Research Article

Association between Vitamin D Level and Muscle Strength in Patients Undergoing Hemodialysis

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Keywords

Hemodialysis · Muscle mass · Handgrip strength · Vitamin D · Physical performance

Abstract

Introduction: Identification of the risk factors and treatment of the decrease in muscle mass or strength are important to improve the prognosis of patients undergoing hemodialysis (HD). Previous studies have investigated the association between vitamin D level and muscle mass or strength in patients undergoing HD. However, there are conflicting results regarding this association. **Objective:** To evaluate the association between vitamin D level and muscle mass indices, strength, or physical performance in patients undergoing HD. **Methods:** This study was performed in a tertiary medical center. We included patients undergoing HD aged ≥ 20 years. A total of 84 patients were enrolled. The patients were divided into tertiles based on the 25-hydroxy (25-OH) vitamin D level as follows: lowest tertile (Lowest T, $n = 28$), middle tertile (Middle T, $n = 28$), and highest tertile (Highest T, $n = 28$). We evaluated the association between the tertiles and clinical outcomes including nutritional status, muscle mass, muscle function, handgrip strength (HGS), physical performance, and health-related quality of life (HRQoL) scales. **Results:** There were no significant differences in the muscle mass indices and nutritional markers according to tertiles of 25-OH vitamin D level. However, 25-OH vitamin D level as a continuous variable or the tertile of 25-OH vitamin D level as a categorical variable was positively associated with HGS. Logistic and linear regression analyses showed a consis-

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tent superiority of the Highest T in HGS compared with the Lowest or Middle T. Although the statistical significance was weak, the scores of various physical performance tests and the HRQoL scales were highest in the Highest T among the 3 tertiles. **Conclusion:** The present study demonstrated that serum vitamin D level is associated with HGS in patients undergoing HD regardless of muscle mass indices or nutritional status.

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Introduction

End-stage renal disease is a health problem that requires renal replacement therapy. Hemodialysis (HD) is the most common renal replacement modality, and the prevalence of HD among all patients undergoing dialysis was estimated to be 63.1% in the USA and 71% in Korea [1, 2]. A previous report has shown that patients undergoing HD are prone to an accelerated aging process [3]. Among the factors accelerating aging, decrease in muscle mass or strength, caused by various pathologies such as uremic toxicity, upregulation of the renin-angiotensin system, inflammation, or anorexia, has been an important issue in patients undergoing HD. Previous studies have shown an association between poor prognosis and sarcopenia in patients with end-stage renal disease [4–6]. Identification of the risk factors and treatment of the decrease in muscle mass or strength are important to improve the prognosis of patients undergoing HD.

The role of vitamin D in patients undergoing HD is multifactorial. Vitamin D was originally described as a factor that contributes to maintaining bone health and/or the homeostasis of calcium/phosphorus. Recent studies have shown the role of vitamin D in muscle health and function [7]. Experimental studies have suggested that vitamin D has favorable effects on muscle through its indirect effect via calcium homeostasis and direct effect via vitamin D receptors in skeletal muscle [7]. Previous studies have investigated the association between vitamin D level and muscle mass or strength in patients undergoing HD [8–12]. However, there are conflicting results regarding this association. Gordon et al. [8] investigated 49 patients undergoing HD and observed that those with vitamin D replacement had increased thigh muscle area (TMA) and strength compared with those without replacement. However, they did not evaluate vitamin D level. Hewitt et al. [13] performed a randomized controlled trial with patients undergoing HD with low vitamin D level but did not find a positive association between vitamin D replacement and muscle strength or functional capacity. Considering these conflicting results or heterogeneity in study design, further investigations are needed to identify the definite association between vitamin D level and muscle health. Our study aimed to address these issues and to evaluate the association between vitamin D level and muscle mass indices, strength, or physical performance through comprehensive measurements in patients undergoing HD.

Patients and Methods

Study Population

This study was performed in a tertiary medical center between September 2012 and March 2015. We included all patients undergoing HD aged ≥ 20 years, with dialysis duration ≥ 6 months, ability to ambulate without an assistive device, ability to communicate with the interviewer, and no hospitalization within the last 3 months before enrollment. A total of 84 patients were enrolled. Informed consent was obtained from all patients. None of the patients were taking opioids, antihistamines, or antidepressants, which are drugs associated with

decreased physical activity and cognitive function. The patients were divided into tertiles based on the 25-hydroxy (25-OH) vitamin D level as follows: lowest tertile (Lowest T), middle tertile (Middle T), and highest tertile (Highest T).

Study Variables

Data concerning sex, age, presence of diabetes mellitus (DM), dialysis vintage, Charlson's comorbidity index, and use of vitamin D agents were collected as demographic data. Data regarding hemoglobin (g/dL), high-sensitivity C-reactive protein (mg/dL), blood urea nitrogen (mg/dL), creatinine (mg/dL), aspartate transaminase (U/L), alanine transaminase (U/L), calcium (mg/dL), phosphorus (mg/dL), sodium (mEq/L), potassium (mEq/L), chloride (mEq/L), intact parathyroid hormone (pg/mL), total cholesterol (mg/dL), albumin (g/dL), 25-OH vitamin D, and spKt/Vurea were collected as laboratory data.

Serum 25-OH vitamin D level (ng/mL) was measured using an electrochemiluminescent immunoassay (LIAISON; DiaSorin Inc., Saluggia, Italy). We defined each serum 25-OH vitamin D level by using the average value of 2 measurements. Based on this, we divided the patients into two groups: deficient or nondeficient groups. The deficient group was defined as <20 ng/mL of 25-OH vitamin D level, according to previous guidelines [14]. DM was defined as a patient-reported history and a medical record of a DM diagnosis or medication. Charlson's comorbidity index was calculated using the age-adjusted method, as described in a previous report [15]. Use of vitamin D agents was defined as intake of vitamin D supplementation as cholecalciferol or calcitriol, or vitamin D analogs such as paricalcitol at enrollment. Erythropoiesis stimulating agents were evaluated as units per week. In our study, all patients used darbepoetin- α or erythropoietin- α . The conversion ratio from darbepoetin- α to erythropoietin- α was 200:1. The use of vitamin D or erythropoietin- α dose was defined as supplementation in the week during which the muscle mass indices, strength, or physical performance were measured. spKt/Vurea was calculated using Daugirdas's formula [16].

Assessment of Muscle Mass Indices and Subjective Global Assessment

We performed 2 muscle mass measurements using whole-body dual X-ray absorptiometry (DEXA) and computed tomography (CT) of the thigh. Two measurements were performed at midweek following the HD session. DEXA was performed by a technologist using a Prodigy Advance instrument (GE Medical Systems Lunar, Madison, WI, USA) while each patient was in a supine position and wearing a light gown. Appendicular skeletal muscle mass (appendicular lean mass [ALM], kg) was defined as the sum of both extremities. After the DEXA measurement, each patient underwent a multi-slice, mid-thigh CT scan using a 320-slice CT scanner (Aquilion ONE; Toshiba Medical Systems Corp., Tokyo, Japan). An axial image was obtained at the midpoint of a line extending from the superior border of the patella to the greater trochanter (3-mm thickness, 5 slices). The images were analyzed using an image analysis software (ImageJ 1.45S; National Institutes of Health, Bethesda, MD, USA). Finally, TMA (cm^2) was calculated. ALM and TMA were adjusted using height squared (Ht^2) in meters.

Body mass index (kg/m^2) was calculated using body weight per Ht^2 . Subjective global assessment (SGA) was calculated using scores from 7 items (weight loss, dietary intake, gastrointestinal symptoms, functional capacity, comorbidity, decreased fat, and decreased muscle) [17].

Assessment of Strength, Physical Performance, and Health-Related Quality of Life

Handgrip strength (HGS) was measured in all patients. Each patient performed 3 trials with the dominant hand using a manual hydraulic dynamometer (Jamar® Hydraulic hand dynamometer; Sammons Preston, Chicago, IL, USA). The maximum strength over the 3 trials

was recorded. The low HGS group was defined following a previous report (HGS <26 kg for men and <18 kg for women) [18].

Each patient underwent the Short Physical Performance Battery (SPPB) test, sit-to-stand for 30 s test (STS30), 6-min walk test (6-MWT), and timed up-and-go test (TUG). The SPPB test consisted of usual gait speed (GS), sit-to-stand test performed 5 times (5STS), and balance tests, with scores ranging from 0 to 12 [19]. For GS, the patients were asked to walk a 4-m distance and the time taken (in seconds) to walk the distance was recorded. For the 5STS test, each patient was seated on a chair with the arms crossed and the hands touching the shoulders [20]. The patients were asked to stand up and sit down 5 times as quickly as possible, and the time taken in seconds was recorded. For the STS30, the patients were seated on a chair with the arms crossed and the hands touching the shoulders. Scores were defined as the number of stands a patient could complete in 30 s without using the arms as support [21]. For the 6-MWT, the patients were asked to walk at their usual pace for 6 min, and the distance covered was recorded in meters [22]. For the TUG, the patients were instructed to stand up from an armchair, walk 3 m, turn around, return to the chair, and sit down [23]. The time in seconds was recorded. We also defined low physical performance groups for the SPPB and GS tests. The low SPPB group was defined as patients with a score of ≤ 10 . The low GS group was defined as those with a speed of ≤ 1 m/s [18].

The average number of steps was measured using a pedometer. The presence of frailty was defined using Johansen's method [24]. Briefly, slowness, poor endurance, physical inactivity, and unintentional weight loss were components of frailty. The presence of each frailty component was scored as 1, and the scores of all components were summed. Those patients scoring ≥ 3 points were defined as having frailty.

Sarcopenia was defined using cut-off values from the Asian Working Group for Sarcopenia [18]. Patients with both low muscle mass (<7.0 kg/m² for men and <5.4 kg/m² for women) and low HGS (<26 kg for men and <18 kg for women) were classified as having sarcopenia.

Health-related quality of life (HRQoL) was assessed using the Kidney Disease Quality of Life (KDQOL)-SF™ 1.3, Korean version [25]. Briefly, KDQOL-SF 1.3 includes the short-form 36 scale (36 items) and the kidney disease-specific scale (11 items). The total score (from 0 to 100) was calculated for each domain. A low score means a low quality of life. The physical component scale and mental component scale were calculated according to previous reports [26, 27]. The kidney disease component scale was defined as the sum of scores from 10 kidney disease-specific items except sexual function. Questionnaires were completed during the dialysis sessions.

Statistical Analysis

The data were analyzed using the statistical software IBM SPSS Statistics version 21 (SPSS Inc., Chicago, IL, USA). Categorical variables were expressed as counts (with percentages). Continuous variables were expressed as mean $\pm$ standard deviation. For continuous variables, means were compared using the *t* test. The correlation between 2 continuous variables was assessed using Pearson's correlation analysis. Linear regression analysis was performed to assess the independent predictors of HGS. Logistic regression analysis was used to estimate the odds ratios and 95% confidence intervals (95% CIs), which were used to determine the relationship between the Highest T and the low HGS group. Multivariate analysis was adjusted for age, sex, ALM/Ht², serum albumin, and DM. The level of statistical significance was set at $p < 0.05$.

Results

Participants' Clinical Characteristics

The 25-OH vitamin D level in the Lowest, Middle, and Highest T was 5.9 ± 1.1 , 10.1 ± 1.2 , and 18.4 ± 8.4 ng/mL, respectively. The mean patient age in the Lowest, Middle, and Highest

Table 1. Participants' clinical characteristics

	Lowest T (n = 28)	Middle T (n = 28)	Highest T (n = 28)	p value
Sex (male)	15 (53.6)	10 (35.7)	19 (67.9)	0.054
Age, years	55.5±11.7	58.2±13.1	55.9±11.2	0.664
Diabetes mellitus	19 (67.9)	14 (50)	11 (39.3)	0.096
Dialysis vintage, years	3.6±5.4	4.8±4.8	5.3±5.2	0.482
Charlson's comorbidity index score	5.9±2.1	5.9±2.7	5.1±1.9	0.291
Hemoglobin, mg/dL	11.0±0.7	11.1±0.6	10.8±0.5	0.301
High sensitivity C reactive protein, mg/dL	0.41±0.49	0.32±0.41	0.54±0.82	0.402
Blood urea nitrogen, mg/dL	55.5±12.8	60.8±14.0	62.0±16.6	0.213
Creatinine, mg/dL	9.8±2.3	9.8±2.3	11.3±3.0	0.042
Aspartate transaminase, U/L	16.5±4.0	18.4±6.0	18.7±7.1	0.316
Alanine transaminase, U/L	14.5±5.8	16.7±9.2	16.3±7.2	0.510
Serum calcium, mg/dL	8.2±0.6	8.4±0.6	8.5±0.8	0.200
Serum phosphorus, mg/dL	5.3±1.4	5.4±1.2	5.5±1.1	0.891
Serum sodium, mEq/L	137±3	137±3	139±3	0.075
Serum potassium, mEq/L	5.0±0.6	5.1±0.5	5.0±0.6	0.310
Serum chloride, mEq/L	97.9±3.6	98.2±3.7	99.4±2.8	0.208
Intact parathyroid hormone, pg/mL	308.5±217.1	243.3±147.4	2,38.9±177.3	0.286
Total cholesterol, mg/dL	154.7±34.2	165.7±40.6	141.3±22.4*	0.027
spKt/Vurea	1.36±0.35	1.44±0.34	1.29±0.20	0.204
Vitamin D agents				0.795
None	12 (42.9)	12 (42.9)	9 (32.1)	
Vitamin D	4 (14.3)	3 (10.7)	6 (21.4)	
Vitamin D analog	12 (42.9)	13 (46.4)	13 (46.4)	
Erythropoietin-α dose, units/week	6,803±5,670	7,553±4,597	8,000±6,848	0.737

Data are expressed as mean ± standard deviation for continuous variables and as number (percentage) for categorical variables. Lowest T, lowest tertile; Middle T, middle tertile; Highest T, highest tertile; 25-OH vitamin D, 25-hydroxy-vitamin D. *p* values were tested using one-way ANOVA, followed by a post hoc Tukey comparison for continuous variables and Pearson's χ^2 or Fisher's exact tests for categorical variables. * *p* < 0.05 compared with Middle T.

Table 2. Comparison of muscle mass indices and nutritional markers according to the tertiles of vitamin D level

	Lowest T	Middle T	Highest T	p value
ALM/Ht ² , kg/m ²	6.6±1.1	6.3±0.8	6.8±1.0	0.152
SGA score	5.8±0.9	5.7±1.0	5.6±1.2	0.812
Serum albumin, mg/dL	3.8±0.3	3.9±0.2	3.8±0.3	0.295
Body mass index, kg/m ²	24.5±4.0	23.4±3.2	23.3±3.7	0.428
TMA/Ht ² , cm ² /m ²	36.9±7.9	35.3±5.4	38.4±7.5	0.268

Data are expressed as mean ± standard deviation. ALM/Ht², appendicular lean mass per height squared; SGA, subjective global assessment; TMA/Ht², thigh muscle area per height squared; Lowest T, lowest tertile; Middle T, middle tertile; Highest T, highest tertile.

T was 55.5 ± 11.7, 58.2 ± 13.1, and 55.9 ± 11.2 years, respectively (Table 1). The proportion of male patients in the Lowest, Middle, and Highest T was 53.6, 35.7, and 67.9%, respectively. The proportion of patients with DM and Charlson's comorbidity index value was similar among the 3 groups. There were no significant differences in hemoglobin, blood urea nitrogen, aspartate transaminase, alanine transaminase, serum calcium, phosphorus, sodium, potassium, chloride, intact parathyroid hormone, dose of erythropoietin-α, and spKt/Vurea

Fig. 1. Correlation between 25-OH vitamin D level and handgrip strength.

Table 3. Logistic regression analysis of low handgrip strength according to vitamin D level

	Univariate		Multivariate	
	OR (95% CI)	p value	OR (95% CI)	p value
Age	1.04 (0.99–1.09)	0.178	1.01 (0.96–1.08)	0.654
Sex (ref: men)	0.96 (0.31–2.92)	0.935	0.09 (0.01–0.64)	0.017
Diabetes mellitus	2.06 (0.64–6.65)	0.227	2.75 (0.64–11.87)	0.174
Serum albumin	0.92 (0.12–6.76)	0.932	1.30 (0.08–20.86)	0.855
ALM/Ht ²	0.37 (0.18–0.75)	0.006	0.14 (0.04–0.48)	0.002
Lowest or Middle T (ref: Highest T)	9.00 (1.12–72.4)	0.039	13.06 (1.18–144.32)	0.036

Multivariate analysis was adjusted for age, sex, diabetes mellitus, ALM/Ht², serum albumin, and tertiles according to vitamin D level. OR, odds ratio; 95% CI, 95% confidence interval; ref, reference; ALM/Ht², appendicular lean mass per height squared; Lowest T, lowest tertile; Middle T, middle tertile; Highest T, highest tertile.

among the 3 groups. The number of patients taking vitamin D agents was similar among the 3 groups. Regarding the creatinine level, one-way ANOVA showed a statistically significant trend among the 3 tertiles, but the post hoc Tukey comparison showed a nonsignificant difference among the 3 tertiles ($p = 1.000$ for Lowest T vs. Middle T, $p = 0.072$ for Lowest T vs. Highest T, $p = 0.074$ for Middle T vs. Highest T). The total cholesterol level was greater in the Middle T than in the Highest T.

Association between Vitamin D Levels and Muscle Strength or Muscle Mass Indices

Table 2 shows that the ALM/Ht², body mass index, and TMA, as muscle indices, were not different among the 3 groups. The SGA score and serum albumin level, as nutritional markers, were also not different among the 3 groups. These findings reveal that the tertiles of vitamin D level were not associated with muscle indices and nutritional markers.

The 25-OH vitamin D level was positively associated with HGS ($r = 0.257$, $p = 0.018$; Fig. 1). After the exclusion of outliers, the association was similar ($r = 0.281$, $p = 0.013$; online suppl. Fig. S1; for all online suppl. material, see www.karger.com/doi/10.1159/000506986). The HGS values in the Lowest, Middle, and Highest T were 25.1 ± 5.8 , 23.5 ± 7.3 , and 29.6 ± 7.7 kg, respectively ($p = 0.005$). The post hoc analysis showed that p values were $p = 0.654$ for

Table 4. Linear regression analysis of handgrip strength according to the tertiles of vitamin D level

	Univariate		Multivariate	
	standardized β (SE)	p value	standardized β (SE)	p value
Age	–0.31 (0.07)	0.004	–0.24 (0.06)	0.010
Sex (ref: men)	–0.56 (1.35)	<0.001	–0.38 (1.49)	<0.001
Diabetes mellitus	–0.20 (1.59)	0.070	–0.17 (1.26)	0.049
Serum albumin	–0.03 (2.90)	0.795	–0.08 (2.31)	0.351
ALM/Ht ²	0.50 (0.72)	<0.001	0.22 (0.79)	0.042
Lowest or Middle T (ref: Highest T)	–0.34 (1.61)	0.002	–0.18 (1.33)	0.039

Multivariate analysis was adjusted for age, sex, diabetes mellitus, ALM/Ht², and tertiles according to vitamin D level. SE, standard error; ref, reference; ALM/Ht², appendicular lean mass per height squared, Lowest T, lowest tertile; Middle T, middle tertile; Highest T, highest tertile.

Lowest T versus Middle T, $p = 0.049$ for Lowest T versus Highest T, and $p = 0.004$ for Middle T versus Highest T, respectively. Among the 3 tertiles, the Highest T had the highest HGS value. The number of patients with low HGS in the Lowest, Middle, and Highest T was 7 (25.0%), 7 (25.0%), and 1 (3.6%), respectively ($p = 0.027$). Among the 3 tertiles, the Highest T showed the lowest proportion of patients with low HGS.

Logistic and Linear Regression Analyses of HGS according to the Tertiles of Vitamin D Level

Univariate logistic regression analysis showed that patients in the Lowest or Middle T had a 9.00 odds ratio (95% CI, 1.12–72.4) for low HGS compared with those in the Highest T (Table 3). Linear regression analysis showed that the Lowest or Middle T had an inverse association with the HGS value compared with the Highest T (Table 4). Multivariate analysis adjusted for age, sex, DM, serum albumin, and ALM/Ht² showed similar results to those of univariate analysis.

Association between Vitamin D Level and Physical Performance or HRQoL

We analyzed the association between additional performance tests and tertiles of vitamin D level (online suppl. Table S1). The number of patients with low SPPB or frailty significantly decreased as the tertile of vitamin D level increased. GS, SPPB, STS30, and 6MWT, as continuous variables, increased as the tertile of vitamin D level increased. In addition, STS5 and TUG decreased as the tertile of vitamin D level increased. The average step count was lowest in the Lowest T among the 3 tertiles. However, statistical significance was not obtained for GS, SPPB, STS30, 6MWT, STS5, TUG, and average step count.

The physical component scale score in the Lowest, Middle, and Highest T was 66.5 ± 16.0 , 69.8 ± 18.9 , and 70.0 ± 18.7 , respectively ($p = 0.712$). The mental component scale score in the Lowest, Middle, and Highest T was 70.7 ± 17.9 , 71.8 ± 14.6 , and 73.5 ± 16.8 , respectively ($p = 0.819$). The kidney disease component scale score in the Lowest, Middle, and Highest T was 69.4 ± 9.3 , 69.0 ± 8.4 , and 71.1 ± 10.3 , respectively ($p = 0.670$). The highest scores in the 3 scales were observed in the Highest T among the 3 tertiles; however, statistical significance was not reached.

The results according to the presence of vitamin D deficiency are shown in online supplementary Table S2. The deficient group had significantly lower HGS than the nondeficient group. Univariate logistic regression analysis showed that the patients with deficient 25-OH vitamin D level had a 2.76 odds ratio (95% CI, 0.85–8.93; $p = 0.091$) for low HGS compared to the patients with nondeficient 25-OH vitamin D level. Multivariate analysis adjusted for age,

sex, DM, serum albumin, and ALM/Ht² showed that patients with deficient 25-OH vitamin D level had a 3.65 odds ratio (95% CI, 0.87–15.34; $p = 0.077$) for low HGS compared to those with nondeficient 25-OH vitamin D level. Statistical significance was not obtained, but the trend showed a positive association between the deficient group and low HGS.

Subgroup Analyses according to Sex and DM

For men, the HGS value in the Lowest, Middle, and Highest T was 27.5 ± 5.7 , 28.3 ± 7.9 , and 32.7 ± 7.3 kg, respectively ($p = 0.080$). For women, the HGS value in the Lowest, Middle, and Highest T was 22.3 ± 4.6 , 20.8 ± 5.6 , and 23.0 ± 3.1 kg, respectively ($p = 0.478$). For patients without DM, the HGS value in the Lowest, Middle, and Highest T was 27.1 ± 6.6 , 24.5 ± 6.7 , and 30.4 ± 9.3 kg, respectively ($p = 0.134$). For patients with DM, the HGS value in the Lowest, Middle, and Highest T was 24.2 ± 5.3 , 22.4 ± 8.0 , and 28.4 ± 4.5 kg, respectively ($p = 0.059$). Although statistical significance was not obtained, HGS was highest in the Highest T among the 3 tertiles in all subgroup analyses.

We did not evaluate the subgroup analysis for use of vitamin D agents. In our study, approximately 33 (39.3%) patients did not use vitamin D agents. It is difficult to analyze data after the exclusion of patients with use of vitamin D agents due to the very small sample size in this study. However, we added the data for multivariate analyses after inclusion of the use of vitamin D agent as a covariate. Multivariate logistic regression analysis showed that patients in the Lowest or Middle T had a 13.27 odds ratio (95% CI, 1.17–151.05) for low HGS compared with those in the Highest T. Multiple linear regression analysis showed that the standardized β was 0.18 (SE, 1.33) and there was statistical significance ($p = 0.039$). The results were similar to those without the addition of the use of vitamin D as a covariate.

Discussion

In our study, there were no significant differences in the muscle mass indices and nutritional markers according to tertiles of 25-OH vitamin D level. However, 25-OH vitamin D level as a continuous variable or the tertile of 25-OH vitamin D level as a categorical variable was positively associated with HGS. Logistic and linear regression analyses showed a consistent superiority of the Highest T in HGS compared with the Lowest or Middle T. Although the statistical significance was weak, the scores of various physical performance tests and the HRQoL scales were highest in the Highest T among the 3 tertiles. Subgroup analyses showed similar trends to those of the total cohort.

Experimental data have shown favorable effects of vitamin D on muscle. Some studies showed a positive association between muscle health and vitamin D level or supplementation in patients undergoing dialysis. Wanic-Kossowska et al. [28] investigated 8 patients undergoing dialysis and observed improvements in clinical manifestations and an increase in serum creatinine levels after calcitriol treatment for 15 months. After their report, 4 cross-sectional studies showed a positive association between vitamin D and muscle health in patients undergoing HD. Gordon et al. [8] investigated 49 patients undergoing HD with or without vitamin D supplementation, and observed that patients undergoing HD with vitamin D supplementation had better nutritional status, muscle mass, and strength. However, they did not evaluate the 25-OH vitamin D level and physical performance tests. The other studies divided the patients according to 25-OH vitamin D level and showed a positive association between muscle strength and 25-OH vitamin D level; however, their data on physical performance or muscle mass were insufficient [9, 11, 12]. Taskapan et al. [29] studied patients with vitamin D deficiency among those with chronic kidney disease stage 3 and 4 and undergoing peri-

toneal dialysis. Among the total patients, those with vitamin D supplementation showed improvement of muscle strength, functional ability, and balance.

Some studies have shown partially positive associations. Mori et al. [10] compared the total muscle mass between patients with and those without vitamin D supplementation regardless of the 25-OH vitamin D level. They found a positive association only in men. Bučar Pajek et al. [30] investigated patients undergoing dialysis and a healthy population. They observed a positive association with 25-OH vitamin D level in some performance tests, but not in others, regardless of dialysis. Two studies showed negative associations. Heaf et al. [31] enrolled patients with chronic kidney disease stage 3, 4, or 5, or those undergoing peritoneal dialysis, and did not observe an association between 25-OH vitamin D level and HRQoL scales or muscle function. Hewitt et al. [13] performed a randomized controlled trial with 60 patients undergoing HD with decreased 25-OH vitamin D level. They compared muscle strength, functional capacity, and HRQoL scales between patients with cholecalciferol supplementation and those who received placebo. They did not observe significant differences in outcomes between the 2 groups.

The conflicting results regarding the association between 25-OH vitamin D level and muscle mass, strength, or physical performance test emphasize the need for additional studies. The strength of our study is the comprehensive evaluation including nutritional status, muscle function, muscle strength, physical performance, and HRQoL scales. We attempted to show the independent association of 25-OH vitamin D level with each outcome. Our data included CT measurements of the thigh for the accurate quantitation of muscle mass and DEXA of the whole body for the quantitation of whole-body lean mass. Each variable was adjusted for Ht^2 . We evaluated nutritional status using serum albumin level and SGA score; muscle strength using HGS; and physical performance using SPPB, GS, STS30, 6MWT, STS5, TUG, average steps, and presence of frailty as categorical variables. In addition, HRQoL scales using the Korean version of the KDQOL were evaluated. Our study revealed no significant difference in muscle mass indices and nutritional status; however, muscle strength was greater in patients in the Highest T than in those in the other tertiles. Favorable scores in the physical performance tests and HRQoL scales were obtained in patients in the Highest T; however, the statistical significance was weak.

In our study, the 1,25-dihydroxy-vitamin D (1,25-OH vitamin D) level was not evaluated. 1,25-OH vitamin D level is the active form of vitamin D, but it has a short half-life (4 h) and much lower level (1/1,000th) than 25-OH vitamin D level. The Endocrine Society recommends using the serum circulating 25-OH vitamin D level to evaluate vitamin D status [14]. Although additional data for 1,25-OH vitamin D level may be helpful in chronic kidney disease, the KDIGO guideline does not recommend a routine measurement of 1,25-OH vitamin D level, which would be associated with incomplete standardization and no data indicating the association between the 1,25-OH vitamin D levels and clinical outcome [32]. Therefore, most epidemiologic studies have evaluated 25-OH vitamin D rather than 1,25-OH vitamin D level as vitamin D status. Regarding the creatinine level, the trend showed the greatest creatinine level in Highest T, which may be associated with greater muscle mass rather than lesser renal function in HD patients. In addition, determining the estimated glomerular filtration rate using creatinine would be inappropriate in patients undergoing maintenance HD, because serum creatinine is a non-steady-state condition and can be removed by extra-renal elimination in HD patients [33]. In addition, the 1- α hydroxylase level would be influenced by parathyroid hormone, calcium, and phosphorus levels, but in our study, there were no significant differences in these levels. Residual renal function would be helpful to evaluate the activity of 1 α -hydroxylase, but there are few data that provide any insight in the relationship between the two variables. Therefore, 25-OH vitamin D level would be highly correlated with 1,25-OH vitamin D level as an active form in our study.

Data from DEXA and CT may be a little repetitive. However, DEXA can measure all appendicular muscle mass and CT measures muscle area from the thigh on one side. Muscle mass measurement from one point would be more precise in CT than in DEXA. However, regarding the overall muscle measurements, DEXA measurements would be helpful to overcome the error from measurement of one point using CT.

Our study has some inherent limitations. First, this study was performed in a single center and is limited by the small number of patients. Further, this study had a cross-sectional design and was a retrospective analysis using a cohort from a previous study [34]. Therefore, we did not calculate the sample size to confirm statistical significance. We included all patients who provided informed consent. We believe that the lack of statistical significance in physical performance tests and/or HRQoL may be associated with the small number of patients. Second, 25-OH vitamin D levels were determined with electrochemiluminescent immunoassay, and we did not consider the effect of the season or month of blood sampling collection. Measurements using electrochemiluminescent immunoassay would lead to underestimation of 25-OH vitamin D levels compared with radioimmunoassay or liquid chromatography-tandem mass spectrometry [35, 36]. In addition, 25-OH vitamin D level alone does not reflect the exact bioavailability, and a combination of recent methods such as vitamin D-binding protein level may help to represent the vitamin D status [37]. Third, our study did not include sufficient biomarkers of inflammation, which are associated with vitamin D deficiency. In our study, high-sensitivity C-reactive protein as a positive inflammatory marker and serum albumin as a negative acute-phase protein were evaluated. There was no significant difference in high-sensitivity C-reactive protein and albumin levels among the tertiles. In addition, our study included only stable HD patients. These reveal that the effect of inflammation as a confounding factor may not be large. However, our study did not completely exclude the effect of inflammation. A longitudinal study including more precise methods and a large number of patients is warranted to overcome these limitations. Further, another unresolved issue is whether vitamin D supplementation in patients undergoing HD with low vitamin D level could be effective in improving muscle mass, strength, or physical performance.

In conclusion, the present study demonstrated that serum vitamin D level may be associated with HGS in patients undergoing HD regardless of muscle mass indices or nutritional status.

Statement of Ethics

This study was approved by the institutional review board of a Medical Center (approval No. 12-07). The board waived the need for informed consent because the subjects' records and information were anonymized and de-identified prior to the analysis.

Disclosure Statement

The authors declare that they have no financial conflicts of interest.

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Author Contributions

S.H.K. conceived and designed the study, performed the analysis and interpretation of data, and wrote the manuscript. J.-H.C., H.Y.J., and D.H.Y. performed the generation and collection of data. J.Y.D. and J.C.K. drafted and revised the manuscript. All authors approved the final version of the manuscript.

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