysis. Paired *t*-tests were performed to assess differences between the CKD and ESRD-D groups on the standard physical performance measures

Results

Demographic and Clinical Characteristics

Demographic and clinical characteristics are presented in Table 1. The mean age of the sample was 58.7 (13.6). The CKD group was slightly older with a mean age of 64.81(12.12) compared to the ESRD-D group whose mean age was 52.63(3.78). The ESRD-D group had

higher rate of unemployment compared to the CKD group. This may have been due to the younger age of the group and fewer people falling into the "retirement" category. The ESRD-D group was slightly more educated than the CKD group. Most people in both groups reported exercising at least 1x/week, with the ESRD-D group reporting slightly less overall exercise. The groups did not differ much in terms of prevalence of heart disease indicators, diabetes, and # of medications. The CKD group had a slightly higher BMI (mean 30.9, SD 2.16)) compared to the ESRD-D group (mean = 28.5, SD = 5.56). Hypertension was more prevalent in the CKD group (100%) than the ESRD-D group (40%).

Table 1. Descriptive Summary

	ESRD-D (n=10)	CKD (n=11)
Age	52.63 (3.78)	64.81 (12.12)
Gender (Female)	54.5%	45.5%
Ethnicity		
Caucasian	27.3%	72.7%
Hispanic	27.3%	9.1%
Asian	18.2%	0%
Pacific Islander	9.1%	18.2%
Black	18.2%	0%
Highest Level of Education		
Completed 8th Grade	18.2%	0%
High School/GED	18.2%	18.2%
Attended college	18.2%	36.4%
College Degree	9.1%	27.3%
Graduate Degree	9.1%	18.2%
Employment Status		
Full Time	0%	9.10%
Part Time	18.0%	0%
Retired	18.2%	54.50%
Disabled	63.6%	36.0%
Exercise Frequency		
Never	18.2%	9.1%
1x/week	27.3%	9.1%
2-3x/week	27.3%	36.4%
>3x/week	27.3%	36.4%
Health History Data		

BMI	28.5 (2.16)	30.99 (5.56)
Diabetes	36.0%	45.5%
Hypertension	40.0%	100%
Prevalent Heart Disease	54.5%	45.5%
Sensory Loss	18.2%	27.3%
eGFR CKD-EPI (ml/min per 1.73m^2)	n/a	34.81 (15.96)
Systolic BP (mmHg)	154.64 (8.91)	155.36 (20.60)
Medication #	8.45 (0.79)	8.82 (4.06)
HD Vintage (months)	25.09 (7.06)	n/a
Current Smoker	9.10%	9.10%
Current Alcohol Use	9.10%	27.30%

eGFR= estimated glomerular filtration rate based on the CKD-EPI equation, HD=hemodialysis. *Note: percentages are given for categorical variables and means (standard deviations) for continuous variables.*

Test-Retest Reliability of Standard Physical Performance Measures

Test-retest reliability of the standard physical performance measures is reported in Table 2. One subject had knee pain and was unable to complete the quadricep dynamometry on visit 2, so this subject was excluded from the analysis. Excellent test-retest reliability was found for the, SPPB (ICC = .91), FSTS (ICC = .95), QS (ICC_{left} = .90 and ICC_{right} = .94), GS (ICC = .96), and the 2MWT (ICC = .94). Good test-retest reliability was found for gait speed (ICC = .89) and NSB (ICC = .81).

Table 2. Test-Retest ICCs of standard physical performance using a 2-Way Random Effects Model

		95% Confidence Interval			
Measure	**ICC**	**Lower Bound**	**Upper Bound**	**F-Test (*df 1, 2*)**	***p***
SPPB (n=21)	0.906	0.772	0.961	10.71 (20,20)	<.01**

FSTS (n=21)	0.952	0.882	0.981	22.09 (20,20)	<.01**
Gait speed (n=21)	0.886	0.717	0.954	9.59 (20,20)	<.01**
2MWT (n=21)	0.936	0.842	0.974	15.0 (20,20)	<.01**
NSB (n=21)	0.809	0.538	0.922	5.63 (20,20)	.01**
L QS (n=21)	0.898	0.740	0.960	15.0 (20,20)	.01**
R QS (n=20)	0.944	00.792	0.981	10.73 (19,19)	<.01**
GS (n=21)	0.961	0.905	0.984	0.96 (20,20)	<.01**

ICC= intraclass correlation coefficient, *df*= degrees of freedom, SPPB= Short Physical Performance Battery, FSTS = Five Times Sit to Stand, 2MWT = 2 Minute Walk Test, NSB = Ninety Second Balance Test, R = right, L = left, QS = quadricep strength, GS = grip strength, **= *p.01*

Test-Retest Reliability Instrumented Physical Performance

Test-retest reliability of the instrumented parameters is presented in Table 3. There was missing data resulting in the loss of two subjects for visit 2 bilateral gait speed and stride length, so this subject was omitted from that analysis. One extreme outlier was identified from turn duration and this case was deleted from the analysis. Three extreme outliers were identified (2 were due to loss of balance) resulting in the omission of 3 cases from the usual base postural sway analysis. Moderate reliability was found the following instrumented gait parameters and turn parameters: stride length (L, ICC= .59; R, ICC = .60), gait speed (L, ICC=.47, R, ICC=.43), turn velocity (ICC=.60), turn duration (ICC=.62) and strong reliability was found for number of steps in turn' (ICC=.75). Strong reliability was found for the instrumented sit-stand duration (ICC=.87). Strong reliability was found for the following instrumented sway parameters: usual and narrow base and PATH (ICC_{usual} = .77 and ICC_{narrow} = .85) and narrow base JERK (ICC=.77). Moderate reliability was found for the following instrumented sway parameters:

VELOCITY (ICC_{usual}= .62 and ICC_{narrow} = .62) and usual base JERK (ICC= .60) and narrow base RMS (ICC_{usual} = .63 and ICC_{narrow} = .67).

Table 3. Test-Retest ICCs of instrumented physical performance using a 2-Way Random Effects Model

Measure	ICC	95% Confidence Interval		F-Test (*df*)	*p*
		Lower Bound	Upper Bound		
Gait Parameters					
L Stride Length (n= 20)	0.533	-0.217	0.817	2.09 (19)	.06
R Stride Length (n=20)	0.524	-0.234	0.814	2.058 (19)	.06
L Limb Gait Speed (n=20)	0.665	0.146	0.868	2.922 (19)	.01**
R Limb Gait Speed (n=20)	0.677	0.176	0.873	3.026 (19)	.01*
Turns: Duration (n=20)	0.621	0.087	0.843	2.61 (19)	.02*
Turns: Step # (n=20)	0.752	0.382	0.900	3.91 (19)	<.01**
Turns: Velocity (n=20)	0.601	0.025	0.835	2.47 (19)	.02*
FSTS					
Sit-Stand Duration	0.871	0.680	0.948	8.04 (19)	.01*
Postural Sway					
Usual Base					
RMS (n=17)	0.632	-0.015	0.795	1.40 (16)	.64
PATH (n=17)	0.766	0.372	0.915	4.81 (16)	<.01**
VELOCITY (n=17)	0.620	3.21	0.376	0.61 (16)	.85
JERK (n=17)	0.604	-0.470	0.858	2.00 (16)	.06

Narrow Base					
RMS (n=20)	0.672	0.176	0.868	2.96 (19)	.01*
PATH (n=20)	0.854	0.639	0.942	6.92 (19)	<.01**
VELOCITY (n=20)	0.617	0.009	0.850	2.54 (19)	.06
JERK (n=20)	0.711	0.293	0.884	3.55 (19)	.02*

ICC= intraclass correlation coefficient, *df*= degrees of freedom, L = left, R = right, RMS = root mean squared, PATH = acceleration pathlength, VELOCITY = acceleration velocity, JERK = jerkiness; **p <.05,* **p<.01

Between Group Differences on Standard Physical Performance Measures

There were no significant differences between CKD and ESRD-D groups on FSTS, SPPB, NSB time, quadricep strength, or grip strength (Table 4).

Table 4. Differences in Traditional Physical Performance Measures between CKD and CKD-D

	ESRD-D		CKD		Mean Differences	
Measure	Mean	SD	Mean	SD	T-Test	*p*
SPPB (n=21)	9.64	1.80	9.00	2.49	0.69	.50
FSTS (n=21)	13.84	5.85	15.22	4.34	-0.63	.54
Gait speed (n=21)	0.82	0.21	0.82	0.22	0.06	.95
2MWT (n=21)	132.97	33.19	130.22	45.05	0.02	.19
NSB (n=21)	58.12	22.84	55.71	26.67	0.23	.82
L QS (n=21)	27.28	10.21	27.28	10.21	0.38	.71
R QS (n=21)	27.37	11.87	29.43	6.54	-0.50	.62
GS (n=21)	29.82	15.73	21.95	10.71	1.37	.19

SPPB= Short Physical Performance Battery, FSTS = Five Times Sit to Stand, 2MWT = 2 Minute Walk Test, NSB = Ninety Second Balance Test, L = Left, R = Right, QS = quadricep strength, GS = grip strength.; p= <..05

Between Group Differences on Instrumented Performance Measures

Extreme outliers for the following sway variables were omitted: 1 for usual base PATH and JERK and narrow base and narrow base RMS, VELOCITY, and JERK. Two extreme outliers were removed for narrow base JERK. There were no significant differences in inertial sensor measures between the CKD and ESRD-D groups (Table 5).

Table 5. Group Differences in Instrumented Physical Performance Measures

	ESRD-D		CKD		Mean Differences	
Measure	Mean	SD	Mean	SD	T-test	*p*
Gait						
L Stride Length (n=21)	1.23	0.29	1.14	0.19	-0.44 (19)	.67
R Stride Length (n=21)	1.20	0.28	1.13	0.19	-0.39 (19)	.79
L Gait Speed (n=21)	1.18	0.27	1.12	0.29	-0.49 (19)	.67
R Gait Speed (n=21)	1.14	0.27	1.10	0.28	-.387 (19)	.70
Turn duration (n=21)	2.22	0.43	2.35	0.47	.674 (20)	.51
Number of steps in turn (n=21)	4.36	0.76	4.05	0.50	-1.16 (20)	.26
Turn velocity (n=21)	199.41	47.19	163.87	45.38	-1.80 (20)	.09
FSTS						
Sit-to-stand Duration (n=21)	1.00	0.07	1.15	.07	1.95	.07
Postural Sway						
Usual Base						
RMS (n=21)	0.09	0.04	0.08	0.02	-0.38	.71
PATH (n=20)	7.17	2.51	6.73	1.63	-0.46	.65
VELOCITY (n=21)	.21	0.14	0.16	0.07	-0.95	.36
JERK(n=20)	1.70	1.42	1.56	1.05	-0.25	.81
Narrow Base						

RMS (n=20)	.11	0.044	0.10	0.03	-0.70	.50
PATH (n=20)	10.21	5.18	9.03	2.98	-0.62	.55
VELOCITY (n=20)	.25	0.16	0.23	0.094	-0.34	.74
JERK (n=19)	3.78	4.68	2.27	1.44	-9.28	.35

ICC= intraclass correlation coefficient, *df*= degrees of freedom, L = left, R = right, RMS = root mean squared, PATH = acceleration pathlength, VELOCITY = acceleration velocity, JERK = jerkiness; *p*= <.05

Discussion

This study found a reliable battery of standard and instrumented physical performance measures. The following standard measures had good to excellent reliability, meeting the clinically acceptable standard of >0.75 for use of these measures in rehabilitation: SPPB, FSTS, gait speed, 2MWT, NSB, QS, GS.[57] The following instrumented physical performance parameters also had good reliability and met the clinically acceptable standard for reliability of measures for use in rehabilitation: number of steps in turn, sit to stand duration, and sway PATH.

Gait speed demonstrated good reliability in this study (ICC=.89) which is inconsistent to a recent large study that found poor test-retest reliability (ICC=.406) of 4-meter gait speed in a large healthy adult sample (ages 18-85), despite using a similar method of test administration.[58] This study's findings may have been due to the same evaluator performing the test on each subject in this study minimizing the effects of inter-rater error. Four-meter gait speed has clinical utility in that it is inexpensive, requires little space, and it is easy for a patient to understand. The results of this study indicate that it has adequate reliability for use in CKD and ESRD-D. Notably, both CKD and ESRD-D groups had similar and slower than expected gait speed (.82±.21 and .82±.22, respectively) when compared to published norms for their age

groups which are >1.0 m/s.[58] Being below 1.0 m/s also puts both groups below the cut-point for being at risk for mobility disability.[44]

As previously reported, balance assessment is scarce in the renal literature and to my knowledge the NSBT has not been reported. This study showed good reliability (ICC=.80), supporting its use to assess balance in the renal population. Of note, most of the sample was unable to stand and maintain balance on one leg indicating that regardless of age or HD status, had worse than expected balance impairment compared to norms, and were at higher risk of falls.[59] This is consistent with Wilkinson's et al. in a study reporting mild postural instability in standing in those with CKD that was associated with reduced cognitive and physical functioning.[31]

Most human studies of skeletal muscle function in CKD focus on muscle size, body composition, and lab-based isokinetic strength measures.[7] QS dynamometry, though simple to perform, is infrequently utilized both in research and clinical settings despite its predictive potential.[60] The current study showed that the use of its testing technique (maximum performance from 3 trials using the "make test" technique for isometric quadricep force at 90 degrees of seated knee flexion) for quadricep dynamometry demonstrated excellent reliability (ICC .90-.94). This finding suggests that this testing technique has clinical and research utility in populations of those with CKD. In a study of 274 healthy older adult women (>65 years), leg muscle isometric dynamometry was associated with significantly low physical performance, after adjusting for age, fat, cognition, and depression.[60] Functional, sub-maximal strength as assessed by the FSTS was found to have excellent reliability (ICC=.952) which is consistent with reports in other populations.[61,62] Handheld QS dynamometry and the FSTS are easily

administered, and when used in tandem have the clinical utility to measure maximum and submaximal functional muscle performance in CKD and ESRD-D.

The instrumented physical performance measures for lower limb gait speed and stride length were not found to be adequately reliable for clinical use and these findings differ from previous reports that these measures are adequately reliable in PD and those with vestibular disorders[50,51] There are several potential reasons for this discrepancy in findings. First, this study used only a section of "fast" gait speed from the 2MWT which may have decreased the reliability due to the acceleration/deceleration required for turns and variable pacing that may occur with a test aimed to assess a maximal distance accomplishment. Previous studies have used a course of a set distance (between 4-10 meters) and a usual gait speed. Second, there may have been a practice effect on the 2nd testing day, leading to a change of pacing over the course of the 2 minutes for the retest visit. Thirdly, subjects in this study did not necessarily wear the same pair of shoes to each visit, affecting the positioning of the sensors as well as their gait pattern. Due to the sensitivity of IMUs, slight changes in orientation of the IMU can affect the results.[33] Future studies regarding IMU measurement of gait speed and stride length in CKD and ESRD-D should consider using a 4 to 10-meter straight course and consistent shoe wear to attempt to improve reliability.

The gait parameter of number of steps in turns was acceptably reliable (ICC=.752). It is possible that this measure is not as sensitive to changes in linear acceleration and deceleration as stride length and gait speed. It is also possible that the number of steps in turns may have been also been less susceptible to changes in sensor placement.

The instrumented sway parameter of PATH (ICC = .78 usual base and .85 narrow base) demonstrated good reliability which is consistent with previous reports in those with PD and

matched controls.[55] The other sway parameters (JERK, RMS, and VELOCITY) were not found to be adequately reliable though they still demonstrated moderate-good reliability. These findings are consistent with a previous report of reliability of these measures in healthy older adults (mean age 67.9) that found moderate-good reliability in these measures, yet also found that the reliability was below the clinically accepted standard for use in rehabilitation.[55] The same study found that for those with PD, these measures were adequately reliable for clinical use. These findings suggest that reliability of these measures may be dependent on the population being observed.

Reliability appeared slightly improved for the narrow base condition of the instrumented sway which is counterintuitive. This finding may be due to a practice effect as the usual base balance occurred first in the testing sequence. Additionally, the sample size for the usual base was smaller due to omitted outliers which may partially have affected the results.

The hypothesis that the ESRD-D group would have worse physical performance than the CKD group was rejected. This finding contrasts with previous studies that have reported that physical function declines with the onset of HD.[8] Due to the small sample size, there is also a potential for Type II error, meaning that the sample was not large enough to detect a difference. Another potential explanation for this finding is that the groups were not age-matched, and the CKD group was significantly older than the ESRD-D group. Since age has a negative effect on physical performance, age-matching of the groups is necessary for drawing conclusions. Though the groups were not age-matched, it should be noted that relative to published age-matched strength norms, both groups had below average performance in strength. The mean quadricep isometric strength of the ESRD-D sample (mean age of 52.63 years) was 27 kg, less than published norms for ages 50-59 years which are between 30-46 kg.[63] The CKD group (mean age

of 64.81) had a mean isometric strength between 27-29 which was within the age-predicted norms of 26-29 kg.[63] While QS was considered within normal ranges for the non-HD group only, both groups had FSTS mean times which were greater than published norms, indicating worse than expected performance.[40,64]

Limitations

This study had several limitations. The sample size was small impacting the power of the statistical analysis. Statistics using small sample sizes (<30) make imprecise estimates which limit the interpretation and true values of the confidence intervals and *p*-values.[65] This study excluded those who were frail, biasing the results to a healthier population of those with CKD and ESRD-D. As previously mentioned, the lack of age-matched CKD and ESRD-D groups limits the ability to accurately interpret the lack of differences found between the groups.

Conclusions

The results of this study demonstrate good-excellent test-retest reliability of a battery of standard physical performance measures in a sample of those with CKD and ESRD-D, suggesting these to be reliable measures for the CKD and CKD-D population. The instrumented parameters of number steps in turn, sit-stand duration, and the postural sway parameter (PATH) showed clinically acceptable test-retest reliability indicating they are adequately reliable for use with this population. This study found no difference between CKD and ESRD-D groups on measures of physical performance, possibly due to a lack of age-matched groups and small sample size. The results of this study should be interpreted with caution and lack generalizability due to the small sample size. Additional research is needed to determine if physical performance

measures (standard and instrumented) have the potential to be sensitive detectors of functional decline and disability in adults with CKD and ESRD-D.

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Chapter 4

The Acute Effects of Dialysis on Physical Performance in Adults with Hemodialysis Dependent End Stage Renal Disease

Abstract

Background: Poor physical performance and post-dialysis fatigue (PDF) are prevalent in adults with hemodialysis (HD) dependent end-stage renal disease (ESRD-D). It is unknown how HD immediately affects physical performance, nor what dialysis factors may be related to these changes. The purpose of this study was to examine the acute effect of HD on physical performance in adults with ESRD-D by addressing the following aims: (1) to examine the changes in physical performance immediately pre versus post HD in measures of gait, strength, endurance, and balance; (2) to determine whether pre-post HD differences in physical performance are correlated with variables related to a HD exposure.

Methods: Eleven adults with ESRD-D completed standard and inertial measurement unit (IMUs) instrumented physical performance tests. Measures were collected immediately before and after mid-week HD. Standard physical performance measures included the Short Physical Performance Battery (SPPB), Five Times Sit to Stand (FSTS), usual gait speed (UGS), 2-Minute Walk Test (2MWT), Ninety Second Balance Test (NSB), and handheld dynamometry of the quadricep strength (QS) and grip strength (GS). Instrumented measures of gait included the following: gait speed, stride length, turn duration, steps per turn, and turn peak velocity. Static postural sway was under 4 testing conditions: usual base of support (eyes open and closed) and narrow base of support (eyes open and closed) and to assess inertial sensor measures of sway area (AREA), jerkiness (JERK), velocity of sway path (VELOCITY), path length (PATH), and root mean squared (RMS). HD exposure variables included HD vintage (# of months on dialysis), Kt/V (dialysis adequacy), intradialytic hemodynamic instability (HI) (maximal intradialytic blood pressure change), and intradialytic weight change. Paired *t*-tests were

conducted to assess differences in pre-post HD physical performance and fatigue. Pearson correlations were examined to assess the relationship between changes in physical performance and PDF with the following HD exposure variables: HD adequacy (Kt/V), pre-post HD weight change, and # of months on HD.

Results: Statistically significant differences from pre-post HD were found on quadricep strength dynamometry (t (10) = 3.35, p <.01). No significant differences in pre-post HD were present in SPPB, FSTS, gait speed, 2MWT, or GS performance. There were significant positive correlations between HI and PDF (r = 0.72), indicating that PDF was associated with increased HI. There was a significant positive correlation between FSTS and HI instability (*r = 0.63)* indicating that poorer performance on the FSTS was related to increased HI.

Conclusions: Maximum quadricep strength was significantly lower immediately following HD, compared to pre-HD in adults with ESRD-D, suggesting that HD may result in changes to muscle performance. Additionally, HI was associated with increased PDF and slower FSTS times. The results of this study should be interpreted with caution due to the small sample size, however, these finding warrant further research related to changes in strength pre -post HD.

Background and Purpose

End stage renal disease (ESRD) affects more than 661,000 Americans, and 71% of these individuals are dependent on hemodialysis (HD) for survival.[1] Poor physical performance affects a majority of those with ESRD dependent on HD (ESRD-D) and has been associated with reduced physical activity, poor quality of life, frailty, falls, increased hospitalization, and mortality.[2-7] Although numerous factors have been reported to be associated with reduced physical performance in those with ESRD-D, there is little evidence on the relationship of HD to acute changes in physical performance.[8,9] This relationship is important to rehabilitation professionals who evaluate function and develop interventions for minimizing the effects of poor physical performance on participation in life's daily activities.

Muscle strength is fundamentally essential for human movement. Low muscle mass and low muscle strength affects 18-80% of those with ESRD-D.[10-12] Handgrip strength (HGS) is a commonly used proxy for overall muscle function in ESRD and is reported below the 50th percentile of healthy population norms in over half of adults with ESRD-D.[13] Factors that are associated with low muscle mass and strength in ESRD are aging, protein-energy wasting, physical inactivity, low albumin (indicating poor nutrition), inflammation, cardiovascular disease, low insulin-like growth factor, metabolic acidosis, declining GFR, and decreased anabolism.[10,14-16] Carrero assesses muscle atrophy using a subjective global assessment tool and reports that after controlling for age, sex, inflammation, diabetes, cardiovascular disease, GFR, and time on HD, patients with ESRD-D with mild atrophy have a higher risk of death (hazard ratio (HR)= 1.76, CI=1.02-3.01) and that those with severe muscle atrophy were at an even higher risk (HR = 3.04, CI=1.61-5.71). [11] There are few studies that investigate the acute effect of HD on muscle strength, limiting our understanding of HD's effects on muscle strength and

function. Small studies assessing the acute effect of HD on muscle strength offer varying results, with some showing improvement in strength while others show decline from pre-post HD.[17]

Evidence of reduced physical performance in domains other than strength is strong in those with ESRD-D.[2,18] In the ACTIVE-ADIPOSE study, 23.5% of the 750 adults (ages 19-92) on long-term HD walked at a gait speed slower than 0.6 m/s., which suggests that they would be limited community ambulators and at high risk for falls.[19] Kutner et al. reports slow gait speed and impaired community ambulation was prevalent and that walking <1 meter/sec is associated with an increased odds of hospitalization (OR=2.04) and disability with activities of daily living (ADLs) (OR = 3.88) in a cohort of 752 HD patients[20] Bucar et al. compares patients with ESRD-D and low-level comorbidity to control subjects without renal disease and finds HD subjects had a 101.5 meter shorter distance on a 6-Minute Walk Test, even after controlling for co-morbidities.[21] Fall index scores assessed with a posturographic balance system were significantly worse ($p < .01$) for those on HD (n=53) compared to healthy controls (n=53).[22]

A multitude of physiologic factors have been studied that may explain change in physical performance from pre-post HD.[17] A reduction in cardiac capacity post-dialysis may contribute to poor cardiac endurance.[23] Some studies report declines in oxygen saturation and vascular reactivity from pre-post dialysis.[17,24] Neuromuscular function may also be altered by the rapid changes in electrolytes (potassium, calcium, and magnesium) that occur following HD.[17,23,25,26] Most patients with ESRD-D dialyze 3-times in a 7-day week creating a shifting pattern of toxicity with the worst window being the period in which they go 2 days without dialysis (termed the "intradialytic period"). Retention of sodium during the intra-dialytic period can lead to hypervolemia which has symptoms such as headache, HTN, orthopnea, edema, and dyspnea, though hypervolemia can present without any symptoms at all. Fluid removal during dialysis

may lead to hypovolemia with potential symptoms of cramps, fatigue, and orthostatic hypotension which would negatively affect physical function following HD. The nature and rigid schedule of HD sessions has also been suggested to be contributory to declines in physical activity, which in turn contributes to reductions in physical performance.[5,27] A HD session lasts ~4 hours and requires a patient to be sedentary as blood is circulated extracorporeally thru an artificial kidney. Johansen found those on HD have low self-reported physical activity and this was related to declines in physical performance in gait speed, balance, and chair rising time.[28] The overall objective of this study was to examine the acute effect of HD on physical performance in adults with ESRD-D. This study had the following aims: 1) To examine the changes in physical performance immediately pre versus post HD in measures of gait, strength, endurance, and balance; 2) To determine whether pre-post HD differences in physical performance are correlated with variables related to a HD exposure. It was hypothesized that physical performance will decrease immediately following HD. Further, it is hypothesized that there will be relationship between PDF and physical performance with dialysis exposure variables.

Methods

Study Design, Setting, and Participants

A pre-post analysis of physical performance was conducted in eleven adults (ages 34-79) with ESRD-D were recruited from greater Seattle area dialysis centers between September 2019 and January 2020. Data was collected at 2 Seattle-area Northwest Kidney Centers just before (within 1 hour) and immediately after (within 20 minutes) of a mid-week HD session. Mid-week HD was chosen to limit the effects of the intradialytic session. Inclusion criteria were 1) >3 months of standard 4-hour HD; 2) undergoing thrice weekly HD; 3) Able to ambulate 100'

independently (use of an assistive device was acceptable). Exclusion criteria were 1) <18 years old; 2) severe cardiopulmonary diagnosis; 3) dementia diagnosis; 4) initiation of dialysis within the past 3 months. Study approval was granted by the University of Washington Institutional Review Board and participants completed an informed consent process.

Demographic and Clinical Data

Demographic information and medical history were collected via patient report. Monthly lab values were obtained from the dialysis center medical record and included hemoglobin (Hgb), hematocrit (Hct), potassium (K^+), bicarbonate (CO_2), and albumin (Alb). Values were obtained as close as possible to physical performance data collection. The following measures were obtained from the medical record on the day of the dialysis session: dialysis adequacy (Kt/V), pre-post dialysis weight change (DWC), and maximal interdialytic systolic blood pressure change (BPC). Blood pressure was taken prior to physical function testing. Light touch protective sensation testing was performed on the feet (1^{st}, 3^{rd}, 5^{th} metacarpal heads; plantar surface of distal hallux, and third toe) using a 5.07-gauge Semmes Weinstein monofilament. Protective sensation was defined as impaired if > 2 areas on one foot were diminished.[29]

Measures

Fatigue Numeric Rating Scale (FNRS). Assessment of fatigue was conducted directly before and immediately after dialysis using the FNRS**.** The FNRS is a single item scale that asks a patient to rate their fatigue from 0-10 (0= less fatigue). This scale has evidence for validity and discrimination in patients with autoimmune disease as well as stroke and is useful for repeated assessment of fatigue over a short time interval.[30]

Short Physical Performance Battery (SPPB). The SPPB is a combined test that assesses physical function in 3 domains: balance, lower extremity power, and gait speed. Balance is assessed by standing in place for 10 seconds in 3 progressively more difficult conditions, lower extremity strength is assessed using a Five Times Sit-to-Stand Test, and gait speed is assessed with a 4-meter 'usual pace' timed walk. Scores for each component are added up and a summary score from 0-12 is created.[31] Excellent reliability of the SPPB has been reported in a small group of adults undergoing hemodialysis (ICC = 0.94, CI = 0.91-0.97).[32]

Five Times Sit-to-Stand (FSTS): The FSTS is a functional test that requires a patient stand as quickly as they can 5 times from a standard height (18") chair without the use of their arms. The FSTS duration is an indicator of lower extremity strength and power. High test-retest reliability of the stopwatch FSTS (ICC = 0.95) is reported in older adult females with CKD.[33] Validity has been demonstrated via a strong correlation to the Timed Up and Go ($r = 0.64$, $p < .05$).

Gait Speed. A 4-meter walk test and comfortable speed was used to obtain usual gait speed (m/sec). Participants were asked to walk at their comfortable speed from a static standing start and walk past tape that was placed at the 4-meter mark. A stopwatch started timing at the initiation of the walk and stopped when the first foot completely crossed the 4-meter line. The fastest of two trials was used to calculate usual gait speed in gait speed meters/second.

2-Minute Walk Test (2MWT). The 2MWT test assesses the distance in meters that a patient can ambulate when instructed to cover as much distance as they over two minutes. A 7-meter course marked by 2 pieces of tape was used and participants were instructed to perform laps by turning after both feet crossed the course markers. Test-retest reliability has been established in a population-based sample of US adults (ICC = .82, 95% CI = .76-.87) and aged-matched norms are available.[34]

The Ninety Second Balance Test (NSB). The NSB assesses static balance by asking a person to stand in progressively challenging balance positions (semi-tandem, tandem, and single leg) for 30 seconds. The total time that the person can maintain balance in each position is summed for a total NSB time between 0-90 seconds.

*Quadricep and Grip Strength Dynamometr*y. Quadricep strength (QS) was measured using a Lafayette Instruments handheld dynamometer (HHD) (model 01163; Lafayette Instrument Company, Lafayette, Ind., USA). The HHD was programmed to measure peak force in kilograms during a 5-second isometric muscle contraction. The pad of the HHD was placed at the anterior lower leg between the lateral and medial malleolus. Participants were positioned in supported sitting with their knee at 90º of knee flexion. Participants was asked to exert maximum force against the dynamometer. Three trials on each leg were conducted. The maximum strength obtained for each side was used for this analysis. HHD of QS has been reported to be valid in the community dwelling elderly with strong correlations with the gold standard Biodex isometric measurements ($r = 0.91$, $p = < 0.0001$).[35]

Right handgrip strength (HGS) was measured using a Jaymar™ handheld dynameter and the maximum of 3 trials was used. Suitable reliability of HGS using isometric dynamometry strength has been reported over multiple time points for a duration of 24 weeks (ICC: >0.60) in a group of 257 older (mean age = >75 years), malnourished, sarcopenic adults. (23).

Instrumented Physical Performance. Instrumented testing of physical performance was conducted using the APDM Opal inertial measurement units (IMUs) and the accompanying Mobility Lab System™ (APDM, Inc, Portland, OR**).** The APDM consists of six small IMUs, called “Opals” that are placed on the participants’ wrists, L5 lumbar region, sternum, and feet. These IMUs contain tri-axial accelerometers, gyroscopes, and magnetometers which record data

that is transmitted wirelessly and processed by the APDM Mobility Lab™ software. Studies support the use of inertial sensor technology in adults with other chronic health conditions with known mobility deficits including neuropathy, PD, and multiple sclerosis.[36]

Gait Measures. Fast walking gait parameters were taken from a 28-meter segment of 2MWT. The segment that was extrapolated from the raw Mobility Lab data for this analysis was the second and third laps of the 2MWT. This smaller segment was used to capture steady state walking and eliminate potential acceleration and deceleration at the beginning and end of the test. Also, mid-walk segments limit the effects of fatigue due to sustained energy consumption that may have occurred later in the test. APDM measures of gait included: gait speed (meter/sec) and stride length (meters), processed via Mobility lab software. These APDM parameters have been found to have excellent reliability (ICC > 0.93) in able-bodied adults and be sensitive to mobility decline in Parkinson's disease.[37,38] Age-associated normalized values are available for these spatiotemporal gait parameters.[39] Turning parameters were analyzed over the 4 turns of the 28-meter segment of the 2MWT and included turn duration (sec), steps per turn, and turn peak velocity (degrees/sec). APDM turn duration and peak velocity have been reported to have excellent agreement with gold-standard laboratory-based motion capture measures (ICC = 0.96-0.98) in cognitively impaired older adults.[40]

Sit-to-stand duration. The average duration (sec) of 5sit-to-stand segments of the FSTS was processed via Mobility Lab software.

Postural Sway. Data for instrumented postural sway was collected in 4 static stance conditions (1) usual base, eyes open; (2) narrow base, eyes open; (3) usual base, eyes open; (4) usual base, eyes closed. The participant was instructed to stand unsupported at a distance 2 feet from a wall with their arms at their sides. A piece of tape was placed at the participant's eye level and they

were asked to fix their gaze straight ahead on the tape for the 'eyes open' conditions. A plastic wedge was placed between the participant's feet for usual base stance to standardize the distance between heels at 10cm. For the narrow base stance, the participant stood with feet together. The following sway parameters were collected: total area of acceleration sway path area (m/s^2) (AREA), and sway jerkiness (m^2/s^2) (JERK), and sway acceleration velocity (m/s) (VELOCITY), total length of sway acceleration trajectory (PATH), and root mean square (RMS) of acceleration time series (m/sec^2). PATH and JERK were found to have concurrent validity to gold standard force-plate center of pressure for measures of postural sway in cognitively impaired older adults.[41] In Parkinson's disease (PD) PATH and RMS were found highly correlated with force plate measures (r = 0.73 and 0.74, respectively*)*.[42] Test-retest reliability of these measures has been reported as good to excellent in PD for RMS (ICC = 0.83), PATH (ICC = 0.81), and JERK (ICC = 0.86), with JERK and PATH being the most reliable.[42] Excellent reliability for VELOCITY has been reported in adults with vestibular disorders (ICC=0.82).[43]

Statistical Analysis

Statistical tests were performed using SPSS Version 26.0 and were conducted at the nominal significance level of $p < 0.05$. Complete case analysis was used, and outliers (defined as >3 times the interquartile range) were assessed and excluded if determined to be an error or untrue observation. Paired samples two-tailed *t*-tests were used to assess mean differences in physical performance measures ratings and fatigue ratings pre versus post HD. Pearson correlations were generated to assess the relationships between fatigue and physical performance in relation to dialysis exposure variables. The Pearson correlations were interpreted using the following conventional approach: values of < 0.00-0.10 indicate a poor association, values

between 0.10-0.39 indicate a weak association, values between 0.40-0.69 indicate a moderate association, values between 0.70-0.89 indicated a strong association, and values > 0.90 indicated a very strong association.[44]

Results

Demographic and Clinical Characteristics

Descriptive data for each group is reported in Table 1 with percentages for categorical variables and means (standard deviations (SD)) for continuous variables. The mean age of this sample was 52.54 (SD = 12.56) years. There were 5 males and 6 females. Only one subject reported regular smoking or drinking. Sixty-three percent reported employment disability at the time of the study. Over half of the sample reported exercising at least 1x/week. This group had below normative Hgb (11.03 gm/DL) and Hct (33.9%) levels, and CO_2 (23.09) and slightly elevated K^+ (5.21 mmol/L) levels. The number of months that this sample had been on dialysis ranged from 3 months to >5 years. Dialysis adequacy (mean Kt/V=1.63, SD = 0.28) was considered adequate for this sample. Hemodynamic instability was present in 10/11 participants.

There were no extreme outliers identified on the instrumented gait parameters. For the instrumented sway parameters, one subject was omitted from the usual and narrow based eyes open and the narrow base eyes closed conditions due to a loss of balance, and one extreme outlier (>3 SD) was omitted from the eyes open conditions. One extreme outlier was identified on the FSTS for the post-dialysis visit and this case was omitted from the analysis. Two extreme outliers were identified for peak turn velocity and were omitted.

Table 1. Demographic and Clinical Characteristics

Demographics	(n=11)
Age	52.64 (12.56)
Gender (Female)	54.4%
Ethnicity	
Caucasian	27.3%
Hispanic	27.3%
Asian	18.2%
Pacific Islander	9.1%
Black	18.2%
Highest Level of Education	
Completed 8th Grade	18.2%
High School/GED	18.2%
Attended college	18.2%
College Degree	9.1%
Graduate Degree	9.1%
Employment Status	
Full Time	0%
Part Time	18.2%
Retired	18.2%
Disabled	63.6%
Exercise Frequency	
Never	18.2%
1x/week	27.3%
2-3x/week	27.3%
>3x/week	27.3%
Health History Data	
BMI	28.5 (7.16)
Diabetes	36.4%
Hypertension	40.0%
Prevalent Heart Disease	54.5%
Sensory Loss Impaired	18.2%
eGFR CKD-EPI (ml/min per 1.73m^2)	<15
Systolic BP (mmHg)	154.64 (8.91)
Medication #	8.45 (2.62)
Current Smoker	9.10%
Current Alcohol Use	9.10%
Lab Values	
Hgb (gm/Dl)	11.03 (1.26)
Hct (%)	33.92 (2.99)

K^+ (mmol/L)	5.21 (0.80)
CO_2 (mmol/L)	23.09 (3.02)
Dialysis Variables	
Dialysis Vintage (months)	25.09 (20.40)
Kt/V	1.63 (0.28)
Pre-Post max BP change (kg)	32.36 (12.35)
Pre-Post weight change (kg)	-1.58 (1.02)

eGFR= estimated glomerular filtration rate based on the CKD-EPI equation, Hgb= hemoglobin, Hct= hematocrit, K^+= potassium, CO_2= bicarbonate, Kt/V= measure of dialysis adequacy, pre-post BP change: maximal change in systolic blood pressure during dialysis. *Note: percentages are given for categorical variables and means (standard deviations) for continuous variables.*

Differences in Physical Performance Pre-Post Dialysis

There were no significant differences between pre-post dialysis physical performance on SPPB, FSTS, usual gait speed, 2MWT, NSB, GS or instrumented physical performance parameters (Table 2 & 3). There was a significant difference in the maximum quadricep strength (t (10) = 3.35, p <.01) between pre-post dialysis with pre-dialysis quadricep strength being significantly higher (Figure 1). Fatigue ratings did not change pre-post dialysis.

Table 2. Paired-samples *t*-tests of standard physical performance measures and fatigue rating

	Pre-Dialysis		**Post Dialysis**		**Mean**			
	M	**SD**	**M**	**SD**	**Difference**	***t*-test**	***df***	***p***
Fatigue								
FNRS	2.81	2.1	3.18	2.23	-0.37	-1.17	10	.27
Physical Performance Measures								
SPPB (n=11)	9.90	1.14	9.82	1.4	-0.08	0.23	10	.82
FSTS (n=10)	13.82	4.18	14.05	2.99	0.23	-0.28	10	.79
Gait speed (n=11)	0.90	0.3	1.01	0.61	0.11	-1.04	10	.32
2MWT (n=11)	124.71	44.14	122.73	23.82	-1.98	0.2	10	.85
NSB (n=11)	75.28	17.01	76.18	18.88	-0.90	-0.33	10	.75
QS (n=11)	31.80	11.76	27.78	10.59	-4.02	3.35	10	<.01**
GS (n=11)	30.18	14	29.27	14.87	-0.91	1.04	10	.33

M=mean, SD=standard deviation, SPPB= Short Physical Performance Battery, *df* = degrees of freedom, FNRS = fatigue numeric rating scale, FSTS = Five Times Sit to Stand, UGS = usual gait speed, 2MWT = 2 Minute Walk Test, NSB = Ninety Second Balance Test, QS = quadricep strength, GS = grip strength; ** = *p<.01.*

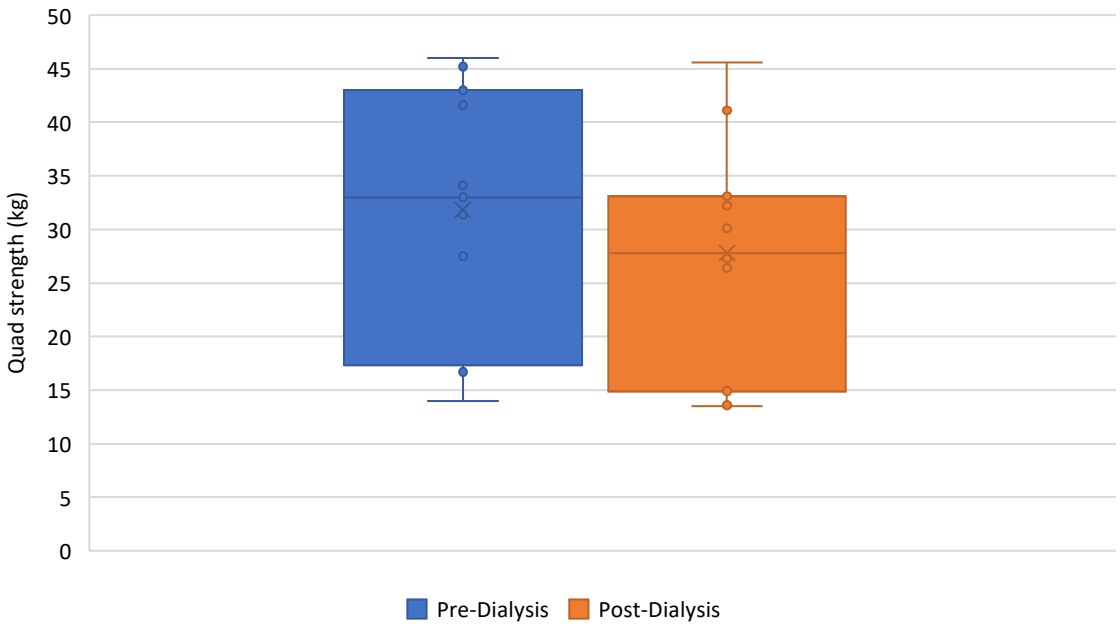
Table 3. Paired-samples *t*-tests of instrumented physical performance

	Pre-Dialysis		Post-Dialysis		Mean			
	M	**SD**	**M**	**SD**	**Difference**	***t-test***	***df***	***p***
Gait Parameters (n=11)								
SPPB (score)	9.91	1.14	9.81	1.40	0.81	0.23	10	.82
Gait speed (m/s)	1.17	0.20	1.06	0.28	-0.08	1.78	10	.11
Stride length (m)	1.03	0.17	1.07	0.25	0.04	1.02	10	.33
Turn duration (s)	2.27	0.37	2.25	0.45	-0.02	0.08	10	.50
Steps in turn (#)	4.48	0.85	4.38	0.85	0.30	0.69	10	.51
Peak turn velocity (deg/s)	188.61	41.47	189.95	39.23	1.34	-0.70	10	.50
Sit to Stand Parameters (n=11)								
Sit to Stand Duration (s)	0.94	0.09	1.01	0.16	-0.07	-1.92	10	.08
Postural Sway Parameters								
Usual Base, Eyes Open **(n=9)**								
AREA (m^2/s^4)	0.48	0.03	0.14	0.29	-0.09	-1.00	8	.34
JERK (m^2/s^5)	1.80	0.29	7.50	14.69	5.70	-1.21	8	.26
VELOCITY (m/s)	0.21	0.12	0.26	0.27	0.05	-0.55	8	.60
PATH (m/s^2)	7.30	2.32	9.39	4.70	2.09	-1.48	8	.17
RMS (m/s^2)	0.10	0.03	0.17	0.21	0.07	-1.62	8	.28
Usual base, eyes closed **(n=10)**								
AREA (m^2/s^4)	0.05	0.02	0.13	0.20	0.08	-1.29	9	.23
JERK (m^2/s^5)	2.09	1.16	3.99	3.72	1.90	-1.84	9	.10
VELOCITY (m/s)	0.19	0.10	0.24	0.15	0.05	-1.55	9	.16

PATH								
(m/s^2)	7.66	1.62	9.90	4.62	-2.24	-1.74	9	.12
RMS (m/s^2)	0.10	0.02	0.15	0.10	.052	-1.76	9	.11
Narrow base, eyes open **(n=9)**								
AREA								
(m^2/s^4)	0.08	0.04	0.10	0.07	0.02	-0.93	8	.38
JERK								
(m^2/s^5)	1.95	0.97	2.37	3.72	0.42	-1.28	8	.23
VELOCITY	0.25	0.08	0.21	0.13	-0.04	0.75	8	.47
PATH								
(m/s^2)	8.92	1.71	9.23	2.91	0.31	-0.27	8	.79
RMS (m/s^2)	0.11	0.03	0.12	0.05	0.01	-0.57	8	.58
Narrow base, eyes closed **(n=10)**								
AREA								
(m^2/s^4)	0.05	0.02	0.13	0.20	0.08	-1.30	9	.23
JERK	4.66	2.50	5.74	6.26	1.07	-	9	
(m^2/s^5)						0.74		.48
VELOCITY								
(m/s)	0.28	0.14	0.26	0.11	0.02	-0.32	9	.75
PATH								
(m/s^2)	12.62	4.41	13.13	5.90	0.51	-0.48	9	.64
RMS (m/s^2)	0.15	0.05	0.15	0.06	0.01	-0.51	9	.62

Area= area of sway path, JERK = jerkiness, VELOCITY = acceleration velocity, PATH = acceleration pathlength, RMS = root mean squared, m=meters, s = seconds; *p <.05.*

Figure 1. Quadricep Strength Pre-Post Dialysis



NRS fatigue was not significantly correlated with change in any of the physical performance measures, however, a correlation of moderate strength was observed between the post-dialysis NRS fatigue score and the FSTS (*r* = 0.51*)*. The correlations between hemodynamic instability measured by maximum change of intradialytic systolic blood pressure and FSTS were moderate and statistically significant; FSTS (r = 0.63, p < .05) and with post-dialysis NRS fatigue rating (r = 0.61, p < .05) (Figures 2 & 3).

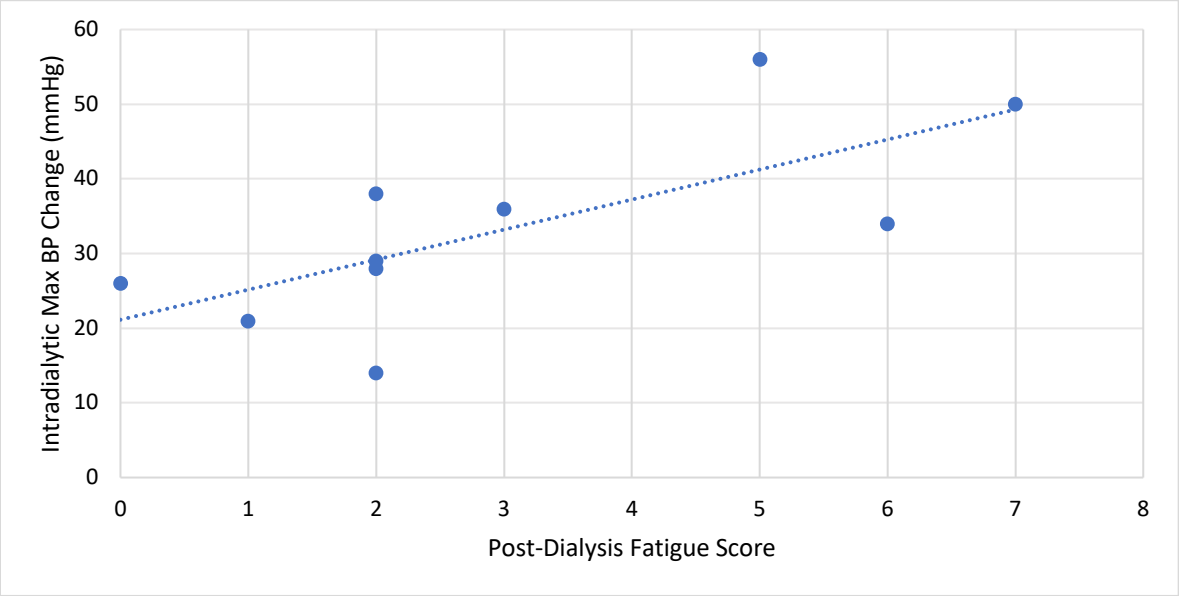
Table 4. Correlations between Dialysis Exposure Variables and Pre-Post Differences on Clinical Physical Performance Measures and Post-Dialysis Fatigue Ratings (n=10)

	Fatigue	**Kt/V**	**Weight Change**	**Max Systolic BP Change**	**Dialysis Vintage**
Fatigue	-	0.12	0.35	0.72*	-.18
FSTS	0.51	0.33	0.16	0.63*	-.16

UGS	0.27	-0.38	0.06	0.21	-.51
NSB	0.24	0.28	0-.09	0.42	.02
2MWT	-0.05	0.47	-0.08	0.18	.30
QS	-0.25	-0.32	-0.43	-0.24	.38
GS	0.19	0.39	0.23	0.03	.09

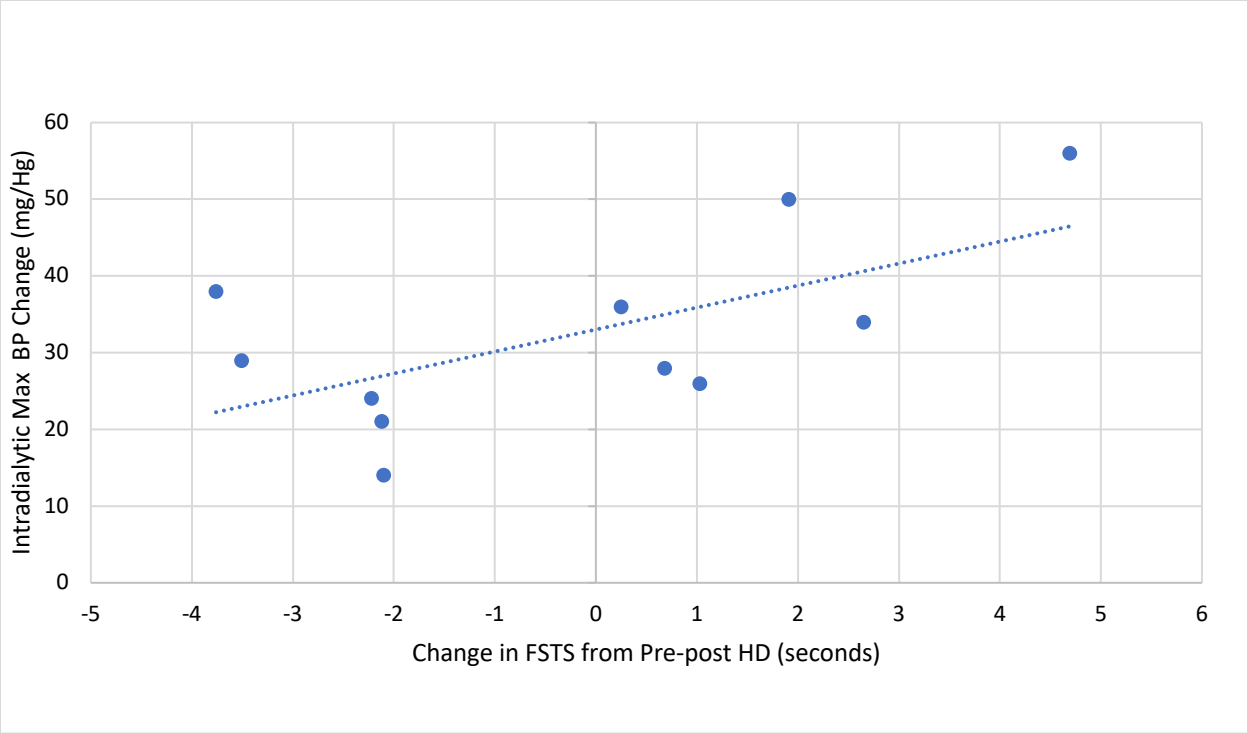
FSTS= Five Times Sit to Stand, UGS = usual gait speed, NSB= Ninety Second Balance Test, 2MWT= 2 Minute Walk Test, WS= quad strength, GS= grip strength. Fatigue= numeric rating of fatigue post-dialysis, max= maximum, BP= blood pressure, * = *p<.05*

Figure 2. Scatterplot of Post-Dialysis Fatigue NRS Score and Maximum Intra-dialytic SBP change



BP= systolic blood pressure, FSTS= Five Times Sit to Stand

Figure 3. Scatterplot of Difference in Pre-Post Five Sit to Stand Duration and Maximum Intra-dialytic SBP change



BP= systolic blood pressure, FSTS= Five Times Sit to Stand, HD= hemodialysis

Discussion

This study examined changes in physical performance pre versus post HD. The hypothesis that physical performance would decrease following HD was accepted for maximal QS, while all other physical performance measures (standard and instrumented) did not show statistically significant change.

This study found a reduction in strength post-HD. Three previous studies have examined strength in relation to HD, two using grip strength and one using quadricep strength. Grip strength is commonly used as a proxy for total body strength, though a potential benefit to using quadricep over grip dynamometry to assess muscle performance is the ability to assess bilaterally vs. grip being limited to unilateral testing due to the HD access site.[45] Consistent with this study, Pinto et al. found a post-HD decline in maximal grip strength in 137 HD patients.[13] Leal

reported differing finding, reporting that grip strength increased post-HD in men and there was no difference in women in a group of 43 patients. Saiki et al. studied 11 HD patients found that quadricep muscle strength was unchanged in one patient, increased in 6 patients, decreased in 3 patients. The lack of consistent findings suggests that there may be influential factors affecting pre-post HD strength that warrant further investigation.

Inflammation and proteolysis may be mechanistically related to changes in strength following HD. Though limited to studies of low-medium methodologic quality, reports consistently suggests that there is an acute increase in protein breakdown during dialysis, and that this breakdown is associated with an inflammatory response.[17] Inflammatory markers, specifically interleukin-6, has been shown to increase in both muscle and plasma following HD, potentially affecting muscle, nerve, and cardiac function.[26]

Another potential mechanism for declines in strength following HD is intradialytic hemodynamic instability (HI). HD is characterized by acute effects on cardiovascular hemodynamics which result in systemic hypoperfusion. A key measure of HI during HD is intradialytic hypotension (IDH); defined by a drop in systolic blood pressure of more than 20 mmHg or in mean arterial pressure by 10mmHg during HD. HI has been reported in up to 40% of those who undergo HD and has also been proposed as a contributory factor post dialysis fatigue (PDF) and reduced physical performance.[13,46,47] In healthy individuals, volume reduction is normally followed by increased sympathetic and endocrine activity which act as a compensatory mechanism to reduced volumes. In patients on HD, this compensatory mechanism is overwhelmed and can fail, resulting in muscle cramps and systemic hypoperfusion that can affect the muscle's contractile ability.[46-48] Without these compensatory mechanisms triggered, arterial oxygen tensions fall up to 25% during HD, though most patients are asymptomatic.[46]

These ischemic effects on muscle potentially remain present immediately following HD, affecting the muscle's ability to maximally contract. A recent systematic review of the acute effects of HD on skeletal muscle perfusion, metabolism, and function reports that no studies were identified that measured changes in muscle perfusion in response to a HD session, identifying an important direction for future research.[17] The current study found 10 of 11 participants experienced intradialytic HI, and that this HI was significantly associated with reduced physical performance and post-HD fatigue ratings. This relationship is consistent with Pinto et al. who reported a relationship between HI and grip strength reduction post-dialysis.[13] There are limited pharmacologic treatment options for treatment of HD-related HI, but intradialytic exercise has been suggested to improve both HI and PDF.[49]

Although it was hypothesized that physical performance would show acute decline following HD, it is possible that physical performance improves or remains the same in some physical domains. Surprisingly, differences were not found on any of the standard or instrumented physical performance measures, though the FSTS duration had a trend in being longer post-dialysis (p=.08), indicating worse performance. These findings were consistent with Soangra et al. who evaluated the sit-stand duration of a stand-to-walk test on 6 HD patients and reports that after dialysis, patients were slower to get out of a chair compared to pre-dialysis.[50] Albeit, this observation is inconsistent with Harrison et al. who evaluated the number of times 25 patients on HD could rise from a chair in 30 seconds and found that from pre-post dialysis there was a 6% increase in the number of stands post-dialysis compared to pre-dialysis.[51] Each of these studies, including the current one, used differing measures of sit-stand which may explain the variability in findings.

The 2MWT did not change significantly though a previous study did report of a decline on the 6MWT following HD.[21] This study used a shorter test (2-Minute vs. 6-Minute), and though found to be sensitive to change in older adults, this shorter test potentially was less sensitive to change in this younger sample. [34] It is also possible that HD does not have a large effect on short walking duration, but when subjects are required to walk for longer periods of time an effect emerges.

There were no differences pre-post HD on balance measures. This is inconsistent with Erken et al. who reported that used a posturographic balance system to assess changes in balance after HD and found that balance was worse from pre-post HD.[22] Instrumented sway may have limitations of a floor effect and is potentially not appropriate measure for those prone to a loss of balance. As with the instrumented postural sway measures, the NSBT also did not show a significant change. The NSBT may have also had a floor effect since as this test starts in a narrow semi-tandem stand, a challenging position for those with significant balance impairment. In stroke patients who have significant balance impairment, the Balance Evaluations Systems Test (BEST) test has been found to have limited floor effects and, though longer to administer, may be useful to assess a wider range of balance abilities in ESRD-D.[52]

Limitations

It is possible that this study was unable to detect differences due to Type II error related to its small sample size. Type II error occurs when there is non-rejection of the null hypothesis when in fact, there is a true difference. Detecting effects requires appropriate power, and larger sample sizes are needed to detect smaller effects.[53] The findings related to postural sway may have been affects due to observations that were removed from the instrumented balance analysis due to losses of balance, leading to an extremely small sample and a higher potential for Type II

error. This sample also represented a wide age-range for adults but did not include many people who are elderly which potentially biased the sample towards a less frail phenotype. This study was also conducted at only 2 associated HD centers whose HD protocols were very likely similar, making these results difficult to generalize.

Conclusions

This study examined the effects of a dialysis session on physical performance using a battery of physical performance measures in adults with ESRD-D. Quadriceps strength was significantly lower following HD, suggesting that HD has an acute effect on muscle performance. In addition, interdialytic hemodynamic instability was associated with increased self-reported fatigue and slower repetitive chair stand performance following a HD session. The results of this study should be interpreted with caution due to the small sample size, however, these findings warrant further research related to changes in strength pre versus post dialysis in adults with ESRD-D. The methods used in this study demonstrated feasibility and the initial findings warrant continued investigation with a larger sample size.

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Chapter 5

Final Discussion and Conclusions

Final Discussion and Conclusion

Chronic kidney disease (CKD) and end stage renal disease (ESRD) are global health problems associated with changes to body systems and functions which contribute to reduced physical performance and functional ability. These problems contribute to both reduced quality of life and loss of functional independence. Research is needed to better understand physical performance to inform rehabilitation interventions and treatment planning for those with CKD/ESRD, therefore, this dissertation explores questions related to physical performance and in adults with CKD/ESRD.

Summary of Findings

Chapter 2 examines the associations of fatigue with physical performance measures and mobility disability in adults with stage 2-4 CKD. The key findings of this study are as follows:

- There was a significant association between lower extremity physical performance (gait speed and five times sit to stand) and higher fatigue
- Mobility disability was not associated with fatigue
- 51% of the participants with Stage 2-4 CKD were at risk for mobility disability

Chapter 3 examines the test-retest reliability of both standard and instrumented physical performance in adults with CKD and dialysis dependent ESRD (ESRD-D) and compares physical performance between those with CKD and ESRD-D. The key findings of this study are as follows:

- Clinically acceptable reliability is demonstrated in standard physical performance measures, including the Short Physical Performance Battery, gait speed, Five Times

Sit-to-Stand, 2-Minute Walk Test, and quadricep (QS) and grip (GS) strength dynamometry

- Clinically acceptable reliability was demonstrated in inertial measurement unit (IMU) instrumented parameters, including sway pathlength, number of steps per turn, and sit to stand duration
- No differences in physical performance were observed between the CKD and ESRD-D groups.

Chapter 4 examines whether changes physical performance occur pre versus post a hemodialysis (HD) session in adults with ESRD-D. In addition, correlations were examined between dialysis-related exposure variables. The key findings of this study are as follows:

- Lower extremity quadricep strength was significantly decreased post HD
- Intradialytic hemodynamic instability was associated with increased fatigue and longer sit to stand duration following HD

Clinical Relevance

These findings have implications for rehabilitation clinical practice. Rehabilitation professionals who are working with those with CKD and providing interventions for physical performance impairments may benefit from assessing and tracking fatigue to better align their exercise prescriptions and interventions. The results of this study indicate that those with CKD are at risk for mobility disability and should be screened accordingly to assess need for intervention and disability prevention. There was a subset of physical performance measures and IMU instrumented measures that demonstrated clinically acceptable reliability in those with CKD/ESRD. These measures should be considered for assessing physical performance in this

population and may be combined to form a composite measure of physical performance for use with this population. Furthermore, monitoring of intradialytic hemodynamic instability may be important for predicting post-dialysis physical performance and fatigue in those with ESRD-D to informing rehabilitation planning.

Future Directions

Questions remain regarding which factors influence the relationship between fatigue and physical performance, offering opportunity for future research. For example, the type of fatigue (mental vs. physical), physical activity, sleep quality, and nutrition may influence this relationship. Causal mechanisms of fatigue and poor physical performance also remain poorly understood and remain a topic for further investigation. Further work to investigate psychometric properties other than reliability (e.g., minimally detectable change, minimally important clinical difference, sensitivity, and specificity) of physical performance measures can aid the development of a psychometrically strong clinical toolkit to assess physical performance in adults with CKD/ESRD. Mechanistic studies to unveil the physiologic processes responsible for changes in strength after a HD session are needed. For example, testing the theory that intradialytic muscle hypoperfusion may be mechanistically related to post-dialysis strength decline.

The studies presented in Chapters 3 and 4 of this dissertation were limited by their small sample sizes. Continued research with larger samples and age-matched groups is needed to confirm the preliminary findings reported here.

Conclusion

This dissertation, “Physical Performance in Chronic Kidney Disease”, contributes to the understanding of physical performance in adults with CKD/ESRD to guide rehabilitation assessment and planning. Specifically, this dissertation identified: 1) a relationship between fatigue and physical performance; 2) a set of clinically reliable physical performance measures; and 3) evidence that strength may decline immediately following a hemodialysis session. Future research directions include detection of the direction of causal relationships between fatigue and physical performance, development of a psychometrically strong composite physical performance outcome measure for CKD/ESRD, and identification of pathophysiological mechanisms related to strength decline following dialysis.