Relation of Serum 25-Hydroxyvitamin D Status with Skeletal Muscle Mass and Grip Strength in Patients on Peritoneal Dialysis

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Summary The aim of this study was to investigate the association of serum 25-hydroxyvitamin D (25(OH)D) with skeletal muscle mass (SMM) and grip strength in patients on peritoneal dialysis. In this single center retrospective study, a total of 113 incident peritoneal dialysis patients (65 men, 48 women) were included. Serum concentrations of 25(OH)D were measured through radioimmunoassay. Hypovitaminosis was classified when the level of serum 25(OH)D was <20 ng/mL. SMM was assessed through bioelectrical impedance analysis, whereas grip strength was assessed through handgrip dynamometer. On the basis of expert consensus of the Asian Working Group for Sarcopenia, low muscle mass was defined as relative skeletal mass index (RSMI)<7.0 kg/m² for men and <5.7 kg/m² for women. The general linear and noncondition logistical regression model were employed to explore the association between vitamin D and both muscle mass and grip strength. The mean serum 25(OH)D level was 19.3(±8.4) ng/mL. Compared with 25(OH)D<20 ng/mL, the mean values of SMM, appendicular skeletal muscle mass (ASM), ASMI, and grip strength were higher for ≥20 ng/mL. Subjects (25(OH)D<20 ng/mL) had a greater proportion of low SMM (55.8%) and low grip strength (66.4%). After adjusting for multiple factors, serum 25(OH)D was positively associated with grip strength (β=0.18, p=0.009), ASM (β=0.14, p<0.001), and RSMI (β=0.07, p<0.001); 25(OH)D<20 ng/mL was significantly associated with low grip strength (OR=2.97, 95% CI: 1.17–7.55), and low SMM (OR=2.73, 95% CI: 1.15–6.45). The present study demonstrated a positive association between serum vitamin D status and skeletal muscle mass and grip strength in patients on peritoneal dialysis.

Key Words vitamin D, hypovitaminosis, sarcopenia, muscle function, end-stage renal disease

Chronic kidney disease (CKD) is a global health problem with a prevalence of ~10% (1). Sarcopenia, a syndrome characterized by progressive and generalized low skeletal muscle mass (SMM) and function (muscle strength and performance), is common among patients with CKD, especially in patients with end-stage renal disease (ESRD) (2, 3). Loss of muscle mass leads to a decrease in physical performance and may be associated with a decline in glomerular filtration rate (GFR) and poor clinical outcomes (4–7).

Multiple mechanisms, such as hormonal imbalance, malnutrition, ATP and glycogen depletion, inadequate oxygen transport as a consequence of anemia, metabolic acidosis and electrolyte disorder, lifestyle changes, contribute to the development of sarcopenia in patients with CKD (8). With associations between low vitamin D and various extra skeletal conditions reported in various studies over the past several years, the potential effect of vitamin D on SMM and muscle function has been receiving increased attention in recent years. A few recent reports have indicated that muscle mass, strength, and performance are reduced in CKD patients with low serum vitamin D, whereas the risk of falls is increased (9, 10). A recent study reported that the serum 25-hydroxyvitamin D (25(OH)D) level was positively associated with muscle strength of the lower extremities, estimated using a micro manual muscle tester, in hemodialysis patients (11). However, there is limited knowledge regarding the effects of vitamin D on skeletal muscle mass and function in patients on peritoneal dialysis (PD). A deeper understanding of the relationship between vitamin D and muscle mass and function in the PD patients may help in developing a novel way to slow the loss of muscle mass and maintain muscle function. Therefore, in the present study, we investigated the association between serum 25(OH)D status and SMM, and grip strength in patients on PD.

PATIENTS AND METHODS

Patients. This was a cross-sectional study using data of all incident patients who used PD as their first renal replacement therapy (RRT) modality at the PD center of HwaMei Hospital, University of Chinese Academy of Sciences, Ningbo, China from January 1, 2016, to June 31, 2018. The included subjects were grouped according to the serum 25(OH)D status: (1) <20 ng/mL and; (2) ≥20 ng/mL. Subjects younger than 18 y, without bio-
electrical impedance analysis (BLA) data, grip strength data or vitamin D values were excluded. Data from 113 subjects were finally analyzed in this cross-sectional study. The study was conducted in compliance with the ethical principles of the Helsinki Declaration (http://www.wma.net/en/30publications/10policies/b3/index.html) and approved by the Human Ethics Committees of HwaMei Hospital, University of Chinese Academy of Sciences (NBEY-KY-2017-041-01).

Data collection. The characteristics of subjects were analyzed. Demographic data included age and sex. Body mass index (BMI) was calculated as weight/height² (kg/m²). Clinical and biochemical data included serum creatinine, blood urea nitrogen, serum albumin, hemoglobin, corrected serum calcium, phosphorus, intact parathyroid hormone (iPTH), total cholesterol (TC), triglycerides (TG), low- and high-density lipoprotein (LDL-C and HDL-C), high-sensitivity C-reactive protein (hsCRP), dialysis vintage, exercise, occupation, education, normalized protein equivalent of protein nitrogen appearance (nPNA), total Kt/V, comorbidities, and medication use. The modified quantitative subjective global assessment (MQ-SGA), a fully quantitative scoring system (the dialysis malnutrition score) consisting of seven components was used in our study (12). Each component was assigned a score from 1 (normal) to 5 (very severe). The sum of all seven components score lies between 7 and 35.

Vitamin D measurement. Blood samples were collected from the subjects who had undertaken a more
than 8-h overnight fast, immediately transported in cold storage and analyzed within 24 h. Serum 25(OH)D concentrations were measured using an immuno-radiometric assay (Diasource Immuno-Assays S.A., Louvain-la-Neuve, Belgium). Subjects were classified as having hypovitaminosis if the level of serum 25(OH)D was <20 ng/mL (13).

Measurement of skeletal muscle mass and grip strength.

Muscle mass was assessed using a segmental multifrequency BIA (SMF-BIA) device (InBody720, Biospace, Korea) that measured the voltage drop in the upper and lower body. The accuracy of lean body mass measured through the SMF-BIA method has been verified in previous studies (14, 15). The InBody720 uses eight tactile electrodes (at the hands and feet) and six frequencies (1, 5, 50, 250, 500 kHz and 1 M kHz) to detect segmental body composition, including body water, fat, muscle, and mineral content. The subjects were asked to fast for over 2 h, remove their shoes and socks, wear only their underwear, and stand over the electrodes on the machine for 3–5 min. From the InBody720 output, we measured skeletal muscle mass (SMM) and appendicular skeletal muscle mass (ASM) and subsequently calculated the relative skeletal mass index (RSMI) by dividing the ASM (kg) by the square of height (m). Low muscle mass was defined as RSMI <7.0 kg/m² in men and <5.7 kg/m² in women (16).

A handgrip dynamometer (EH101, Camry, Guangdong Xiangshan Weighing Apparatus Group Ltd., Zhongshan, China) was used to measure grip strength. Subjects were instructed to hold the dynamometer in the dominant hand while standing and use maximum isometric effort for about 5 s. Maximum strength was measured twice and the highest recorded value was considered the maximal grip strength. A minimum rest period of 5 min was ensured between each measurement. Low grip strength was defined as handgrip strength <26 kg in men and <18 kg in women (16).

Statistical analysis. Stata version 12.0 (StataCorp, Texas, US) was used for statistical analyses in the present study. Results were expressed as frequencies and percentages for categorical variables, and means and SDs for continuous variables. Chi-squared and T tests were used to test for differences between the groups stratified by vitamin D status. General linear model was used to calculate the $b$-coefficient and 95% CI of ASM, RSMI, and grip strength by vitamin D status. Noncondition logistic regression model was also employed to explore the association of vitamin D with muscle mass and function. No variable except serum 25(OH)D was included as the independent variable in the unadjusted model. We also included potential confounders (sex, age, BMI, serum albumin and hemoglobin, phosphorus, iPTH, hsCRP and total Kt/V) as independent variables in model, $p<0.05$ was considered statistically significant.

RESULTS

Patients characteristics

In total, 113 patients were enrolled in this study. The mean (±SD) age was 58.7±11.2 y; 57.5% of patients were men. The primary cause of ESRD was chronic glomerulonephritis (53.1%) followed by diabetic kidney disease (22.1%) and hypertension (11.5%). All of the patients received continuous ambulatory PD treatment. Conventional PD solutions (Dianeal 1.5%, or 2.5% dextrose; Baxter Healthcare, Ningbo, China), Y sets, and twin bag systems were used in all PD patients. During the management of our patients, ACEIs/ARBs and $\beta$-blockers were prescribed for 63.7% and 38.9% of patients, respectively.

The mean (±SD) serum 25(OH)D level was 19.3±8.4 ng/mL. Characteristics of the patients stratified by vitamin D status were shown in Table 1. There were no significant differences between groups in sex, age, BMI, serum creatinine, blood urea nitrogen, albumin, hemoglobin, serum calcium, phosphorus, and iPTH, TC, TG, HDL-C, LDL-C, hsCRP, dialysis vintage, exercise, occupation, education, MQ-SGA, nPNA, total Kt/V, comorbidities, and medication use (Table 1).

Vitamin D-based distribution of skeletal muscle mass and grip strength levels

The mean grip strength, SMM, ASM, and RSMI between the groups stratified by vitamin D status differed significantly (Table 2). Furthermore, significant differences were also noted in the rates of low SMM, and low grip strength (Table 2).

Association of vitamin D with skeletal muscle mass and grip strength

As shown in Table 3, serum 25(OH)D was positively associated with grip strength ($b=0.18$, $p=0.009$), ASM ($b=0.14$, $p<0.001$), and RSMI ($b=0.07$, $p<0.001$), after adjusting for sex, age, BMI, and hemoglobin, as

Table 2. Skeletal muscle mass and grip strength stratified by serum 25(OH)D status.

| Variable            | Entire Patients (n=113) | <20 ng/mL (n=63) | ≥20 ng/mL (n=50) | p-Value |
|---------------------|------------------------|------------------|------------------|---------|
| Grip strength (kg)  | 20.3±6.5               | 18.3±6.1         | 22.9±6.2         | <0.001  |
| SMM (kg)            | 24.4±5.2               | 23.4±5.5         | 25.7±4.3         | 0.02    |
| ASM (kg)            | 18.0±4.4               | 16.6±4.4         | 19.8±3.8         | <0.001  |
| RSMI (kg/m²)        | 6.2±1.26               | 5.7±1.20         | 6.8±1.07         | <0.001  |
| Low SMM (%)         | 63 (55.8)              | 42 (66.7)        | 21 (42.0)        | 0.009   |
| Low grip strength (%) | 75 (66.4)            | 52 (82.5)        | 23 (46.0)        | <0.001  |

SMM, skeletal muscle mass; ASM, appendicular skeletal muscle mass; RSMI, relative skeletal mass index.
well as serum albumin, phosphorus, iPTH, hsCRP, and Kt/V. The low grip strength, and low SMM were significantly associated with serum vitamin D status, with or without adjustment (Table 4).

### DISCUSSION

Given the limited knowledge regarding the effects of vitamin D on skeletal muscle mass and function, our study aimed to investigate the association between 25(OH)D and skeletal muscle mass, and grip strength in patients on peritoneal dialysis. In the present retrospective cohort study, we found a positive association between vitamin D and skeletal muscle mass and grip strength in PD patients.

The effects of 25(OH)D on the skeletal muscle mass and function were mostly evaluated on the elderly population. Several studies have reported that vitamin D status is positively associated with muscle strength (17), physical performance (18, 19) and inversely associated with the risk of falling in the elderly (20). As in individuals with normal renal function and vitamin D deficiency (21), patients with CKD have prolongation of the relaxation phases of muscle contraction, independent of serum calcium, parathyroid hormone or serum phosphorus levels (22, 23). In patients with end stage renal failure, low 25(OH)D has also been associated with muscle weakness and risk of falls, but the evidence to support these associations is limited to small observational studies (10, 24). Boudville et al. reported that 25(OH)D deficiency was associated with muscular weakness and falls in dialysis patients, but with a J curve and maximal benefit in the range between 24 and 44 ng/mL of serum 25(OH)D levels (10).

Serum levels of 25(OH)D were found to decline progressively with time in patients on peritoneal dialysis (25). Some authors reported lower levels of 25(OH)D in PD patients compared to those on hemodialysis (26). The serum 25(OH)D level was reported to be associated positively with muscle strength of the lower extremities, estimated using a micro manual muscle tester, in hemodialysis patients (11). However, little is known about PD patients. Our study revealed that 25(OH)D level was positively associated with skeletal muscle mass and grip strength, independent of other covariates in PD patients. To the best of our knowledge, the present study is the first to report an association between vitamin D status and both skeletal muscle mass and function in patients on PD.

Several studies have addressed the mechanism of how vitamin D may relate to the skeletal muscle. Vitamin D receptors (VDRs) have been characterized as members of the steroid hormone super-family, acting as a hormone-inducible transcription factor (27). Vitamin D plays a direct role in skeletal muscle formation via VDRs, most likely through both genomic and non-genomic mechanisms (28, 29). Suitable serum vitamin D levels are associated with the proliferation and differentiation of various cells including skeletal muscle cells (13). Hypocalcaemia or insulin resistance is a common feature of end stage renal disease (30). The vitamin D deficiency might affect muscle protein turnover by inducing hypocalcaemia and decreasing insulin secretion (31). Vitamin D metabolites have been found to affect muscle metabolism in three ways: (1) by mediating gene transcription; (2) through rapid pathways not involving DNA synthesis; and (3) by the allelic variant of the VDR (17).

Several limitations should be considered while inter-
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Interpreting the findings of our study. Firstly, the cross-sectional study design precludes causal inferences regarding the relationship between vitamin D and sarcopenia. Secondly, we used a single measurement of serum 25(OH)D, as a proxy for vitamin D status, and 1,25-dihydroxyvitamin D, the active metabolite, was not available in present study, thus it may not accurately reflect long-term vitamin D status. Furthermore vitamin D measured at tissue levels might be more sensitive to muscle mass than that measured at serum levels; these findings had some discrepancies (32). Finally, we used only grip strength to assess skeletal muscle function. More indicators for muscle strength and physical performance (e.g., regular gait speed, isometric knee extension strength test, timed up and go test, and timed chair stand test) should be included in future studies.

In conclusion, the present study demonstrated a positive association between vitamin D and skeletal muscle mass and grip strength, which highlights a new potential association between vitamin D and skeletal muscle function in patients on peritoneal dialysis.

Disclosure of state of COI
There are no conflicts of interests.

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REFERENCES

1) Jha V, Garcia-Garcia G, Iseki K, Li Z, Naicker S, Plattner B, Saran R, Wang AY, Yang CW. 2013. Chronic kidney disease: global dimension and perspectives. Lancet 382(9888): 260–272.
2) Carrero JJ, Johansen KL, Lindholm B, Stenwinkel P, Cuppari L, Aresani CM. 2016. Screening for muscle wasting and dysfunction in patients with chronic kidney disease. Kidney Int 90(1): 53–66.
3) Stenwinkel P, Carrero JJ, von Walden F, Ikizler TA, Nader GA. 2016. Muscle wasting in end-stage renal disease promulgates premature death: established, emerging and potential novel treatment strategies. Nephrol Dial Transplant 31(7): 1070–1077.
4) Roshanravan B, Robinson-Cohen C, Patel KV, Ayers E, Littman AJ, de Boer IH, Ikizler TA. 2013. Association between physical performance and all-cause mortality in CKD. J Am Soc Nephrol 24(5): 822–830.
5) Painter P, Roshanravan B. 2013. The association of physical activity and physical function with clinical outcomes in adults with chronic kidney disease. Curr Opin Nephrol Hypertens 22(6): 615–623.
6) MacKinnon HJ, Wilkinson TJ, Clarke AL, Gould DW, O’Sullivan TF, Xenophontos S, Watson EL. 2018. The association of physical function and physical activity with all-cause mortality and adverse clinical outcomes in nondialysis chronic kidney disease: a systematic review. Ther Adv Chronic Dis 9(11): 209–226.
7) Hellberg M, Höglund P, Svensson P, Abdullahi H, Clyne N. 2017. Decline in measured glomerular filtration rate is associated with a decrease in endurance, strength, balance and fine motor skills. Nephrology (Carlton) 22(7): 513–519.
8) Fahal IH. 2014. Uraemic sarcopenia: aetiology and implications. Nephrol Dial Transplant 29(9): 1655–1665.
9) Gordon PL, Doyle JW, Johansen KL. 2012. Association of 1,25-dihydroxyvitamin D levels with physical performance and thigh muscle cross-sectional area in chronic kidney disease stage 3 and 4. J Ren Nutr 22(4): 423–433.
10) Boudville N, Inderjeeth C, Elder GJ, Glendenning P. 2010. Association between 25-hydroxyvitamin D, somatic muscle weakness and falls risk in end-stage renal failure. Clin Endocrinol (Oxf) 73(3): 299–304.
11) Zahed N, Chehrazi S, Falaknasi K. 2014. The evaluation of relationship between vitamin D and muscle power by micro manual muscle tester in end-stage renal disease patients. Saud j Kidney Dis Transpl 25(5): 998–1003.
12) Kalantar-Zadeh K, Kleinier M, Dunne E, Lee GH, Liu FC. 1999. A modified quantitative subjective global assessment of nutrition for dialysis patients. Nephrol Dial Transplant 14(7): 1732–1738.
13) Holick MF. 2007. Vitamin D deficiency. N Engl J Med 357(3): 266–281.
14) Ling CH, de Cuen A, Slagboom PE, Gunn DA, Stokkel MP, Westendorp RG, Miëer AB. 2011. Accuracy of direct segmental multi-frequency bioimpedance analysis in the assessment of total body and segmental body composition in middle-aged adult population. Clin Nutr 30(5): 610–615.
15) Kim M, Kim H. 2013. Accuracy of segmental multi-frequency bioelectrical impedance analysis for assessing whole-body and appendicular fat mass and lean soft tissue mass in frail women aged 75 years and older. Eur J Clin Nutr 67(4): 395–400.
16) Chen LK, Liu LK, Woo J, Assantachai P, Auyeung TW, Bailey HS, Chou MY, Chen LY, Hsu PS. 2014. Sarcopenia in Asia: consensus report of the Asian Working Group for Sarcopenia. J Am Med Dir Assoc 15(2): 95–101.
17) Visser M, Deeg DJ, Lips P. Longitudinal Aging Study Amsterdam. 2003. Low vitamin D and high parathyroid hormone levels as determinants of loss of muscle strength and muscle mass (sarcopenia): the Longitudinal Aging Study Amsterdam. J Clin Endocrinol Metab 88(12): 5766–5772.
18) Bischoff-Ferrari HA, Dietrich T, Orav EJ, Hu FB, Zhang Y, Karlson EW, Dawson-Hughes B. 2004. Higher 25-hydroxyvitamin D concentrations are associated with better lower-extremity function in both active and inactive persons aged > or = 60 y. Am J Clin Nutr 80(3): 752–758.
19) Salminen M, Saaristo P, Salo noja M, Vaapio S, Vahb lberg T, Lamberg-Allardt C, Aarnio P, Kivelä SL. 2015. Vitamin D status and physical function in older Finnish people: A one-year follow-up study. Arch Gerontol Geriatr 61(3): 419–424.
20) Snijder MB, van Schoor NM, Pluijim SM, van Dam RM, Visser M, Lips P. 2006. Vitamin D status in relation to one-year risk of recurrent falling in older men and women. J Clin Endocrinol Metab 91(8): 2980–2985.
21) Rodman JS, Baker T. 1978. Changes in the kinetics of muscle contraction in vitamin D-depleted rats. *Kidney Int* 13(3): 189–193.

22) Fahal IH, Bell GM, Bone JM, Edwards RH. 1997. Physiological abnormalities of skeletal muscle in dialysis patients. *Nephrol Dial Transplant* 12(1): 119–127.

23) Fahal IH, Ahmad R, Edwards RH. 1996. Muscle weakness in continuous ambulatory peritoneal dialysis patients. *Perit Dial Int* 16: S419–S423.

24) Bataille S, Landrier JF, Astier J, Giaime P, Sampol J, Sichez H, Ollier J, Gugliotta J, Serveaux M. 2016. The “dose-effect” relationship between 25-hydroxyvitamin D and muscle strength in hemodialysis patients favors a normal threshold of 30 ng/mL for plasma 25-hydroxyvitamin D. *J Ren Nutr* 26(1): 45–52.

25) Gokal R, Ramos JM, Ellis HA, Parkinson I, Sweetman V, Dewar J, Ward MK, Kerr DN. 1983. Histological renal osteodystrophy, and 25 hydroxycholecalciferol and aluminum levels in patients on continuous ambulatory peritoneal dialysis. *Kidney Int* 23(1): 15–21.

26) Cankaya E, Bilen Y, Keles M, Uyanik A, Akbaş M, Güngör A, Arslan Ş, Aydınlı B. 2015. Comparison of serum vitamin D levels among patients with chronic kidney disease, patients in dialysis, and renal transplant patients. *Transplant Proc* 47(5): 1405–1407.

27) Liao L, Chen X, Wang S, Purlow AE, Xu J. 2008. Steroid receptor coactivator 3 maintains circulating insulin-like growth factor 1 (IGF-I) by controlling IGF-binding protein 3 expression. *Mol Cell Biol* 28(7): 2460–2469.

28) Nibbelink KA, Tishkoff DX, Hershey SD, Rahman A, Simpson RU. 2007. 1,25(OH)2-vitamin D3 actions on cell proliferation, size, gene expression, and receptor localization, in the HL-1 cardiac myocyte. *J Steroid Biochem Mol Biol* 103: 533–537.

29) Nguyen TM, Lieberherr M, Fritsch J, Guillozo H, Alvarez ML, Fitouri Z, Jehan F, Garabedian M. 2004. The rapid effects of 1,25-dihydroxyvitamin D3 require the vitamin D receptor and influence 24-hydroxylase activity: studies in human skin fibroblasts bearing vitamin D receptor mutations. *J Biol Chem* 279(9): 7591–7597.

30) Shinohara K, Shoji T, Emoto M, Tahara H, Koyama H, Ishimura E, Miki T, Tabata T, Nishizawa Y. 2002. Insulin resistance as an independent predictor of cardiovascular mortality in patients with end-stage renal disease. *J Am Soc Nephrol* 13(7): 1894–1900.

31) Wassner SJ, Li JB, Sperduto A, Norman ME. 1983. Vitamin D deficiency, hypocalcemia, and increased skeletal muscle degradation in rats. *J Clin Invest* 72(1): 102–112.

32) Wang Y, DeLuca HF. 2011. Is the vitamin D receptor found in muscle? *Endocrinology* 152(2): 354–363.