Serum 25-Hydroxyvitamin D Levels and Longitudinal Changes in Muscle Mass and Function in Peritoneal Dialysis Patients: A Prospective Cohort Study

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Summary Data regarding to how serum 25 hydroxyvitamin D (25(OH)D) levels affect muscle mass and function in end-stage renal disease (ESRD) patients have led to inconclusive results. The main goal of this research was to examine the relationship between 25(OH)D levels and the risk of deterioration in muscle mass and function among ESRD patients on continuous ambulatory peritoneal dialysis (CAPD). Eligible ESRD patients on CAPD were prospectively included, and followed up at 3-mo intervals in Ningbo No. 2 Hospital, the tertiary care center in the Ningbo region, Zhejiang Province, China for 12 mo. The mean 25(OH)D level <20 ng/mL of all visits during the 12-mo follow-up period was the exposure of interest. Primary outcome was defined as the deterioration of muscle mass and function at the end of the 12-mo follow-up. The absolute difference with 95% confidence interval (CI) of the incidence of deterioration of muscle mass and function between the groups with mean 25(OH)D<20 ng/mL and ≥20 ng/mL were estimated. The relationship between 25(OH)D levels and the risk of deterioration in muscle mass and function was examined by employing multivariate logistic regression models. Participants with 25(OH)D<20 ng/mL or 25(OH)D≥20 ng/mL in each visit were included as a sensitivity analysis. Subgroup analysis was conducted based on the age (<60 y and ≥60 y). Two hundred twenty-one eligible participants were included for the final statistical analysis. Among these 221 participants, patients with the mean 25(OH)D<20 ng/mL was 64.7% (143/221). During the 12-mo follow-up period, the incidence of deterioration in muscle mass and function was 37.6% (83/221). Compared to paticipants with mean 25(OH)D≥20 ng/mL, the incidence in paticipants with mean 25(OH)D<20 ng/mL was significantly higher (46.2% vs 21.8%, $p<0.001$), with an absolute difference of 24% (95%CI 12–37%). After adjustment for potential confounding factors, mean 25(OH)D<20 ng/mL was still associated with increased risk of the deterioration in muscle mass and function (OR=3.18, 95%CI 1.51–6.70, $p=0.002$). The association was consistent in the sensitivity analysis (OR=3.22, 95%CI 1.49–6.97, $p=0.003$). In subgroup analysis, the relationship between mean 25(OH)D<20 ng/mL and the deterioration in muscle mass and function remained consistent (OR=5.59, 95%CI 1.82–17.15, $p=0.003$) in paticipants with age ≥60 y; however, no significant relationship was identified in patients with age <60 y (OR=2.05, 95%CI 0.72–5.84, $p=0.18$). Our study demonstrated that lower serum 25(OH)D levels were significantly associated with an increased risk of the deterioration in muscle mass and function in ESRD patients on CAPD, especially in elderly individuals, implicating that vitamin D supplementation might represent an effective way to prevent and treat sarcopenia, frailty and their clinical complications. However, due to inherent limitations in the study, further research is necessary to establish a definitive causal relationship.

Key Words serum 25(OH)D, deterioration, muscle mass and function, sarcopenia, peritoneal dialysis

Sarcopenia, a disorder defined as having a reduction in skeletal muscle mass with declining muscle strength and/or physical performance, is an important clinical condition shown to be prevalent in a clinically significant proportion in end-stage renal disease (ESRD) patients undergoing dialysis (*1–3*). Sarcopenia and its related traits (i.e. low muscle mass, low muscle strength and low physical performance) have been strongly associated with a wide range of adverse clinical outcomes including mortality and cardiovascular events in this

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population (*1*–*5*). Despite different definitions of sarcopenia which may affect the overall prevalence in dialysis populations, the adverse outcomes are generally consistent.

Low serum 25-hydroxyvitamin D (25(OH)D) levels are common in patients with chronic kidney disease (CKD) and the prevalence of this condition increases as kidney function becomes more severely reduced (*6*, *7*). In the general population, low serum 25(OH)D levels have been associated with sarcopenia (*8*–*12*). Since it was assumed that 25(OH)D could not be metabolized to $1,25(OH)_2D$, the active form of vitamin D, in the kidneys of patients with ESRD, the benefit of serum 25(OH)D level measurement in patients undergoing dialysis remains debatable. Although previous studies have shown that low 25(OH)D levels are associated with sarcopenia and its traits in patients undergoing dialysis (*13*, *14*), there is limited knowledge regarding the effects of serum 25(OH)D levels on changes in skeletal muscle mass, muscle strength and physical performance among dialysis patients. Thus, for the related traits of sarcopenia, particularly the dynamic alterations of muscle mass and function, more substantial evidence is requisite to draw definite conclusions regarding the association with 25(OH)D level in dialysis patients.

To our knowledge, no study has investigated the association of serum 25(OH)D levels with dynamic alterations in muscle mass and function based on longitudinal studies among peritoneal dialysis (PD) patients. Therefore, in this study, by utilizing the criteria of Asian Working Group on Sarcopenia in 2019 (AWGS 2019) for sarcopenia diagnoses (*15*), we conducted a prospective cohort study to longitudinally examined the relationship between serum 25(OH)D levels and dynamic deterioration in muscle mass and function among ESRD patients on continuous ambulatory PD (CAPD).

METHODS

Study design. A prospective cohort study was conducted in Ningbo No. 2 Hospital, the tertiary care center in the Ningbo region, Zhejiang Province, China, from July 2022 to June 2024. Immediately after patients' enrollment, baseline follow-up was carried out. In the following 12 mo, regular visits were conducted at 3-mo intervals. Informed consent was obtained from all participants and/or their families. The study was approved by the Ethics Committee of Ningbo No. 2 Hospital (YJ-NBEY-KY-2021-155-01). All research was performed in accordance with the relevant guidelines and regulations (Declaration of Helsinki).

Participants. Participants were recruited among ESRD patients on CAPD in Ningbo No. 2 Hospital. Individuals aged ≥18 y and undergoing CAPD for at least 3 mo were screened. Patients were excluded if they were unable to complete the assessment of muscle mass and function, including bioelectrical impedance analysis (BIA), handgrip strength (HGS) measurement and physical performance tests; or with sarcopenia; or in a catabolic state (including malignancy or recurrent peritonitis); or concurrent with critical illness, including advanced heart diseases or severe lung diseases; or not suitable for the clinical trial. Patients in a catabolic state or with critical illness were in a higher risk of loss to follow-up, and these factors significantly related to the dynamic changes in muscle mass and function could be potential confounders.

Data source, exposure and outcome. After the patients were enrolled, baseline follow-up was conducted immediately. Demographic, clinical, laboratory and other general data together with parameters of muscle mass and function were collected by medical personnel and stored by electronic medical records. From this database, the following baseline data were analyzed: age, gender, body mass index (BMI), dialysis duration, residual renal function (RRF), weekly $Kt/V_{(urea)}$ defined as renal plus peritoneal $Kt/V_{(urea)}$ where K is urea clearance, t is treatment time, and V is the volume of distribution for urea, laboratory parameters (glycated hemoglobin (HbA1c), hemoglobin, albumin, calcium, phosphorus, intact parathyroid hormone (iPTH), 25(OH)D and high-sensitivity C-reactive protein(hs-CRP)), comorbidities (diabetes mellitus, hypertension and congestive heart failure) and concomitant medications (active vitamin D analogues). Dynamic serum 25(OH)D levels were measured using API3200 liquid chromatography-mass spectrometer/mass spectrometer (LC-MS/MS) system (Applied Biosystems, Foster City, CA, USA), and collected at 3-mo intervals during the 12-mo period. Parameters of muscle mass and function, including appendicular skeletal muscle mass index (ASMI), handgrip strength, 6-m walk test and 5-time chair stand test, were assessed in the baseline visit and at the end of the 12-mo follow-up (in the final visit). All the collected data were checked prospectively to ensure their accuracy and completeness by medical personnel who were not informed of details of the study protocol.

The mean 25(OH)D level <20 ng/mL (the average of 25(OH)D levels in the five visits) during the 12-mo follow-up period was the exposure of interest in our study. Although there is no consensus on optimal levels of 25(OH)D as measured in serum, vitamin D deficiency is defined by most experts as a 25(OH)D level of less than 20 ng/mL (*7*). Based on the mean 25(OH)D levels, the participants were divided into two groups (mean 25(OH)D<20 ng/mL and mean 25(OH)D≥20 ng/mL).

The primary outcome of interest was the deterioration in muscle mass and function, defined as evolving to sarcopenia (non-severe sarcopenia or severe sarcopenia) from non-sarcopenia during the 12-mo follow-up period. AWGS 2019 contends that diagnosing sarcopenia requires measurements of both muscle quality and quantity. As per AWGS 2019, sarcopenia was defined as loss of muscle mass, plus low muscle strength or low physical performance. Nevertheless, persons with low muscle mass, low muscle strength and low physical performance were considered as having severe sarcopenia.

Measurements of muscle mass and function. Muscle mass was assessed using a segmental multifrequency BIA device (InBody720, Biospace, Seoul, Korea). Partic-

ipants were asked to empty the bladder and peritoneal dialysate, remove their shoes and socks, wear only their underwear, and stand over the electrodes on the machine for 3–5 min. Appendicular skeletal muscle mass (ASM) were then obtained by adding skeletal muscle mass (SMM) in all four limbs. ASMI was calculated by ASM indexed to height squared (m^2) to adjust for body size. The cut-off value for defining low muscle mass (LMM) was based on the ASMI, with <7.0 kg/m^2 in men and <5.7 kg/m^2 in women according to AWGS 2019.

A handgrip dynamometer (EH101, Camry, Guangdong Xiangshan Weighing Apparatus Group Ltd., Zhongshan, China) was used to measure grip strength. Participants were instructed to hold the dynamometer in the dominant hand in the standing position and use maximum isometric effort for about 3–5 s. Two measurements were made and we used the maximal value for analysis. As per AWGS 2019, the cut-off points for low muscle strength (LMS) were defined as grip strength <28.0 kg for men and <18.0 kg for women.

The participants were asked to empty the peritoneal dialysate before the 6-m walk test and 5-time chair stand test. During the 6-m walk test, participants were instructed to walk with their usual speed for 6 m on a flat and straight path. A stopwatch was used and the timing began with a verbal start command. Participants were instructed to maintain their speed without deceleration at the end of the walking course. The time (s) required to cover the distance was recorded. During the 5-time chair stand test, the participants stood up and sat down five times with their arms folded in front of their chest as quickly as possible on a firm chair. The time (s) required to complete five cycles was measured. AWGS 2019 recommends defining low physical performance (LPP) based on either 6-m walk test >6.0 s or 5-time chair stand test >12.0 s.

Statistical analysis. The number of eligible individuals screened in our PD center determined the sample size. During the 12-mo follow-up period, the missing data of participants lost to follow-up were considered missing completely at random and were not imputed due to a low proportion (defined as $<5\%$).

Individuals with complete follow-up data were used in the statistical analyses (complete-case analyses).

Baseline characteristics were summarized and compared according to the exposure of interest (mean 25(OH)D$<$20 ng/mL and mean 25(OH)D$\geq$20 ng/mL). Continuous variables were assessed for normality using the Shapiro-Wilk test. Variables with normal distributions were expressed as mean and standard deviation, and compared using Student's independent *t*-test; variables that were not normally distributed were expressed as median (interquartile range), and compared using the Mann-Whitney *U* test. Categorical variables were expressed as frequency (n) with percentage (%), and compared using the χ^2 or Fisher's exact test as appropriate.

The absolute difference with 95% confidence interval (CI) of the incidence of deterioration in muscle mass and function between the groups with mean 25(OH)D$<$20 ng/mL and $\geq$20 ng/mL were estimated. Effect modification of age and gender was assessed by logistic regression analysis, and subgroup analysis was conducted when there was an significant interaction. Confounders (age, gender, baseline serum albumin and hs-CRP, and baseline status of muscle mass and function) potentially related to serum 25(OH)D status and dynamic changes in muscle mass and function were adjusted. Odds ratios (ORs) and 95% CIs, with the serum 25(OH)D as a dichotomous variable (mean 25(OH)D$<$20 ng/mL vs mean 25(OH)D$\geq$20 ng/mL) were calculated in the multivariate logistic regression analysis. Multiple models were fitted to check the association: model 1 unadjusted; model 2 adjusted for age and gender; model 3 adjusted for model 2 plus baseline serum albumin and hs-CRP; model 4 adjusted for model 3 plus baseline status of muscle mass and function: low muscle mass (presence vs absence), low muscle strength (presence vs absence) and low physical performance (presence vs absence). To test the robustness of the estimation, participants with 25(OH)D$<$20 ng/mL or 25(OH)D$\geq$20 ng/mL in each visit were included as a sensitivity analysis to examine whether the potential association of serum 25(OH)D status and dynamic changes in muscle mass and function was consistent.

Differences were considered statistically significant at a two-tailed p value<0.05. IBM SPSS statistics version 19.0 for Windows was used to analyze the data.

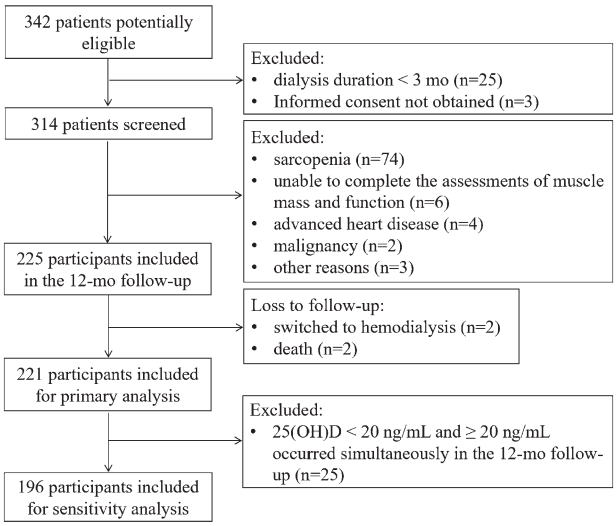

Fig. 1. Flow chart of patients selection for analysis.

RESULTS

Participants and baseline characteristics

Of the 314 CAPD patients screened for inclusion in this study, 225 patients were enrolled to assess serum 25(OH)D status and the dynamic changes in muscle mass and function in the 12-mo follow-up, and at last 221 eligible participants with complete information regarding to exposure and outcome of interest were included for the final statistical analysis (Fig. 1). Among these 221 participants, patients with the mean

Table 1. Baseline characteristics of participants by 25(OH)D status.

	Total (n=221)	Mean 25(OH)D <20 ng/mL (n=143)	Mean 25 (OH)D ≥20 ng/mL (n=78)	$t/Z/\chi^2$	p value
Male, n (%)	112 (50.7)	67 (46.9)	45 (57.7)	2.37	0.12
Age (y)	58 (51, 64)	58 (51, 64)	56 (50, 64)	1.39	0.16
BMI (kg/m^2)	22.0 (21.4, 23.0)	22.0 (21.4, 22.8)	21.5 (21.4, 23.6)	0.40	0.69
Dialysis duration (mo)	30 (29, 35)	30 (29, 35)	30 (24, 39)	0.70	0.48
RRF (mL/min/1.73 m^2)	5.0 (4.2, 5.2)	5.0 (4.2, 5.2)	4.4 (4.2, 5.2)	0.02	0.99
Weekly $Kt/V_{(urea)}$≥1.7, n (%)	176 (79.6)	112 (78.3)	64 (82.1)	0.43	0.51
Diabetes mellitus, n (%)	93 (42.1)	58 (40.6)	35 (44.9)	0.39	0.54
Hypertension, n (%)	161 (72.9)	106 (74.1)	55 (70.5)	0.33	0.56
Congestive heart failure, n (%)	52 (23.5)	20 (25.6)	32 (22.4)	0.30	0.59
HbA1c (%)	6.0 (5.3, 6.7)	6.0 (5.3, 6.8)	6.0 (5.3, 6.7)	0.56	0.57
Hemoglobin (g/L)	112 (105, 121)	112 (105, 121)	111 (104, 122)	0.12	0.91
Albumin (g/L)	34.6±4.1	34.3±3.9	35.1±4.4	1.54	0.12
Calcium (mmol/L)	2.21 (2.13, 2.28)	2.20 (2.09, 2.32)	2.22 (2.16, 2.27)	0.86	0.39
Phosphorus (mmol/L)	1.54 (1.26, 1.82)	1.55 (1.34, 1.85)	1.48 (1.21, 1.79)	0.95	0.34
iPTH (pg/mL)	237 (160, 308)	236 (165, 328)	237 (156, 279)	1.00	0.32
hs-CRP (mg/L)	3.60 (1.43, 10.27)	3.97 (1.44, 17.62)	3.01 (1.43, 7.62)	1.37	0.17
Vitamin D supplementation, n (%)	96 (43.4)	64 (44.8)	32 (41.0)	0.29	0.59
ASMI (kg/m^2)	7.03 (6.19, 7.55)	6.97 (6.11, 7.55)	7.10 (6.33, 7.55)	1.23	0.22
HGS (kg)	19.8 (16.1, 28.6)	19.8 (15.6, 28.4)	20.5 (17.7, 28.7)	0.73	0.47
6-m walk test (s)	5.14 (4.33, 5.81)	5.28 (4.28, 5.86)	5.02 (4.35, 5.60)	0.82	0.41
5-time chair stand test (s)	9.20 (7.88, 11.53)	9.33 (7.66, 11.55)	9.19 (8.03, 10.85)	0.26	0.80
Low muscle mass, n (%)	55 (24.9)	39 (27.3)	16 (20.5)	1.23	0.27
Low muscle strength, n (%)	91 (41.2)	63 (44.1)	28 (35.9)	1.39	0.24
Low physical performance, n (%)	61 (27.6)	43 (30.1)	18 (23.1)	1.24	0.27

BMI, body mass index; RRF, residual renal function; $Kt/V_{(urea)}$, fractional clearance index for urea; HbA1c, glycated hemoglobin; iPTH, intact parathyroid hormone; hs-CRP, high-sensitivity C-reactive protein; ASMI, appendicular skeletal muscle mass index; HGS, handgrip strength. Vitamin D supplementation: oral calcitriol (1,25(OH)$_2$D) or alfacalcidol (1-α(OH)D).

Table 2. Serum 25(OH)D levels (ng/mL) of participants at 3-mo intervals.

	Total (n=221)	Mean 25(OH)D <20 ng/mL (n=143)	Mean 25(OH)D ≥20 ng/mL (n=78)
At baseline visit	15.1 (11.8, 22.7)	12.6 (11.2, 14.8)	24.3 (22.5, 27.6)
At 3-mo visit	15.5 (10.7, 22.4)	12.5 (9.7, 15.4)	23.1 (21.8, 24.6)
At 6-mo visit	16.7 (12.1, 22.3)	13.5 (9.6, 16.3)	23.7 (22.1, 26.4)
At 9-mo visit	15.2 (11.4, 21.7)	12.7 (10.6, 14.4)	22.6 (21.3, 24.8)
At 12-mo visit	17.1 (13.8, 21.5)	14.9 (11.8, 16.9)	22.5 (21.1, 26.4)
Average	15.0 (12.7, 23.0)	13.1 (11.8, 14.6)	23.7 (22.7, 24.4)

25(OH)D<20 ng/mL was 64.7% (143/221). Baseline characteristics were summarized and compared in Table 1 according to the mean 25(OH)D levels (mean 25(OH)D<20 ng/mL and mean 25(OH)D≥20 ng/mL). The characteristics of ASMI, HGS, 6-m walk test and 5-time chair stand test at baseline visit were also presented in Table 1. Serum 25(OH)D levels of participants at 3-mo intervals were summarized in Table 2.

25(OH)D levels and deterioration in muscle mass and function

The details of the muscle mass and function at the end of 12-mo follow-up were summarized and compared in Table 3. During the 12-mo follow-up period, the incidence of deterioration in muscle mass and function was 37.6% (83/221). Compared to paticipants with mean 25(OH)D≥20 ng/mL, the incidence of deterioration in muscle mass and function in paticipants with mean 25(OH)D<20 ng/mL was significantly higher (46.2% vs 21.8%, p<0.001), with an absolute difference of 24% (95%CI 12–37%).

Four logistic regression models were carried out to calculate ORs and their corresponding 95%CIs for the effects of serum 25(OH)D levels as a dichotomous variable (Table 4). In the crude model (model 1), the group with mean 25(OH)D<20 ng/mL showed higher odds of the deterioration in muscle mass and function. After adjustment for age and gender in model 2, and further plus baseline serum albumin and hs-CRP in model 3, all associations were still consistent. Baseline status of muscle mass and function: low muscle mass (presence

Table 3. Muscle mass and function of paticipants at the end of 12-mo follow-up.

	Mean 25(OH)D <20 ng/mL (n=143)	Mean 25(OH)D ≥20 ng/mL (n=78)	Difference (%) (95%CI)	Z/χ^2	p value
ASMI (kg/m^2)	6.27 (5.40, 7.11)	6.90 (5.98, 7.52)		3.19	0.001
HGS (kg)	19.4 (15.5, 26.8)	20.5 (16.7, 28.4)		1.18	0.24
6-m walk test (s)	5.65 (4.92, 6.50)	5.10 (4.43, 6.08)		2.49	0.01
5-time chair stand test (s)	10.46 (8.60, 12.45)	9.32 (8.21, 11.34)		1.76	0.08
Low muscle mass, n (%)	89 (62.2)	31 (39.7)		10.29	0.001
Low muscle strength, n (%)	78 (54.5)	35 (44.9)		1.89	0.17
Low physical performance, n (%)	71 (49.7)	27 (34.6)		4.62	0.03
Deterioration of muscle mass and function, n (%)	66 (46.2)	17 (21.8)	24 (12, 37)	12.77	<0.001

ASMI, appendicular skeletal muscle mass index; HGS, handgrip strength.

Table 4. Multivariate logistic regression models for the deterioration in muscle mass and function (mean 25(OH)D<20 ng/mL vs mean 25(OH)D≥20 ng/mL) (n=221).

Model	Covariates	Wald	p value	Odds ratio	95% confidence interval
1	Unadjusted	12.21	<0.001	3.08	1.64–5.78
2	Age and gender	9.04	0.003	2.95	1.46–5.98
3	Model 2 plus baseline serum albumin and hs-CRP	7.84	0.005	2.78	1.36–5.75
4	Model 3 plus baseline status of muscle mass and function	9.21	0.002	3.18	1.51–6.70

hs-CRP, high-sensitivity C-reactive protein. Baseline status of muscle mass and function: low muscle mass (presence vs absence), low muscle strength (presence vs absence) and low physical performance (presence vs absence).

Table 5. Multivariate logistic regression models for the deterioration in muscle mass and function (25(OH)D<20 ng/mL in each visit vs 25(OH)D≥20 ng/mL in each visit) (n=196).

Model	Covariates	Wald	p value	Odds ratio	95% confidence interval
1	Unadjusted	13.07	<0.001	3.31	1.73–6.33
2	Age and gender	7.95	0.005	2.87	1.38–5.96
3	Model 2 plus baseline serum albumin and hs-CRP	7.07	0.008	2.74	1.30–5.96
4	Model 3 plus baseline status of muscle mass and function	8.78	0.003	3.22	1.49–6.97

hs-CRP, high-sensitivity C-reactive protein. Baseline status of muscle mass and function: low muscle mass (presence vs absence), low muscle strength (presence vs absence) and low physical performance (presence vs absence).

vs absence), low muscle strength (presence vs absence) and low physical performance (presence vs absence), were further adjusted in model 4, and the group with mean 25(OH)D<20 ng/mL was still associated with increased odds of the deterioration in muscle mass and function at the end of the 12-mo follow-up (OR=3.18, 95%CI 1.51–6.70, p=0.002). In addition, we also aimed to explore whether active vitamin D supplementation at baseline impacts the results of our study. Therefore, we included it as a covariate in the multiple regression models, and the results were consistent (Table S1, Supplemental Online Material).

Sensitivity and subgroup analysis

Participants with 25(OH)D<20 ng/mL or 25(OH)D ≥20 ng/mL in each visit were included as a sensitivity analysis to examine whether the potential association of serum 25(OH)D status and dynamic changes in muscle mass and function was consistent. The relationship between mean 25(OH)D levels and the deterioration in muscle mass and function was consistent (OR=3.22, 95%CI 1.49–6.97, p=0.003) (Table 5).

There was an significant interaction between age and 25(OH)D levels. Therefore, subgroup analysis using the logistic models was conducted based on the age (<60 y and ≥60 y). The relationship between mean 25(OH)D<20 ng/mL and the deterioration in muscle mass and function remained consistent (OR=5.59, 95%CI 1.82–17.15, p=0.003) in paticipants with age

Table 6. Multivariate logistic regression models for the deterioration in muscle mass and function in subgroups of ages (mean 25(OH)D<20 ng/mL vs mean 25(OH)D≥20 ng/mL).

	Model	Wald	*p* value	Odds ratio	95% confidence interval
<60 y	1	1.09	0.30	1.67	0.64–4.38
(*n*=127)	2	1.79	0.18	2.05	0.72–5.84
≥60 y	1	13.17	<0.001	5.82	2.25–15.06
(*n*=94)	2	9.04	0.003	5.59	1.82–17.15

Model 1, unadjusted; Model 2, adjusted for covariates of gender, baseline serum albumin and high-sensitivity C-reactive protein (hs-CRP), and baseline status of muscle mass and function: low muscle mass (presence vs absence), low muscle strength (presence vs absence), and low physical performance (presence vs absence).

≥60 y; however, no significant relationship was identified in patients with age <60 y (OR=2.05, 95%CI 0.72–5.84, p=0.18) (Table 6).

DISCUSSION

In this study, we aimed to determine whether serum 25(OH)D levels could affect dynamic changes in muscle mass and function among ESRD patients on CAPD. Based on the findings, our study showed a significantly higher incidence of deterioration in muscle mass and function in participants with mean 25(OH)D<20 ng/mL during the 12-mo follow-up period. After adjustment for potential confounders, mean 25(OH)D<20 ng/mL was still significantly associated with increased risk of the deterioration in muscle mass and function. To our best knowledge, this is the first longitudinal study to investigate the relationship between serum 25(OH)D levels and dynamic changes in muscle mass and function in ESRD patients.

There are several possibilities to explain the current findings. In addition to the endocrine effects on calcium homeostasis that are essential for muscle function, in vitro and in vivo studies, along with changes in muscle morphology and metabolism observed in subjects with hypovitaminosis D, have allowed the elucidation of novel pathways by which vitamin D might act directly on skeletal muscle. These include genomic and non-genomic effects (*16*, *17*). Genomic effects are delayed and include the gene expression of contractile proteins and myogenic transcription factors after interacting vitamin D with the vitamin D receptor (VDR) in skeletal muscle cells, which regulate muscle development and metabolism. Several studies confirm that VDR is expressed in muscle cells (*18*, *19*). Although VDR is expressed at low levels in resting adult muscle, markedly VDR expression and 1α-hydroxylase have been observed in neonatal muscle or following muscle injury, supporting the muscle capacity for local production of $1,25(OH)_2D$, and a developmental and regenerative role for vitamin D in this tissue (*20–22*).

Vitamin D may also interact with the VDR in muscle cells by non-genomic effects, which are independent of the intranuclear transcription process. They involve the rapid regulation of membrane calcium channels, suggesting a role for vitamin D in the calcium-mediated muscle functions, such as muscle contraction and mitochondrial function, which leads to an adequate insulin signalling and muscle substrate metabolism (*23*). In addition to changes in muscle metabolic pathways, the impact of vitamin D deficiency on skeletal muscle also concerns muscle morphology. Subjects with mutations of the VDR or severe vitamin D deficiency show generalized muscle atrophy (*20*, *24*). Changes in muscle morphology include derangement of the intermyofibrillar network, increases in intramuscular lipids, and atrophy of the fast-twitch white (type 2) fibres (*25–27*). All these findings may clarify the relationship between vitamin D status and changes in muscle mass and function.

Although several studies have described the association between low 25(OH)D levels with lower muscle strength and mass, increased body instability and falls, worse physical performance and frailty in vitamin D-deficient older adults (*8–12*), only a few studies have been undertaken in CKD patients. Gordon et al. (*28*) observed a relationship between $1,25(OH)_2D$ levels, and physical performance and muscle size in non-dialysis CKD patients. Further, Zahed et al. (*29*) showed that 25(OH)D levels were positively associated with muscle strength of the lower extremities in haemodialysis patients. A separate study also showed that lower serum 25(OH)D levels were associated with sarcopenia independent of traditional risk factors in patients undergoing haemodialysis (*30*). Some authors reported lower levels of 25(OH)D in individuals receiving PD compared to those on hemodialysis (*31*). However, the data has led to inconclusive results in terms of how serum 25(OH)D levels affect dynamic changes in muscle mass and function in ESRD patients on PD. Our study showed that lower serum 25(OH)D levels were significantly associated with increased risk of the deterioration in muscle mass and function in PD patients during a 12-mo period.

During the process of screening, patients with sarcopenia were excluded. This likely had the effect of reducing the variability in the overall baseline metrics of muscle mass and function. Thus, the distribution of muscle mass and function achieved a statistical balance (p>0.05) between the participants with 25(OH)D levels below and above 20 ng/mL. Despite the lack of statistical differences in the percentages of participants with low muscle mass, low muscle strength, or low physical function, which were higher in the group with an aver-

age 25(OH)D level below 20 ng/mL, this trend remains notable. Therefore, we adjusted for these and other potentially relevant confounding factors using logistic regression models and found that a mean 25(OH)D $<$20 ng/mL was still significantly associated with an increased risk of muscle mass and function decline.

To test the robustness of the estimation, participants with 25(OH)D$<$20 ng/mL or 25(OH)D$\geq$20 ng/mL in each visit were included as a sensitivity analysis. The relationship between mean 25(OH)D levels and the deterioration in muscle mass and function was consistent. We also conducted an subgroup analysis because of the effect modification of age. The association between mean 25(OH)D$<$20 ng/mL and the deterioration in muscle mass and function remained consistent in paticipants with age $\geq$60 y; however, no significant relationship was identified in patients with age $<$60 y. Older patients are particularly prone to develop vitamin D insufficiency or deficiency for several reasons, including a reduced cutaneous synthesis and sun daily exposure or various diseases, as gastrointestinal malabsorption (*32*, *33*). Many studies have examined the vitamin D role in muscle strength and physical performance in older adults (*8–12*). Overall, observational studies and mechanistic experiments support a biological link between a low vitamin D level and the age-related decline in muscle mass and muscle quality.

Some limitations of our study should be taken into account. Firstly, because of the inherent drawbacks of observational studies, a causal relationship cannot be clearly established. Even though we took measures during the research process and corrected relevant variables in the subsequent statistical analysis to reduce potential biases, we cannot rule out the possibility that the differences in the study may have been due to potential factors that were not collected, such as low-protein diet, low physical activity and metabolic acidosis. Secondly, we included patients without sarcopenia; however, patients with sarcopenia (non-severe sarcopenia or severe sarcopenia) were not included. Thus, our findings may not be applicable to patients with severe forms of muscle mass and function. Finally, the follow-up duration was relatively short. Consequently, the long-term relationship between serum 25(OH)D levels and dynamic changes in muscle mass and function in patients undergoing dialysis could not be monitored. Conversely, long-term follow-up may provide additional prognostic information.

In conclusion, this study demonstrated a significant association between lower serum levels of 25(OH)D and an increased risk of deterioration in both muscle mass and function among patients undergoing PD. These findings suggest that vitamin D supplementation may serve as an effective intervention for the prevention and management of sarcopenia, frailty, and their associated clinical complications. However, due to inherent limitations in the study design and the potential for Type I error, these results should be interpreted with caution. The generalizability of the findings warrants further investigation to confirm their external validity. Consequently, additional research is essential to establish a robust causal relationship between serum 25(OH)D levels and the dynamic decline in muscle mass and function in dialysis patients.

Authorship

Lailiang Wang and Qun Luo contributed to the conception and design of the research. Congping Xue and Beixia Zhu contributed to participants screening, data collection and acquisition, and muscle mass and function assessment. Fangfang Zhou contributed to statistical analyses and interpretation. Lailiang Wang drafted the manuscript. All authors have read and agreed to approve the final manuscript.

Disclosure of state of COI

The authors declare that they have no competing interests.

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Data availability

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Supporting information

Supplemental online material is available on J-STAGE.

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