Kidney International, Vol. 60 (2001), pp. 1586–1591

Determinants of physical performance in ambulatory patients on hemodialysis

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Background. Physical performance measures, particularly gait speed, have been useful as predictors of loss of independence, institutionalization, and mortality in older nonuremic individuals. Gait speed has not been evaluated as a predictor of these important outcomes in patients on hemodialysis, nor have the determinants of gait speed in the dialysis population been studied.

Methods. We performed a cross-sectional analysis to determine whether demographic, clinical, or nutritional status variables were related to physical performance in a group of 46 hemodialysis patients treated at three University of California San Francisco-affiliated dialysis units. Three physical performance measures were examined, including gait speed, time to climb stairs, and time to rise from a chair five times in succession. Forward stepwise linear-regression analysis was performed with each physical performance measure as the dependent variable and the following candidate predictor variables: age, gender, body mass index, dialysis vintage, Kt/V, albumin, blood urea nitrogen, creatinine, hematocrit, lean body mass, phase angle, ferritin, and the following comorbidities: hypertension, diabetes mellitus, coronary artery disease, peripheral vascular disease, and cerebrovascular disease.

Results. Subjects included 31 men and 15 women aged 22 to 87 years (mean ± SD, 52 ± 17). The mean gait speed for the group was 113.1 ± 34.5 cm/s (low compared with norms established for persons of similar age). Results of multivariable regression showed that age, albumin, and Kt/V were important determinants of gait speed in this population. Overall, the model explained 52% of the variability in gait speed ($r = 0.72$, $P < 0.0001$). Qualitatively similar results were obtained using stair-climbing time or chair-rising time as the dependent variables, except that comorbidity was more important than age for stair climbing. The addition of physical activity level to the models did not eliminate the associations of albumin or Kt/V with physical performance.

Conclusions. Physical performance is significantly impaired in ambulatory hemodialysis patients and is related to age, serum albumin, and dialysis dose. Prospective studies are needed to determine whether modification of dialysis dose or nutritional interventions can improve physical performance in patients on hemodialysis.

Key words: chronic renal failure, gait speed, serum albumin, dialysis dose, nutrition and dialysis, physical function.

Received for publication November 7, 2000
and in revised form March 27, 2001
Accepted for publication April 29, 2001

Limitations in physical functioning are a major problem for patients on hemodialysis. Two studies have assessed the magnitude and scope of the problem in large groups of hemodialysis patients using Karnofsky scores as a measure of physical functioning [1, 2]. Although one study was performed prior to the use of erythropoietin [2] and the other describes a population in which 87% of the patients were treated with erythropoietin [1], the results of these studies were similar. Twenty-four to 36% of hemodialysis patients were unable to perform routine living chores without assistance [1, 2]. Other studies have evaluated the impact of physical functioning on quality of life [3] and mortality [4] and have shown that poor physical functioning is associated with low quality of life and reduced survival.

There has been debate about whether the poor physical functioning observed in this group is due to uremia or whether it is secondary to other conditions that often accompany uremia, such as inactivity and deconditioning, advanced age, malnutrition, or comorbid illness [5]. However, few attempts have been made to determine the factors associated with poor physical functioning in this group. In addition, studies have relied heavily on questionnaires of physical functioning rather than objective assessment of physical functioning [1–4]. In the current investigation, three physical performance tasks were measured, including gait speed, time required to climb a flight of stairs, and time required to stand repeatedly from a chair without assistance. These performance tasks were chosen because they are necessary for the performance of activities of daily living [6, 7], they can be performed by the majority of dialysis patients, and have been associated with morbidity and mortality in other populations [8, 9]. Using these objective measures of physical functioning, the goal of this study was to determine which factors were associated with physical functioning in patients on hemodialysis.

METHODS

Study subjects

Forty-six men and women undergoing hemodialysis three times per week at the outpatient dialysis units at San Francisco General Hospital, the University of California San Francisco-Mount Zion Medical Center, and the San Francisco VA Medical Center participated in the study. Exclusion criteria included assisted living conditions and inability to ambulate, but patients were not excluded if they required assistive devices for ambulation. All subjects gave written informed consent for participation, and the study protocol was approved by the appropriate committees on human research. Results of the physical performance tests for a subset of these subjects were reported previously [10].

Measurements

Physical performance. Physical performance was assessed directly by timing of walking, stair-climbing, and rising from a chair, three tasks that are necessary for performance of activities of daily living (ADLs). Specifically, subjects were timed while walking 50 feet at their usual pace, while climbing a staircase (12 steps, each 7 inches tall) at their usual pace, and while standing from sitting in a chair five times without the use of their arms as rapidly as possible. For each measure, two trials were performed, and the faster of the two was recorded to the nearest 10th of a second. Both trials were completed during the same visit on a nondialysis day within 24 hours of the last dialysis treatment. Gait speed in centimeters per second was the primary measure derived from the walking test. Stair-climbing and chair-standing tests were recorded as time required to complete the test.

Other measurements. Hemodialysis patients underwent evaluation in the General Clinical Research Center at San Francisco General Hospital on a nondialysis day not more than 24 hours after a dialysis session. Evaluation included review of recent (within four weeks) blood tests including predialysis and postdialysis blood urea nitrogen (BUN) and calculated single-pool Kt/V, creatinine, albumin, ferritin, and hematocrit. Albumin was measured by bromocresol green except for six subjects whose values were corrected [11]. Medical history was reviewed for the presence or absence of hypertension, coronary artery disease, diabetes, peripheral vascular disease, and cerebrovascular disease. A simple additive score was given with no adjustment for severity of disease. In addition, patients underwent body composition testing using single-frequency bioelectrical impedance analysis (BIA; RJL Systems, Clinton Twp., MI, USA) and dual-energy x-ray absorptiometry (DXA; Lunar, Madison, WI, USA). Phase angle was calculated from BIA data as the arctangent of the ratio of resistance to reactance multiplied by a constant to convert radians to degrees. Thirty-nine of the subjects underwent measurement of physical activity over a seven-day period using a three-dimensional accelerometer (Tritrac R3D; Professional Products, Madison, WI, USA) as previously described [12].

Data analysis

Group data are presented as mean ± SD unless otherwise noted. Associations among demographic and dialysis-associated or nutritional status indices and physical performance measures were evaluated using Pearson product-moment correlation analysis and forward stepwise linear regression analysis. Candidate predictor variables included age, gender, body mass index, dialysis vintage, Kt/V, albumin, BUN, creatinine, hematocrit, lean body mass, phase angle, ferritin, and the number of the following comorbidities: hypertension, diabetes mellitus, coronary artery disease, peripheral vascular disease, and cerebrovascular disease. A simple additive comorbidity score was calculated based on the presence or absence of each condition. To determine whether the effects of nutritional and dialysis-related variables were independent of the known relationship between physical activity and physical performance, separate analyses were performed using physical activity level as a predictor of physical performance, adjusting only for the variables that entered the forward stepwise regression models. Statistical significance for all analyses was established when a two-tailed P value was less than 0.05. All analyses were performed using STATISTICA software (StatSoft Inc., Tulsa, OK, USA).

RESULTS

Demographic and clinical characteristics of study subjects are reported in Table 1, along with the results of physical performance testing. The mean age was 52 years and ranged from 22 to 87 years. All subjects were dialyzed using high-flux polysulfone dialyzers (Fresenius Inc., Bad Homburg, Germany). The nutritional and dialysis-related parameters of this group show satisfactory dialysis dosing and nutritional status in this group. The average gait speed was 113.1 ± 34.5 cm/s, which is low compared with healthy subjects with a similar age range (139.3 ± 4.7) [13], and the average time to rise from a chair five times was 16.6 ± 9.5 seconds, also poor compared with healthy subjects of similar age or even for older groups (13.2 seconds for men age 71 to 79) [8]. Two subjects were unable to perform the stair-climbing test. The average stair-climbing time for the remaining

Table 1. Characteristics of study subjects

Characteristic	Mean ± SD, $N = 46$
Age *years*	52 ± 17
Gender *M/F*	31/15
Weight *kg*	70.6 ± 13.9
Body mass index *kg/m*^{2}	25.5 ± 4.6
Lean body mass *kg*	48.4 ± 11.4
Phase angle *degrees*	5.29 ± 1.53
Kt/V	1.3 ± 0.3
Dialysis vintage *years*	2.3 ± 2.3
Predialysis BUN *mg/dL*	66.7 ± 14.3
Predialysis creatinine *mg/dL*	10.0 ± 3.7
nPCR *g/kg/day*	1.04 ± 0.22
Albumin *mg/dL*	4.0 ± 0.4
Hematocrit %	35.5 ± 4.5
Ferritin *μg/L*	690 ± 650
Number of comorbidities, *N* (%)	1.6 ± 1.0
Hypertension	42 (91)
Diabetes mellitus	16 (35)
Coronary artery disease	9 (20)
Peripheral vascular disease	3 (7)
Cerebrovascular disease	3 (7)
Gait speed *cm/s*	113.1 ± 34.5
Stair-climbing time *s*[a]	10.3 ± 7.7
Chair-rising time *s*	16.6 ± 9.5

Abbreviations are: BUN, blood urea nitrogen; nPCR, protein catabolic rate normalized to body weight.
[a] $N = 44$ because two subjects were unable to complete the stair-climbing task

Table 2. Univariate associations among predictor variables and physical performance measurements

	Gait speed *cm/s*		Stair-climbing time[a] *s*		Chair-rising time *s*	
Variable	r	*P* value	r	*P* value	r	*P* value
Age *years*	−0.63	<0.0001	0.41	0.006	0.51	0.0003
Phase angle *degrees*	0.58	<0.0001	−0.44	0.003	−0.40	0.006
Comorbidities	−0.53	0.0001	0.57	<0.0001	0.27	0.07
Albumin *g/dL*	0.44	0.002	−0.32	0.03	−0.43	0.003
Kt/V	0.11	0.45	−0.35	0.02	−0.23	0.13
Creatinine *mg/dL*	0.25	0.10	−0.31	0.05	−0.29	0.05

All others are $|r| < 0.20$, $P > 0.10$.
[a] $N = 44$ because two subjects were unable to complete the stair-climbing task

44 subjects was 10.3 ± 7.7 seconds. Each of the physical performance measures correlated with the others ($r = -0.79$ for gait speed and stair climbing, $r = -0.71$ for gait speed and chair rising, and $r = 0.59$ for stair climbing and chair rising, all $P < 0.0001$).

Univariate associations among predictor variables and physical performance are reported in Table 2. Performance declined with age for all measures. In addition, albumin and phase angle were significantly associated with all performance measures, with better performance associated with higher serum albumin concentrations and phase angles. The number of comorbid conditions was associated with worse performance as measured by gait speed and stair-climbing time, but not by rising from a chair. A higher Kt/V value was associated with a faster stair-climbing time, and higher serum creatinine concentration was associated with a faster stair-climbing and chair-rising time. No other candidate predictor variables were associated with any performance measure.

On multivariable analysis, only age, Kt/V, albumin concentration, and number of comorbidities were included in any of the predictive models (Table 3). Combinations involving only these variables explained 45 to 52% of the variability in performance. Kt/V and albumin were significant predictors of all performance measures, while age and number of comorbidities (correlated with each other, $r = 0.66$) canceled each other out in all models. The addition of physical activity level to the models generally weakened the effects of age and comorbidity, but did not affect the strength of the association between Kt/V and any performance measure (Table 4). The significance levels of the associations between albumin and physical performance were reduced slightly when activity was added to the models, but the qualitative relationships were essentially unchanged. The direct correlations between age ($r = -0.62$, $P < 0.0001$), comorbidities ($r = -0.45$, $P = 0.004$), and albumin ($r = 0.57$, $P = 0.0001$) and physical activity account for these findings. Kt/V was not correlated with physical activity ($r = 0.01$, $P = 0.96$). While addition of physical activity level to the gait speed model explained a greater degree of the variability in gait speed ($r^2 = 0.65$), physical activity did not significantly improve the models for stair climbing or rising from a chair.

DISCUSSION

As expected, age and comorbidity were important determinants of physical performance in patients on hemodialysis. In addition, higher serum albumin concentration and Kt/V were associated with better physical performance. Albumin has been proposed as a marker of nutritional status and of inflammation in this population and is strongly associated with mortality [14, 15] and physical activity [12]. Its association with physical performance suggests that nutritional status and/or inflammation are important determinants of physical performance. Albumin was a slightly less important predictor of physical performance when physical activity level was included in the model. This finding is consistent with a potential dual mechanism by which malnutrition and inflammation are associated with poor physical performance. It is possible that malnutrition and inflammation lead to low physical activity and thus to reduced physical fitness and poor physical performance. However, this pathway does not fully explain the association between albumin and physical performance. Inflammation may lead to muscle catabolism and ultimately muscle wasting; the latter may also impair physical performance. The lack of specificity for intracellular versus extracellular water determination by DXA may have limited our ability to show an associa-

Table 3. Results of multivariable regression analysis with physical performance measures as the outcome variables

	Gait speed *cm/s*		Stair-climbing time[a] *s*		Chair-rising time *s*	
Variable	Coefficient	*P* value	Coefficient	*P* value	Coefficient	*P* value
Age *years*	−1.3	<0.0001	—	>0.15	0.3	0.0002
Kt/V	31.1	0.02	−9.4	0.005	−11.9	0.003
Albumin *g/dL*	23.6	0.02	−4.5	0.07	−7.1	0.02
Comorbidities	—	>0.15	3.7	0.0002	—	>0.15
Intercept	44.6	—	34.4	—	44.8	—
r	Overall $r = 0.72$, $r^2 = 0.52$		Overall $r = 0.67$, $r^2 = 0.45$		Overall $r = 0.68$, $r^2 = 0.46$	

$P < 0.0001$ for all models.
[a] $N = 44$ because two subjects were unable to complete the stair-climbing task

Table 4. Results of multivariable regression analysis with physical performance measures as the outcome variables and physical activity level as an additional predictor

	Gait speed *cm/s*		Stair-climbing time[a] *s*		Chair-rising time *s*	
Variable	Coefficient	*P* value	Coefficient	*P* value	Coefficient	*P* value
Physical activity *arbitrary units*	0.00022	0.02	<0.00001	0.20	<0.00001	0.7
Age *years*	−0.66	0.02	—	—	0.22	0.03
Kt/V	27.9	0.03	−10.3	0.004	−12.7	0.005
Albumin *g/dL*	25.8	0.03	−5.2	0.11	−9.0	0.03
Comorbidities	—	—	2.4	0.03	—	—
Intercept	−10.6	—	43.2	—	58.4	—
r	Overall $r = 0.81$, $r^2 = 0.65$		Overall $r = 0.69$, $r^2 = 0.48$		Overall $r = 0.70$, $r^2 = 0.49$	
P	<0.0001		=0.0002		=0.0001	

[a] $N = 38$ because one subject was unable to complete the stair-climbing task

tion between lean (fat-free) body mass and physical performance.

A higher dose of dialysis, measured as single-pool Kt/V, was also associated with better physical performance. Adjustment for physical activity level did not reduce the strength of the association between Kt/V and physical performance. This finding suggests that poor physical functioning may be related to uremia per se in addition to the advanced age, comorbidity, and inactivity of the dialysis population. The concept of a uremic myopathy has been proposed by Diesel and others [16–19], and control of uremia may be important for optimal muscle function [20]. More importantly, the association of dialysis dose with physical functioning raises the possibility that provision of optimal dialysis may improve physical functioning. Measures of physical performance should be incorporated as outcomes in studies of the effects of increasing dialysis dose.

Gait speed over relatively short distances has been shown to correlate with exercise capacity in elderly individuals [21], and walking and stair-climbing time predicted V_{O_2peak} in a study involving dialysis subjects [22]. Data on the relationship between hematocrit and exercise capacity in the end-stage renal disease (ESRD) population are mixed. Significant improvements in functional status and exercise capacity have been reported after correction of anemia with erythropoietin [23–29]. On the other hand, Diesel et al reported that hematocrit was not correlated with V_{O_2peak} in anemic patients on dialysis with a mean hematocrit of 24% [30]. Instead, they showed that leg muscle strength was an important determinant of exercise capacity. In the current group of patients on dialysis, the average hematocrit was 35.5% (range 20 to 45%), and hematocrit was not an important predictor of physical performance. Thus, our results tend to corroborate Diesel's findings regarding the relationship between hematocrit and exercise capacity.

Based on Diesel's work and that of other investigators studying healthy, older subjects, muscle strength is likely to be an important predictor of physical performance [21, 31, 32]. Since we did not measure leg strength, this study provides no direct evidence about the relationship between muscle strength and physical performance. However, indirect evidence is available from the data regarding serum creatinine and phase angle. Muscle mass is an important determinant of serum creatinine and phase angle, and muscle strength is strongly related to muscle size. Therefore, the univariate relationships between serum creatinine and phase angle and physical performance test results suggest that muscle strength is important for performance of these activities. Serum creatinine and phase angle did not enter the multivariable models for any of the physical performance tests we studied. One reason for this may be collinearity between age and serum creatinine ($r = -0.45$, $P = 0.002$) and phase angle ($r = -0.69$, $P < 0.0001$). The decline in muscle mass that occurs with age may be an important reason that physical performance declines with age.

The quantitative assessment of physical performance and the use of multivariable regression analysis in this study allowed simultaneous assessment of the independent contribution of several potential predictor factors. However, the cross-sectional nature of the study and its relatively small size are limitations that preclude the assessment of the association of physical functioning with morbidity or mortality. Larger, prospective studies are needed to determine whether objective measures of physical performance are predictive of important outcomes such as mortality, hospitalization, or institutionalization in the dialysis population. It also will be useful to compare the predictive power of objective measures of physical functioning with that of self-report. Each of these methods of assessment of physical functioning has unique advantages and disadvantages. Measures that rely on self-reporting often cannot be completed by patients with cognitive deficits [33]. On the other hand, physical performance tests only can be used to evaluate patients who can perform the tests. Thus, the current study was limited to subjects capable of walking 50 feet, and our results do not apply to nonambulatory dialysis patients. Quantitative measures of performance might be expected to be more reliable than self-reported functioning and thus might be more predictive of major outcomes or more sensitive to changes over time [33].

Our results should be of value in the debate over whether poor physical functioning in patients with ESRD is related to uremia per se or to other concomitant factors such as advanced age and comorbid illnesses. While age and comorbid illnesses are important, we have demonstrated that some dialysis-related factors are also important contributors. Further studies are needed to determine whether physical performance is associated with mortality in this group and to determine whether interventions designed to increase delivered dialysis dose, improve nutritional status, or reduce inflammation can improve physical performance.

ACKNOWLEDGMENTS

This work was supported by a grant from the National Kidney Foundation of Northern California. The study was conducted in the General Clinical Research Center at San Francisco General Hospital (RR-00083).

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