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Association of 1,25-Dihydroxyvitamin D Levels With Physical Performance and Thigh Muscle Cross-sectional Area in Chronic Kidney Disease Stage 3 and 4

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Abstract

Background—Declines in 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) levels and physical functioning follow the course of chronic kidney disease (CKD). Although the molecular actions of vitamin D in skeletal muscle are well known, and muscle weakness and atrophy are observed in vitamin D–deficient states, there is little information regarding vitamin D and muscle function and size in CKD.

Objective—To examine associations of vitamin D with physical performance (PF) and muscle size.

Design—Cross-sectional.

Setting—CKD clinic.

Subjects—Twenty-six patients (61 ± 13 years, 92% men) with CKD stage 3 or 4.

Main Outcome Measures—Gait speed, 6-minute walk, sit-to-stand time, 1-legged balance, and thigh muscle cross-sectional area (MCSA), measured by magnetic resonance imaging (MRI).

Results—Overall, 73% were 25-hydroxyvitamin D (25(OH)D) deficient (n = 10) or insufficient (n = 9) (Kidney Disease Outcomes Quality Initiative guidelines). 25(OH)D level was associated with normal gait speed only ($r = 0.41$, $P = .04$). Normal and fast gait speed, the distance walked in 6 minutes, and sit-to-stand time were best explained by $1,25(OH)_2D$ and body mass index ($P < .05$ for all) and 1-legged stand by $1,25(OH)_2D$ ($r = 0.40$, $P < .05$) only. There were no associations of age, estimated glomerular filtration rate (eGFR), intact parathyroid hormone (iPTH), or albumin with any PF measures. MCSA was associated with eGFR ($r = 0.54$, $P < .01$) only. Variance in MCSA was best explained by a model containing $1,25(OH)_2D$, plasma Ca^{2+}, and daily physical

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activity (by accelerometry) ($P < .05$ for all). Once these variables were in the model, there was no contribution of eGFR.

Conclusion—These results suggest that $1,25(OH)_2D$ is a determinant of PF and muscle size in patients with stage 3 and 4 CKD.

Circulating levels of 1,25-dihydroxyvitamin D ($1,25(OH)_2D$), the active form of vitamin D, begin to decline early in the course of CKD[1] owing to the decline in proximal tubular production of 1α-hydroxylase, resulting in the development of secondary hyperparathyroidism (SHPT). Following a similar progression, levels of physical activity and physical functioning decline as chronic kidney disease (CKD) progresses to end-stage renal disease (ESRD),[2–5] by which time, significant muscle weakness[6] and muscle atrophy[7] are common. Impaired physical functioning eventually leads to disability, loss of independence, and diminished quality of life,[8] all of which are associated with increased morbidity and mortality in the ESRD population.[9–11] Causes of this decline are multifactorial, but declining availability of the active form of vitamin D may be a factor.

Vitamin D plays an essential role in muscle growth and development and in regulating muscle contractility through the transport of Ca^{2+} and phosphate. Nuclear binding of $1,25(OH)_2D$ in muscle regulates both myoblast proliferation and myotube differentiation, as well as de novo synthesis of proteins essential to muscle function.[12] While the effects of 25-hydroxyvitamin D (25(OH)D) deficiency on muscle function have been widely studied,[13–15] more recently, $1,25(OH)_2D$ levels are reported to correlate with physical performance,[16–18] strength[19] and falls[20] in the elderly, a population with declining kidney function.

The current focus of vitamin D treatment for the prevention of SHPT is on its effects on bone metabolism and tissue calcification, as outlined in the current Kidney Disease Quality Outcomes initiative (KDOQI) guidelines,[21] but there is little information or guidance about other effects. The purpose of this study was to investigate the extent to which vitamin D levels, specifically those of $1,25(OH)_2D$, are related to physical functioning and to muscle size by magnetic resonance imaging (MRI) among patients with CKD stages 3 and 4. We hypothesized that higher levels of the active form of vitamin D, $1,25(OH)_2D$, would be associated with better physical performance test scores and with greater thigh muscle cross-sectional area (MCSA).

Methods

Subjects and Study Design

Patients with stage 3 and 4 CKD were recruited from University of California, San Francisco-affiliated renal clinics, including the San Francisco VA Medical Center (SFVAMC) and San Francisco General Hospital, to participate in an ongoing, randomized, controlled, double-blind trial investigating the effects of paricalcitol on muscle function. Patients were eligible to participate in the study if they were older than 18 years, had CKD with an estimated glomerular filtration rate (GFR) (by Modification of Diet in Renal Disease [MDRD] formula)[22] between 15 and 60 mL/minute/1.75 m^2, and were not currently receiving any active vitamin D metabolites. Additional requirements for eligibility included intact parathyroid hormone (iPTH) level >75 pg/dL, corrected total calcium serum level

<10.0 mg/dL, and phosphorous level <4.6 mg/dL. Potential subjects were excluded if they had iPTH levels >300 pg/mL, a spot urinary calcium to creatinine ratio >0.2, had taken glucocorticoids for >14 days within the past 6 months, had any musculoskeletal condition that prevented muscle strength or functional testing, were unable to safely undergo MRI testing, or were unable to give informed consent.

All subjects gave written informed consent to participate in the study. The study was approved by the Committee on Human Research at the University of California, San Francisco, and the Research and Development Committee of the SFVAMC.

Demographic, Anthropometric, and Laboratory Data

Demographic data, including age, gender, race, and comorbid conditions were obtained by subject interview and review of medical records. GFR was estimated using the MDRD equation[22] to classify patients by stage of CKD according to the KDOQI guidelines.[21] Clinical laboratory tests were performed by standard clinical laboratory methods in the SFVAMC clinical laboratory.

Intact Parathyroid Hormone—iPTH was measured by automated chemiluminescence immunoassay using the Nichols Advantage Specialty System (Nichols Institute Diagnostics, San Clemente, CA).

25-Hydroxyvitamin D—Levels of 25(OH)D were measured in serum using the Nichols Advantage 25(OH)D assay on the Nichols Advantage Specialty System (Nichols Institute Diagnostics, San Clemente, CA). Specificity for 25(OH) is 100%; cross-reactivity with $1,25(OH)_2D$ is 1.1% . The sensitivity of this assay is ≤4 ng/mL.

1,25-Dihydroxyvitamin D—Levels of $1,25(OH)_2D$ were measured in serum by radioimmunoassay. Prior to assay, samples were delipidated and the $1,25(OH)_2D$ was separated from interfering metabolites by immunoextraction. $1,25(OH)_2D$ was quantitated by radioimmunoassay using a highly specific polyclonal antibody and ^{125}I labeled $1,25(OH)_2D$. Specificity for $1,25(OH)_2D$ was 100%. The sensitivity of the assay was 2.1 pg/mL.

Physical Performance Tests

Subjects performed the following standardized physical performance measures previously used in the CKD and ESRD populations.[2,3,23–25]

Gait Speed—Subjects were asked to walk a distance of 20 feet at a comfortable walking pace and again at their maximal walking speed. Six feet were added on either side of the 20-feet course to allow for acceleration and deceleration. The trials were timed within 100th of a second. Two trials were performed at each level, and the best time was recorded.

The 6-Minute Walk—Subjects were asked to walk back and forth along a 100-feet corridor, covering as much distance as possible during the 6-minute time period. Subjects were allowed to rest as necessary, although the clock was not stopped.[26]

Sit-to-Stand Time—Subjects were asked to sit in a chair of standard height, and then asked to stand up completely and sit back down 10 times with arms crossed over the chest. The time to complete 5 and 10 repetitions was recorded.

Static Balance—Subjects were asked to stand on 1 leg for as long as they could for up to 30 seconds. The score was recorded as the time in seconds until the subject needed to touch the examiner, put the other foot down, or move the foot on the floor to maintain balance.[27]

Physical Activity Level—Physical activity levels were measured using a 3-dimensional accelerometer (RT3, Stayhealthy Inc., Monrovia, CA). Each subject wore the device mounted at the waistband for 7 consecutive days.[28,29] Acceleration in all 3 dimensions was acquired and averaged over 1 minute. The data were recorded as the vector magnitude for all 3 dimensions, expressed in arbitrary units, and averaged over the 7 days as the daily activity level.

Muscle Strength

Isokinetic Strength—Strength of the knee extensor was assessed by isokinetic dynamometry, using the Cybex extremity testing unit, a computerized dynamometer (Cybex/HUMAC 6000, Computer Sports Medicine Inc., Stoughton, MA).[30] Isokinetic strength was tested at joint angle velocities of 90 and 180°/second. Subjects performed 5 repetitions at 90°/second and 30 repetitions at 180°/second, and the peak torque was recorded at each velocity.

Isometric Strength—Isometric strength or maximal voluntary contraction (MVC) of the knee extensor muscle group was measured at 60° extension using the isometric testing function of the Cybex extremity testing unit. The best of 5 trials was recorded.

Muscle Size

Knee extensors (quadriceps) muscle size was measured using MRI.[31] Images of the entire thigh were acquired in a 1.5T Siemens Avanto MRI scanner with Total Imaging Matrix technology (Siemens Medical Solutions USA Inc., Malvern, PA). After obtaining a scout image, a series of T-1 weighted axial slices of the thigh (8 mm thickness, 2 interleaved acquisitions) were obtained from the iliac crest to the patella. The echo and repetition times were selected to optimize the signal intensity contrast between muscle and fat. The single slice with the largest quadriceps muscle area and the 2 adjacent slices were selected for analysis. The quadriceps muscle group was chosen for this representative measurement of muscle size because of its functional importance and to reduce the measurement variability by limiting the analysis to a large, well-defined muscle group.

A customized software program written in IDL (Research Systems Inc., Boulder, CO) was used to quantify contractile and noncontractile components of the knee extensor muscle as previously described.[31]

Statistical Analyses

Results are expressed as the mean ± standard deviation, with the exception of non-normally distributed data, which are expressed as the median, 25th and 75th percentile. Pearson moment correlation for normally distributed data, or Spearman's rho for non-normally distributed data, was used to examine associations among 25(OH)D, $1,25(OH)_2D$, clinical laboratory results, physical performance and strength outcomes, physical activity level, and thigh muscle size.

Least squares multivariable regression analysis was used to determine the extent to which serum levels of either form of vitamin D were associated with indicators of physical performance and strength outcomes, as well as thigh muscle size, after adjusting for potential covariates. Potential covariates were considered based on the univariate associations, literature, and on our a priori hypotheses. In the models for physical performance measures, 25(OH)D or $1,25(OH)_2D$ levels were entered first, and then based on previous studies,[17,18,24] age, body mass index (BMI), estimated glomerular filtration rate (eGFR), and physical activity were tested in each model. Similarly, for balance and strength measures, 25(OH)D or $1,25(OH)_2D$ was added, and then covariates considered were age, eGFR, and iPTH.[18,19] For knee-extensor MCSA, potential covariates considered included age, eGFR, physical activity, and albumin.[31,32] In addition, plasma calcium was considered as a potential covariate for MCSA based on the critical role of Ca^{2+} in the regulation of gene expression and protein transcriptional pathways in skeletal muscle.[33] Finally, to investigate whether the effect of $1,25(OH)_2D$ varied by CKD stage, stage and an interaction term between stage 4 and $1,25(OH)_2D$ were added to each model. Results of all analyses were considered statistically significant if the 2-tailed *P*-value was <.05. Analyses were performed using SPSS 12.0.2 (SPSS Inc., Chicago, IL).

Results

Subject Characteristics

Baseline data from the first 26 subjects are presented here (Table 1). The average age of the group was 61 ± 13 years, with a range from 27 to 87 years. The group was equally divided by stage of CKD, with 13 patients at stage 3 and 13 patients at stage 4. The eGFR was inversely associated with plasma phosphorous levels ($r = -0.54$, $P = .005$) and iPTH ($r = -0.40$, $P = .04$) but not with any other clinical measure. With respect to muscle function outcomes, the eGFR was associated with quadriceps MCSA ($r = 0.54$, $P = .006$), isometric knee-extensor strength ($r = 0.49$, $P = .01$), and daily physical activity ($r = 0.43$, $P = .05$).

Vitamin D Levels

Serum vitamin D levels are shown in Table 1. Seventy-three percent of the subjects were either 25(OH)D deficient (<15 ng/mL; n = 10) or in-sufficient (16 to 30 ng/mL; n = 9) according to KDOQI guidelines.[34] The levels of $1,25(OH)_2D$ were weakly associated with those of 25(OH)D ($r = 0.38$, $P = .05$).

Physical Performance, Strength, and Physical Activity Measures

The results of the physical performance tests are shown in Table 2. Although some individuals performed at, or slightly above, age-predicted levels, the majority of subjects had test scores lower than predicted values. As a group, subjects had a comfortable gait speed that was 90% ± 18% of age-predicted values, and a fast gait speed was at a somewhat lower percentage, 84% ± 24%, of age-predicted values.[35] The group achieved 80% ± 19% of the age-predicted distance for the 6-minute walk,[36] and 72% ± 24% of the age-predicted time to rise from a chair and sit back down 10 times.[37] BMI was strongly associated with the 6-minute walk distance ($r = -0.63$, $P = .001$), comfortable gait speed, ($r = -0.60$, $P = .001$), fast gait speed ($r = -0.66$, $P \leq .001$), and sit-to-stand time, ($r = 0.47$, $P = .02$). Age was weakly associated with the 1-legged balance times ($r = -0.37$, $P = .07$), but not with any other physical performance test, strength, or daily physical activity.

Thigh MCSA

MRI scans were obtained on 24 of the 26 subjects. In 1 case, the subject was unable to undergo the MRI procedure because of body size, and in the other, the image was unavailable for analysis. For the 24 subjects, the mean total cross-sectional area (CSA) of the quadriceps muscle group was 70.2 ± 12.7 cm^2 (range, 51.2 to 100.6). The contractile tissue CSA measured 63.8 ± 12.2 cm^2, accounting for 91% ± 6% of the total quadriceps MCSA. The contractile tissue area of the quadriceps muscle was associated with eGFR ($r = 0.51$, $P = .006$) and with daily physical activity level ($r = 0.42$, $P = .06$). As expected, the contractile area of the quadriceps muscle was also significantly associated with the knee extensor isokinetic (90°/second, $r = 0.53$, $P = .01$; 180°/second, $r = 0.49$, $P = .02$) and isometric ($r = 0.68$, $P < .001$) strength measures. There were no associations of the quadriceps muscle area with the more functional, or multijoint, performance measures such as sit-to-stand time, balance, or walking tests.

Associations of Vitamin D With Physical Performance Tests, Strength, and Thigh Muscle Size

The univariate associations of 25(OH)D and $1,25(OH)_2D$ with physical performance and strength measures are shown in Table 3. 25(OH) D was only associated with comfortable gait speed, whereas $1,25(OH)_2D$ was associated with comfortable gait speed, 1-legged balance, sit-to-stand time and isokinetic knee extensor strength at 180°/second.

In multivariable analysis, $1,25(OH)_2D$ remained significantly associated with gait speed, 6-minute walk, and sit-to-stand time even after adjustment for BMI (Table 4). Neither, age, nor eGFR, nor physical activity contributed significantly, and there were no significant effects of CKD stage, or interaction between CKD stage 4 and $1,25(OH)_2D$ level, in any of the models.

$1,25(OH)_2D$ was the only significant predictor in models for the isokinetic and isometric strength measures. There were no significant effects of CKD stage, or interaction between CKD stage 4 and $1,25(OH)_2D$ level, in either of the isokinetic strength models. However, although there was no effect of CKD stage in the model for isometric strength, there was a significant interaction between CKD stage 4 and $1,25(OH)_2D$, such that the relationship

with $1,25(OH)_2D$ was less pronounced among patients with stage 4 CKD than among those with stage 3.

Multivariable models were constructed to examine correlates of muscle size. $1,25(OH)_2D$ and covariates thought to play a role in either muscle size, or vitamin D action in muscle, including age, eGFR, 25(OH)D, plasma calcium level, and daily physical activity were tested. There was no effect of 25(OH)D or age, or interaction between CKD stage and $1,25(OH)_2D$ in any model. There was a significant association of $1,25(OH)_2D$ ($P = .04$) with MCSA after controlling for plasma calcium ($P = .03$), and both covariates became more significant once daily physical activity was entered into the model ($P = .04$) (Table 5), which together explained 54% of the variability in MCSA. Estimated GFR was not associated with MCSA independent of $1,25(OH)_2D$, Ca, and physical activity despite the strong univariate association with of eGFR with MCSA.

Discussion

The results of this study show for the first time, the association of $1,25(OH)_2D$ levels with physical performance and muscle size in patients with stage 3 and 4 CKD. Like others,[38–40] we observed a relatively high prevalence of 25(OH)D deficiency and insufficiency in this group of CKD patients, along with lower levels of $1,25(OH)_2D$.[41,42] The weak association of 25(OH) vitamin D levels with those of $1,25(OH)_2$ and the high prevalence of 25(OH)D insufficiency suggest that in addition to declining 1α-hydroxylase production, reduced substrate availability also could have contributed to lower $1,25(OH)_2D$ levels.[43]

In healthy populations with normal kidney function, 25(OH)D levels may be a reasonable reflection of adequate $1,25(OH)_2D$ levels, and thus be a surrogate measure, but in the setting of CKD, 25(OH)D may no longer be a reliable surrogate for the actions of $1,25(OH)_2D$. Although the association of 25(OH)D deficiency with various aspects of muscle function is well documented in the general population, recent systematic reviews and meta-analyses find the evidence inconclusive.[13–15] There are also inconsistencies in the few studies that have investigated vitamin D and muscle function in the CKD population.[43–45] More consistent have been studies that have specifically investigated associations of $1,25(OH)_2D$ levels with physical performance,[16–18] strength,[19] and falls[20] in the elderly. We found that $1,25(OH)_2D$ levels and BMI best explained the variance in normal and fast gait speeds, distance covered in the 6-minute walk, and chair stand time; however, unlike others,[17] we found no effect of age or eGFR. It may be that the ranges of eGFR and age in this study population were too narrow to discern an association. However, even when CKD was considered by stage, there was no association with these outcomes independent of BMI and $1,25(OH)_2D$.

Postural balance is a complex capability involving the interplay among muscle strength, sensory systems (proprioceptive, visual, and vestibular), and the central nervous system. In addition to their presence in skeletal muscle, $1,25(OH)_2$ vitamin D receptors have been identified in the brain, spinal cord, and motor neurons of rats,[46] and there is evidence that vitamin D has neuroactive and neuroprotective effects,[47] all of which could help explain associations reported between vitamin D, body sway,[48] and neuromuscular function of older

individuals who fall,[49] as well as with standing balance, as was observed in the present study.

We found that both laboratory-based and functional strength measures were associated with serum levels of $1,25(OH)_2D$ in this group of CKD patients. Specifically, $1,25(OH)_2D$ levels were associated with isokinetic strength at the faster joint angular velocity. Similarly, Bischoff et al.[19] found that leg extension power (LEP), measured in 319 ambulatory elderly men and women (mean age, 75 years) was associated with serum $1,25(OH)_2D$ levels, independent of age, gender, and BMI. Although the LEP measure is somewhat different from isokinetic strength, LEP has a very high correlation with isokinetic strength measured at high angular velocity.[50] Type II, fast-twitch muscle fibers play a greater role in power development at higher joint angular velocities,[51–53] and specific atrophy of type II fibers is observed in vitamin D–deficient states.[54] Similarly, rising from a chair, particularly at a fast pace, requires muscle power generated in large part by type II muscle fibers. We found that sit-to-stand times were associated with the levels of serum $1,25(OH)_2D$ and BMI, but not with 25(OH)D levels. Along the same lines, Gallagher[16] showed a positive effect of calcitriol on the age-associated decline in sit-to-stand time over a 3-year period in a group of elderly women who were not 25(OH)D deficient.

There is less information regarding the association of vitamin D with physical performance and strength in CKD patients, and 2 recent studies have reported somewhat disparate results. Similar to our findings, Heaf et al. found no association of 25(OH)D with the sit-to-stand test in 21 CKD stage 3 to 5 patients of similar age in whom both 25(OH)D levels (44.6 ±19 vs. 53.3 ± 25.9 nmol/L) and $1,25(OH)_2D$ levels (52.7 ± 24 vs. 63.8 ± 39.9 pmol/L) were somewhat lower than those in the present study, but unlike the present study, no association with $1,25(OH)_2D$ levels was observed.[43] In contrast, Boudville et al. found that levels of 25(OH)D, but not of $1,25(OH)_2D$, were associated with isometric knee extension strength in 25 CKD-5D patients with levels of 25(OH)D that were similar to those in the present study, but with much lower $1,25(OH)_2D$ levels.[44] Reasons for the disparity in results across these studies, including our own, are unclear and may lie in the complexities of the vitamin D endocrine/intracrine system in which the availability and actions of both 25(OH)D and $1,25(OH)_2D$ in various cells and tissues are critical, but may be perturbed in various chronic disease populations such as CKD. Nevertheless, the ambiguity is similar to that reported in the recent systematic review and meta-analyses of the associations and effects of vitamin D on muscle strength[14] and physical performance[13] in the general population.

In addition to the association of $1,25(OH)_2D$ with physical performance and strength, we also report that quadriceps MCSA was associated with levels of $1,25(OH)_2D$ in conjunction with plasma calcium levels and physical activity in this group of stage 3 and 4 CKD patients. These results are in agreement with our previous study showing that muscle strength and CSA were associated with treatment with active vitamin D derivatives among patients on hemodialysis.[45] In addition to its critical role in regulating the contractile properties of skeletal muscle, $1,25(OH)_2D$ also plays an essential role in the regulation of muscle size. Binding of $1,25(OH)_2D$ to its nuclear receptor in skeletal muscle regulates de novo protein synthesis and stimulates muscle cell proliferation and growth.[54] Patients with ESRD have significantly smaller muscle fiber CSA, particularly of type II muscle fibers.[7,55,56] Although

some suggest that 25(OH)D may have independent effects in skeletal muscle,[57] we found no association between 25(OH)D and MCSA.

Our finding that the association of $1,25(OH)_2D$ levels with quadriceps MCSA was dependent on the presence of plasma calcium and physical activity level in the regression model is an interesting outcome. The nonsignificant inverse association that we observed between plasma calcium levels and physical activity level could be explained by the observation that low activity states result in the loss of muscle cell electrolytes into the circulation, decreased energy production, and reduced cell mass.[58,59] Physical activity levels were low in this group of CKD patients compared to levels of sedentary healthy individuals in a similar age range measured by our group.[4] Zorbas et al. found that when the level of physical activity of healthy young men was restricted to approximately the normal routine of sedentary persons in a carefully controlled study in which walking was limited to 1.3 ± 0.1 km/day, plasma calcium levels incrementally increased over a period of 1 year, matched by an incremental decrease in intracellular calcium of skeletal muscle cells.[59] This phenomenon is attributed to muscle cell damage induced by extracellular fluid shifts, the disruption of mitochondrial oxidative metabolism, and deficits in ATP production resulting in the loss of electrolytes into plasma.[58,59]

There are several limitations of this study. First, the cross-sectional nature of the associations of $1,25(OH)_2D$ with physical performance and muscle size do not allow us to infer a causal relationship. Secondly, the study is small with few women and includes patients who are likely healthier than unselected patients with stage 3 and 4 CKD. Thus, it is possible that the findings are not generalizable to the stage 3 and 4 CKD population as a whole. Further, we have no reason to expect that these associations would be specific to healthier patients.

We believe that the physiological evidence for the critical functions of $1,25(OH)_2D$ in skeletal muscle and the results of prior cross-sectional and interventional trials involving $1,25(OH)_2D$ support the findings presented here; that declining levels of $1,25(OH)_2D$ observed in stage 3 and 4 CKD appear to play a role in the deficits in physical performance and thigh muscle size. Whether or not very small doses of active vitamin D at somewhat earlier stages of SHPT than are currently recommended can slow the decline in muscle function without deleterious effects on CKD mineral bone disease (MBD) remains to be seen once the ongoing randomized trial of the effects of paricalcitol is complete.

Practical Applications

In this cohort of patients with stage 3 and 4 CKD, patients with lower eGFR were less physically active and had smaller and weaker quadriceps muscles. Physical performance measures were more closely related to $1,25(OH)_2D$ levels than to other possible correlates or mediators, and muscle size was related to $1,25(OH)_2D$ as well as to physical activity and serum calcium. These findings lay the foundation for interventions to determine whether repletion of $1,25(OH)_2D$ could increase muscle size, strength, or function.

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Table 1

Subject and Clinical Characteristics

Characteristic	Mean ± SD, n = 26
Age, years	61 ± 13
Gender M/F	24/2
Race/ethnicity n (%)	
African American	10 (38%)
Asian or Pacific Islander	3 (12%)
Caucasian	10 (38%)
Hispanic	2 (8%)
Native American	1 (4%)
Number of comorbid conditions n (%)	
Hypertension	25 (96%)
Diabetes mellitus	15 (58%)
Coronary artery disease	12 (46%)
Body mass index, kg/m^2	29.9 ± 6.5
Plasma creatinine, mg/dL (μmol/L)	2.55 ± 0.72 (225.26 ± 63.81)
eGFR, mL/minutes/1.73 m^2 *	32 ± 10
Stage 3 CKD, n = 13	39 ± 7
Stage 4 CKD, n = 13	25 ± 5
BUN, mg/dL (mmol/L)	43 ± 18 (15.4 ± 6.5)
Plasma phosphorous, mg/dL (mmol/L)	3.53 ± 0.55 (0.82 ± 0.13)
Plasma calcium, mg/dL (mmol/L)	9.01 ± 0.43 (2.25 ± 0.10)
PTH, pg/mL (pmol/L) †	132 (103, 182) (14 [11, 19])
25-hydroxyvitamin D, ng/mL (nmol/L)	21 ± 10 (53.3 ± 25.9)
1,25-dihydroxyvitamin D, pg/mL (pmol/L)	24.5 ± 15.4 (63.8 ± 39.9)
Serum albumin, mg/dL	4.1 ± 0.6
Hemoglobin, mg/dL	12.3 ± 1.7
Hematocrit, %	36 ± 5

BUN, blood urea nitrogen; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

Laboratory results reported in conventional units with SI units in parentheses.

Data presented as the mean ± SD.

* By Modification of Diet in Renal Disease (MDRD).

† Reported as the median (25th, 75th) because of non-normal distribution.

Table 2

Results of Physical Performance Testing, Physical Activity by Accelerometry, and Muscle Size by MRI

Measurement	Mean ± SD, n = 26
Physical performance measures	
Usual gait speed, cm/second	123 ± 25
Fast gait speed, cm/second	176 ± 53
6-minute walk, feet (m)	1,434 ± 371 (437 ± 113)
Sit-to-stand time (10 times), seconds	25 ± 9
Standing balance, 1 leg, seconds	18 ± 12
Isokinetic strength	
Knee extension at 90°/second, N·m	92 ± 30
Knee extension at 180°/second, N·m	64 ± 23
Isometric strength	
MVC knee extension at 60°, N	444 ± 143
Daily activity: accelerometry, arbitrary units	126,233 ± 64,715
Quadriceps muscle (contractile area) CSA, cm^2	63.8 ± 12.2

N·m, Newton meter; MVC, maximal voluntary contraction; N, Newton; CSA, cross-sectional area; SD, standard deviation.

Data presented as the mean ± SD.

Table 3

Associations Between Levels of 25-Hydroxyvitamin D (25(OH)D) and 1,25-Dihydroxyvitamin D ($1,25(OH)_2D$) and Physical Performance Measures

	Usual Gait Speed (cm/second)	Fast Gait Speed (cm/second)	6-Minute Walk	Static Balance (1 Leg)	Sit-to-Stand Time (5 Repetitions)	Isokinetic Strength (90°/second)	Isokinetic Strength (180°/second)	Isometric MVC
Serum 25(OH)D	$r = 0.41$	$r = 0.14$	$r = 0.20$	$r = 0.07$	$r = -0.32$	$r = 0.01$	$r = 0.04$	$r = 0.02$
	$P \pm .04$	$P = .51$	$P = .33$	$P = .75$	$P = .13$	$P = .95$	$P = .86$	$P = .78$
Serum $1,25(OH)_2D$	$r = 0.46$	$r = 0.36$	$r = 0.38$	$r = 0.42$	$r = -0.42$	$r = 0.35$	$r = 0.48$	$r = 0.35$
	$P \pm .02$	$P = .08$	$P = .06$	$P \pm .03$	$P \pm .04$	$P = .08$	$P \pm .02$	$P = .08$

MVC, maximal voluntary contraction.

Table 4

Results of Multivariable Regression Analyses on Physical Performance Measures

n = 26	Usual Gait Speed (cm/second)		Fast Gait Speed (cm/second)		6-Minute Walk (feet)		Sit-to-Stand Time (10 repetitions) (seconds)	
Predictor Variable	**Coefficient**	***P* Value**	**Coefficient**	***P* Value**	**Coefficient**	***P* Value**	**Coefficient**	***P* Value**
$1,25(OH)_2D$ serum level, pg/mL	0.74	.002	1.19	.02	8.93	.02	−0.25	.02
BMI, kg/m^2	−2.25	<.001	−5.40	<.001	−36.06	<.001	0.704	.006
Intercept	172.42	–	307.67	–	2293.67	–	11.09	–
r	Overall $r = 0.76$ $r^2 = 0.57$		Overall $r = 0.75$ $r^2 = 0.55$		Overall $r = 0.73$ $r^2 = 0.54$		Overall $r = 0.64$ $r^2 = 0.40$	
Significance of the model	$P < .001$		$P < .001$		$P < .001$		$P = .003$	

$1,25(OH)_2$, 1,25-dihydroxyvitamin D; BMI, body mass index.

Table 5

Results of Multivariable Regression Analysis on the Quadriceps Muscle Area

n = 24	Cross-sectional Area of Quadriceps (cm^2)	
Predictor Variable	**Coefficient**	***P* Value**
$1,25(OH)_2D$ serum level, pg/mL	0.370	.02
Plasma calcium, mg/dL	−13.981	.02
Physical activity, per 1,000 arbitrary units *	0.07756	.04
Intercept	170.68	–
r	Overall *r* = 0.73 $r^2 = 0.54$	
Significance of the model	*P* = .005	

$1,25(OH)_2$, 1,25-dihydroxyvitamin.

* By 3-dimensional accelerometry.