Physical Function in Older Candidates for Renal Transplantation: An Impaired Population

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Background and objectives: Although physical function is a major determinant of health outcomes and quality of life in older adults, standard tools for its assessment have not been routinely applied to the fastest growing segment of the kidney transplant candidate population, which is at high risk of comorbidity and disability—people over age 60. The objective of this study was to describe the baseline physical function in older adults with renal failure referred for transplantation and compare them with older adults with other significant comorbidity.

Design, setting, participants, & measurements: An observational sample comparing physical performance in renal transplant candidates over age 60 (Renal Failure) to older people with diastolic heart failure (Heart Failure), chronic obstructive pulmonary disease (COPD), or at high risk for cardiovascular disease (High CV Risk) was studied.

Results: Older people with Renal Failure were significantly impaired by objective measures of physical function, including lower Short Physical Performance Battery, slower gait speed, and lower grip strength.

Conclusions: Older people referred for renal transplantation had poorer physical performance than older adults with other common chronic diseases and may be at high risk for disability while awaiting transplantation.

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The continued rapid growth of the incident ESRD population over age 65 (1) coupled with increased awareness that renal transplantation confers a survival advantage over remaining on dialysis, even in the older age categories (2), has lead to an unprecedented demand for renal transplantation by older patients. The age group over 65 yr is the fastest growing segment of patients added to the national kidney transplant waiting list. Over the past decade, the proportion of persons in this older age category has steadily increased from 8 to 15% of waiting list candidates and from 6 to 14% of kidney transplant recipients (3). As more of these high-risk patients are placed on the waiting list, the process of evaluating and maintaining candidacy consumes increasing resources. Although older patients with renal failure are at high risk for mobility limitations and functional dependence (4–6), the standard pretransplant evaluation is heavily weighted on cardiovascular risk assessment and malignancy screening (7). Such an approach largely ignores physical function, the risk for disability, and their potential effect on outcomes. Furthermore, recent publications that recommend that transplant candidacy be based on "biologic rather than chronological age" do not provide any objective or reproducible measures of biologic age (8).

It is well documented that the general dialysis population has significant reductions in strength and markedly impaired exercise capacity (9–13), yet clinicians often attribute these functional impairments to inadequate dialysis, anemia, or cardiopulmonary disease, even when symptoms seem out of proportion to the underlying condition. By contradistinction, exertional fatigue and dyspnea are well recognized consequences of both heart failure and chronic obstructive pulmonary disease (COPD). Poor physical performance on exercise testing is predictive of outcomes such as hospitalization and mortality in patients with heart failure and COPD (14–20). Assessment of physical function has been proposed as a standard component of the pretransplant evaluation in people referred for lung transplantation (18–20). Although it is well known that patients with ESRD are functionally impaired, standardized measures of physical performance have not been examined rigorously in candidates for renal transplantation. Considering the expected expansion of older ESRD patients demanding transplantation, it is prudent to identify factors that predict outcome in this population. The goal of this study was to describe the baseline physical function in older renal failure patients referred for renal transplantation and compare them with older adults with other significant comorbid conditions.

Materials and Methods
Subjects and Protocol Overview
In this observational study, subjects were age 60 or greater with advanced chronic kidney disease (Stage IV or V) or requiring dialysis

who were either undergoing a kidney transplant evaluation or had already been placed on the kidney transplant waiting list at our center (referred to as the Renal Failure group). Eligible persons lived within a 60-mile radius of the center; were able to maintain sitting or standing balance and ambulate without assistance from another person; and did not have a major cognitive defect, an active lower extremity musculo-skeletal problem, or unstable coronary artery disease. All dialysis-dependent participants were tested on a nondialysis day. The Wake Forest University Institutional Review Board approved the study protocol and written informed consent was obtained from all subjects.

A total of 144 kidney transplant candidates over age 60 were identified by review of the weekly transplant evaluation minutes and the center renal transplant waiting list. Of the 80 people excluded from this study, 32 lived too far from the medical center, 22 were medically unsuitable for transplantation at the time of recruitment, and 26 had an incomplete medical work-up. Of the 64 people who potentially fit the inclusion/exclusion criteria and were invited to participate in the study, 38 did not respond to recruitment strategies (mailings and phone calls) or refused to participate, leaving 26 (40.6%) participants in the study with an average age of 67 yr (range 61 to 78 yr). There were 11 women and ten African Americans. Seven participants were not yet on dialysis at the time of evaluation; the estimated GFR by the modified Modification of Diet in Renal Disease equation in these individuals ranged from 13 to 26 cc/min. Of the remaining subjects, the average time on dialysis was 2.78 yr (range of 4 mo to 6.3 yr). Diabetes mellitus was present in 17 and 11 had known coronary artery disease. Three had previous transplants (one heart, one kidney, and one liver transplant recipient).

The comparison groups (Table 1) were older patients with a defined comorbidity who were enrolled in other trials supported by the Wake Forest University Claude D. Pepper Older Americans Independence Center (WFU OAIC). Baseline assessments in all comparison groups were performed before the described intervention. The Pharmacologic Intervention in the Elderly trial (referred to as "Heart Failure" hereafter) was a randomized, controlled, double-blind trial in 71 subjects designed to test the hypothesis that spironolactone would improve exercise tolerance and quality of life in elderly patients with isolated diastolic heart failure (personal communication, Dr. Dalane Kitzman). The Reconditioning Exercise and Chronic Obstructive Pulmonary Disease Trial II (21) was designed to determine the effect of two different strategies for delivering a physical activity intervention on physical activity levels, physical functioning, self-reported disability, health-related quality of life, and exercise capacity in older adults (176 were enrolled) with COPD

(hereafter referred to as "COPD"). The Trial of Angiotensin Converting Enzyme Inhibition and Novel Cardiovascular Risk Factors (22) (hereafter referred to as "High CV Risk") was a double-blind, crossover, randomized, placebo-controlled trial of 294 older adults who were at high risk for cardiovascular disease but did not have a specific cardiovascular condition such as previous myocardial infarction. This study assessed the effects of 6 mo of treatment with angiotensin-converting enzyme inhibition with fosinopril *versus* placebo on several markers of fibrinolysis, inflammation, endothelial function, and extracellular matrix remodeling.

Subjects in the comparison groups had to have at least one objective measure of physical function (*e.g.*, grip strength or walking speed) to be included in the analysis. After excluding individuals with missing data, there were 52 subjects in the Heart Failure group, 153 subjects in the COPD group, and 279 subjects in the High CV Risk group.

Physical Function Assessment
Performance-Based Testing

The Short Physical Performance Battery (SPPB) captures a range of functioning and has been shown to predict the onset of disability in large population-based studies of aging in older adults (23–27). The SPPB, as described by Guralnik *et al.* (23–25), is a simple and brief performance battery that can be performed at the bedside without any special equipment. It is based on (1) the time needed (in seconds) to walk 4 m at a normal pace; (2) the time needed to stand up and sit down five times as quickly as possible from a chair with the arms folded across the chest; and (3) a timed balance test that measures the ability to maintain balance with feet together in three positions (side by side, semi-tandem, and tandem).

Each of the three performance measures are assigned a score ranging from 0 to 4, with 0 being the inability to complete the test and 4 indicating the highest level of performance. Scoring for the faster of two walking tests was: 1, ≥ 5.7 s; 2, 4.1 to 5.6 s; 3, 3.2 to 4.0 s; and 4, ≤ 3.1 s. Scores for the repeat chair stand test were: 1, ≥ 16.7 s; 2, 16.6 to 13.7 s; 3, 13.6 to 11.2 s; and 4, ≤ 11.1 s. For the standing balance test, subjects were scored 1 if they cold hold a side-by-side stand for 10 s but were unable to hold the semi-tandem stand for 10 s; 2 if they could hold the semi-tandem stand for 10 s but were unable to hold the full tandem stand for more than 2 s; 3 if they could hold the full tandem stand for 3 to 9 s; and 4 for holding the full tandem stand for 10 s (23,24). The total SPPB performance score ranges from 0 (worst performers) to 12 (best performers) and is calculated by adding walking speed, chair stands, and standing balance subscores.

Table 1. Overview of study populations

Major Comorbidity	Trial Population	Trial Name
Renal failure, candidates for renal transplantation	26 subjects age ≥ 60 yr	Physical Function and Quality of Life in Older Candidates for Kidney Transplantation
Diastolic heart failure	71 subjects age ≥ 65 yr	Pharmacologic Intervention in the Elderly (PIE)
Chronic obstructive pulmonary disease	176 subjects age 55 to 80 yr	The Reconditioning Exercise and Chronic Obstructive Pulmonary Disease Trial II (REACT II) (21)
High risk for cardiovascular disease	294 subjects >55 to 80 yr of age	Trial of Angiotensin Converting Enzyme Inhibition and Novel Cardiovascular Risk Factors (TRAIN) (22)

Hand grip strength is a commonly used and well accepted measure of upper body skeletal muscle function and is a general indicator of frailty (28,29). Grip strength in both hands was measured using an adjustable, hydraulic grip strength dynamometer (Jamar Hydraulic Hand Dynamometer, Model No. BK-7498, Fred Sammons, Inc. Burr Ridge, Illinois). If a participant reported wrist or hand pain, or had undergone surgery of the upper extremity in the past 3 mo, the affected hand was not tested and results of the other hand were used. The best performance of two trials for each hand was selected for the analysis.

Disability Questionnaire

The Pepper Assessment Tool for Disability (PAT-D) is a 19-item self-report disability questionnaire that was developed and refined at the WFU OAIC to assess difficulty with functioning (30–32). The PAT-D has been widely used in randomized controlled trials and observational studies in a variety of chronic health conditions. In addition to being a valid measure with excellent psychometric properties, it has been shown to be sensitive to change in previous intervention studies (33). There are three domains: mobility, activities of daily living disability, and instrumental activities of daily living disability. The questionnaire asks respondents how much difficulty they have had with a range of activities in the past month and if they believe any perceived difficulties were related to their health. For each item, respondents answer whether they experience (1) no difficulty, (2) a little difficulty, (3) some difficulty, (4) a lot of difficulty, (5) unable to do, or a box can be checked that reads "usually did not do for other reasons." The summary score, a mean of the three domain scores that ranges from 1 to 5, is an indication of a person's overall perceived disability.

Body Composition Measurement

Upper and lower extremity muscle mass, a major contributor to decreased strength in older adults, declines as age increases (34,35). Low muscle strength is associated with a higher risk for mobility limitations (36). Total body fat mass also seems to play a role because it is positively associated with muscle mass and strength and negatively associated with physical function, particularly in women (37). To adjust for body composition in the analysis, dual-energy x-ray absorptiometry was performed to estimate total body lean and fat mass.

Statistical Analyses

Data were analyzed using SAS 9.1 (SAS, Cary, North Carolina). Outcome measures (grip strength, SPPB, gait speed, repeated chair-rise time, standing balance, and disability questionnaire score) for the Renal Failure group were compared with the subjects in the Heart Failure, COPD, and High CV Risk groups. Analysis of covariance was used to adjust for patient characteristics such as age, gender, and race for all of the outcomes except for standing balance. In addition, we also adjusted for body mass index (BMI), total body lean mass, and total body percent fat, respectively. Therefore, for each outcome measure, there were three models. The adjusted means (least-square means) of Heart Failure, COPD, and High CV Risk groups were compared with those of the Renal Failure group. The Bonferroni procedure was used to adjust for multiple comparisons.

For standing balance, we compared the SPPB subscore, coded as 0, 1, 2, 3, and 4 as described earlier, because the three tasks themselves are not suited for a more refined analysis. The number of patients having 0, 1, and 2 scores were few, therefore they were combined into one category for the analysis. The proportional odds model for ordinal response was used to adjust for patient characteristics and BMI, total body lean mass, or total body percent fat. Proportional odds assumptions were valid for each model. Odds ratios and the corresponding 95% confidence intervals between the Heart Failure, COPD, High CV Risk, and Renal Failure groups were calculated.

Results

Patient Characteristics

The four groups were well matched by age, gender, race, and BMI.

Performance-Based Testing

Table 2 shows the unadjusted baseline results by study pop-

Table 2. Baseline results by study population[a]

Parameter	Renal Failure $n = 26$ Mean (SD)	Heart Failure $n = 52$ Mean (SD)	COPD $n = 153$ Mean (SD)	High CV risk $n = 279$ Mean (SD)
Age (yr)	67.48 (4.89)	69.89 (7.53)	67.16 (9.80)	66.03 (7.47)
Body mass index (kg/m^2)	30.69 (7.40)	29.90 (5.03)	28.39 (6.50)	29.10 (4.73)
Disability questionnaire (PAT-D) score (1 to 5)	1.42 (0.53)	1.88 (0.54)	1.83 (0.58)	1.44 (0.54)
SPPB score (0 to 12)	8.35 (2.76)	9.71 (1.61)	10.38 (1.46)	10.34 (1.51)
4-m walk subscore (0 to 4)	3.19 (1.06)	3.94 (0.24)	2.20 (1.87)	3.78 (0.81)
five chair-rise subscore (0 to 4)	1.81 (1.27)	2.20 (1.04)	2.74 (1.22)	2.66 (1.05)
Standing balance subscore (0 to 4)	3.35 (1.02)	3.54 (1.00)	3.84 (0.40)	3.85 (0.44)
Gait speed (m/s)	0.80 (0.19)	1.17 (0.22)	0.99 (0.22)	1.25 (0.24)
Five chair-rise time (s)	15.88 (4.60)	15.17 (3.90)	13.34 (4.96)	13.84 (4.10)
Grip strength (kg)	26.56 (11.02)	28.78 (8.56)	35.68 (12.61)	39.49 (13.52)
Whole body lean mass by DEXA (kg)	56.67 (13.00)	46.90 (9.37)	53.08 (12.56)	56.10 (11.85)
Whole body total fat by DEXA (kg)	29.26 (10.87)	31.19 (9.73)	27.36 (11.37)	29.30 (9.70)
Whole body percent fat by DEXA (%)	32.74 (7.55)	38.50 (7.84)	32.41 (7.86)	33.21 (8.23)

[a]COPD, chronic obstructive pulmonary disease group; PAT-D, Pepper Assessment Tool of Disability; SPPB, Short Physical Performance Battery; DEXA, dual energy x-ray absorptiometry.

ulation. The models in Tables 3 and 4 are adjusted for age, gender, race, and body composition.

In the adjusted model (Table 3), Renal Failure patients scored an average of 8.42 (range 2 to 12) on the SPPB, which was significantly lower when compared with Heart Failure patients (9.92, $P = 0.0003$), people with COPD (10.17, $P < 0.0001$), and the High CV Risk group (10.18, $P < 0.0001$). Average grip strength was also significantly lower at 24.4 kg when compared with subjects in the Heart Failure, COPD (both 36.2 kg), and High CV Risk (38.0 kg) groups ($P < 0.0001$, all comparisons).

Renal Failure patients tended to have longer repeated chair-rise times (not statistically significant) when compared with the other three groups. Renal Failure patients also had a significantly slower average gait speed of 0.80 m/s when compared with subjects in the Heart Failure (1.20 m/s, $P < 0.0001$), COPD (0.96 m/s, $P = 0.0053$), or the High CV Risk (1.22 m/s, $P < 0.0001$) groups.

Renal Failure patients had worse balance scores as compared with the other groups (the odds ratio calculation is shown in Table 4). Renal Failure patients more often had a score of 0, 1, or 2 (15%) *versus* Heart Failure (10%), COPD (1%), and High CV Risk (3%) patients. Kidney Failure patients had fewer scores of 4 (61%, compared with 75% in Heart Failure, 85% in COPD, and 88% in High CV Risk patients).

Disability Questionnaires

Renal Failure subjects had a mean PAT-D score of 1.42, which was not different than those in the High CV Risk group (PAT-D = 1.47). When compared with the other two groups, we found that COPD (PAT-D = 1.87, $P = 0.0003$) and Heart Failure (PAT-D = 1.78, $P = 0.0401$) patients were much more likely to report impairment than older people with Renal Failure.

Discussion

Our study demonstrates that older patients who have advanced chronic kidney disease or are on dialysis are as functionally impaired, perhaps even more so, as older people with heart failure or COPD. One should note that our population was selected from a higher functioning cohort of older people with kidney disease because they were candidates for renal transplantation. The scope of functional disability is likely much more severe in the general older dialysis population. It is interesting to note that although Renal Failure patients in our study had lower SPPB scores, reduced grip strength, and slower walking speeds, they were less likely to report that they had functional impairment on disability questionnaires when compared with matched controls with other comorbid illnesses. We speculate that people with renal failure were less likely to report impairment because dyspnea and exercise intolerance are not recognized as predominant symptoms of chronic renal failure and patients may not be aware of their impairment when it occurs over the course of several years, as is the case in slowly progressive renal disease.

Physical functioning by both subjective and objective measures strongly predict morbidity and mortality in both epidemiologic and clinical research studies of community-dwelling older adults (38–42). Although measures of physical performance are not common outcome measures in studies of dialysis patients, a relationship between physical function and outcomes is becoming apparent (43,44). A recent epidemiologic study utilizing data from the Dialysis Morbidity and Mortality Wave 2 study showed a positive association between physical activity reported on the Kidney Disease Quality of Life Short Form and survival. Likewise, severe limitations in moderate or vigorous physical activity were strongly associated with an increased risk of mortality (45). A prospective study examining

Table 3. Functional assessment by study population, adjusted results[a]

Parameter		Renal Failure	Heart Failure	COPD	High CV Risk
Total disability score (PAT-D) (1 to 5)	Adjusted mean (SE)	1.42 (0.11)	1.78 (0.10)	1.87 (0.05)	1.47 (0.04)
	P value compared with Renal Failure	–	0.0401	0.0003	1.0000
SPPB score (0 to 12)	Adjusted mean (SE)	8.42 (0.30)	9.92 (0.24)	10.17 (0.18)	10.18 (0.11)
	P value compared with Renal Failure	–	0.0003	<0.0001	<0.0001
Gait speed (m/s)	Adjusted mean (SE)	0.80 (0.04)	1.20 (0.03)	0.96 (0.02)	1.22 (0.02)
	P value compared with Renal Failure	–	<0.0001	0.0053	<0.0001
Five chair-rise time (s)	Adjusted mean (SE)	15.92 (0.86)	14.68 (0.63)	14.00 (0.46)	14.38 (0.28)
	P value compared with Renal Failure	–	0.7260	0.1428	0.2575
Grip strength (kg)	Adjusted mean (SE)	24.4 (1.7)	36.2 (1.8)	36.2 (0.8)	38.0 (0.7)
	P value compared with Renal Failure	–	<0.0001	<0.0001	<0.0001

[a]The models are also adjusted for age, gender, race, and body mass index. The results were similar when adjusted for lean mass and percent fat.

Table 4. Odds ratio calculation for the standing balance portion of the SPPB[a]

Parameter	Renal Failure[b]	Heart Failure (OR, CI)	COPD (OR, CI)	High CV Risk (OR, CI)
Body mass index	1	0.31 (0.10,0.90)	0.25 (0.09,0.70)	0.22 (0.09,0.54)
Whole body lean mass by DEXA	1	0.32 (0.11,094)	0.24 (0.09,0.66)	0.22 (0.09,0.53)
Whole body percent fat by DEXA	1	0.26 (0.09,0.78)	0.21 (0.07,0.60)	0.18 (0.07,0.46)

[a]The models are also adjusted for age, gender, and race. OR, odds ratio; CI, confidence interval.
[b]Renal Failure is the reference group. The model probability is the tendency to not complete the balance test, so an odds ratio <1 indicates better performance as compared with Renal Failure patients.

physical function by the physical performance component of the Short Form 36 found that transplant candidates that rated their physical function poorly had increased rates of posttransplant hospitalization and mortality (46), especially in people over age 55 yr.

Objective tests of physical performance have been proposed as "vital signs" that may help screen older adults for risk of falls, deconditioning, hospitalization, or other major healthcare-related outcomes that affect independence and survival (47). Because exercise testing is not practical and may be too difficult for older patients to perform, we utilized a simple bedside measure of physical function, the SPPB. Although the Renal Failure patients in our study had significantly lower SBBP scores than the comparison groups, further examination of the time needed to perform the 4-m walk and chair-rise tests (does not apply to the balance test because it cannot be converted to a continuous variable) showed that the four groups had similar sit-to-stand times; therefore, we conclude that the repeated chair-stand time may not be the optimal test of physical function in older, more impaired patients with renal failure. Because there is a wide spectrum of physical function and we aim to capture the early stages of disability when an intervention may be helpful, we believe that of the three subtests, walking speed may better differentiate the stages of disability in the older ESRD patient. The finding that Renal Failure patients scored poorly on the balance test was unexpected; the significance of this finding is unclear and requires further study.

Other studies of older adults utilizing the SPPB have also shown that of the three individual components, it appears that the gait speed gathered from the short walk time may be the most clinically useful to assess an older individual's current and future health (48). Gait speed is felt to be an overall predictor of health status because it integrates cardiopulmonary, musculoskeletal, and neurologic systems and is increasingly used across disciplines in clinical studies of various patient populations (47). A gait speed of 1 m/s has been identified and validated as a clinically meaningful cutpoint; individuals with repeated values below 1 m/s are at high risk of persistent severe lower extremity limitations, death, and hospitalization (48).

The limitations of this study include the single-center nature of the study; the voluntary participation; and the lack of an assessment of current levels of physical activity, repeated measures across time, and long-term outcomes data. However, describing the baseline function of older renal transplant can-

didates provides important groundwork for developing and testing interventions, because low physical functioning can usually be improved with physical conditioning programs, even in older dialysis patients and renal transplant recipients (13,49). This study adds to the knowledge base supporting the recommendation that physical activity be incorporated both before and after transplantation to maintain function and prevent disability.

Conclusions

The age group over 60 yr is rapidly increasing on the national kidney transplant waiting list, yet little attention is being given to the unique aspects of the pretransplant evaluation of older candidates. Decreased mobility is associated with decreased quality of life in older adults and increased dependence on others for care. Our study suggests that older renal transplant candidates should be regarded as high risk for physical disability. Performance measures take less than 5 min to perform and require little training; therefore, they can easily be incorporated into the pretransplant evaluation. However, the ability of objective and subjective measures of physical function to predict outcomes in older transplant candidates needs to be examined in longitudinal studies. With the increased demand for transplantation, the expected increase in waiting times, and the negative effect of prolonged time spent on dialysis, we feel that it is vital to develop and refine tools that will aid clinicians in both screening for disability and identifying which patients will benefit from the survival advantage of renal transplantation.

Disclosures

None.

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