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Original Article

Associations between serum 25-hydroxyvitamin D_3 level and skeletal muscle mass and lower limb muscle strength in Japanese middle-aged subjects

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Abstract

Objectives: One of the important risk factors of falling is decreased muscle mass and muscle strength. Recently, there has been an increasing concern on the role of vitamin D in muscle strength and physical activity. Aim of our study is to examine the relationships between vitamin D status and muscle mass and muscle strength in middle-aged healthy adults.
Methods: Subjects were 40 healthy volunteers aged 42.0 ± 10.6 years old. Evaluation was made for serum vitamin D_3 metabolites including 25-hydroxyvitamin D_3 [25(OH)D_3] and 24,25-dihydroxyvitamin D_3 [24,25$(OH)_2D_3$] concentrations, lower limb muscle strength, and dietary intake by food frequency questionnaire. Body composition was measured by dual-energy X-ray absorptiometry (DXA), and appendicular skeletal mass index (ASMI) was calculated as skeletal muscle mass/squared height.
Results: 70% of the subjects had vitamin D insufficiency/deficiency (serum total 25(OH)D < 20 ng/mL), and female subjects had significantly lower serum total 25(OH)D level compared with males. Vitamin D insufficiency/deficiency group had significantly higher body fat, lower SMI and muscle strength, probably reflecting higher percentage of female subjects. Serum vitamin D_3 metabolites levels were significantly correlated with whole and site-specific ASMI, and lower limb muscle strength, except for the correlation between serum 24,25$(OH)_2D_3$ concentration and lower limb muscle strength. In addition, serum 25(OH)D_3 level was a positive significant predictor for both ASMI and lower limb muscle strength, while serum 24,25$(OH)_2D_3$ level was not their significant predictor.
Conclusions: Serum 25(OH)D_3 level was significantly correlated with both skeletal muscle mass and lower limb muscle strength.

Keywords: 25-hydoxyvitamin D_3; 24,25-dihydroxyvitamin D_3; Skeletal muscle mass; Lower limb muscle strength; Japanese subjects

1. Introduction

Non-vertebral fractures are mostly caused by falling. Although vitamin D is well known to be an essential nutrient for bone health, there has been an increasing concern on the role of vitamin D in maintaining muscle strength and physical activity. A meta-analysis has indicated that the vitamin D supplementation effectively reduces the risk of falls in older

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adults [1]. Also in the observational study of elderly Japanese women, lower serum 25-hydroxyvitamin D [25(OH)D] was significantly associated with an increased risk of falls [2]. Decreased muscle mass and strength is one of the important risk factors for falling, mobility, and disability [3].

Vitamin D receptors (VDR) have been identified in muscle cells [4]. 1,25 dihydroxyvitamin D [1,25$(OH)_2$D] binds to the nuclear vitamin D receptor (VDR), and forms a complex with the retinoid receptor (RXR). 1,25$(OH)_2$D/VDR/XDR complex then modulates various gene transcription. 1,25$(OH)_2$D is also postulated to bind to a putative membrane receptor which activates MAP kinase (MAPK) and phospholipase C (PLC) pathways leading to non-genomic effects [5]. Several observational studies have shown the positive relationship between serum 25(OH)D level and muscle function [6,7]. A recent meta-analysis has shown that vitamin D supplementation has a small positive effect on lower limb muscle strength [8]. However, studies related to these issues have been quite scarce in Japan. Thus, we have studied the relationship between vitamin D status, and muscle mass and strength in middle-aged Japanese elderly.

Our paper is also characterized by that vitamin D metabolites other than 25(OH)D is measured. Antibody and vitamin D binding protein (DBP) which are commonly used in the automated assay for serum 25(OH)D, bind to 25(OH)D and 24,25-dihydroxyvitamin D_3 [24,25$(OH)_2D_3$] with similar affinity. Thus, "serum total 25(OH)D" concentration actually reflects the summated levels of 25$(OH)D_3$ and 24,25-dihydroxyvitamin D_3 [24,25$(OH)_2D_3$] [9]. 25$(OH)D_3$ is either metabolized to the active form of vitamin D; 1,25$(OH)_2D_3$ or alternatively to 24,25$(OH)_2D_3$, the latter being the first step in the inactivation process and catalyzed by an enzyme, 24-hydroxylase (CYP24) [10]. There have been reports to suggest that 24,25$(OH)_2D_3$ is not merely an inactive metabolite but has its own biological action [11]. Previous reports, however, have only studied the relationship between serum total 25(OH)D level, and muscle mass and strength. In this paper, we have studied the possible different relationship of muscle mass and strength, and serum vitamin D_3 metabolites.

2. Methods

2.1. Subjects

Study subjects were forty healthy volunteers (M/F: 16/24) mostly consisting of clinical staffs working at Tamana Central Hospital. They were encouraged to participate in this study from June to July 2015. The above selection method was applied, since it would yield a group of subjects with rather uniform level of physical activity. Detailed information was given and written consent was obtained. The study protocol was approved by the ethical committee of Osaka Shoin Women's University (ID: 27-04. Approved: 11 June 2015). This study was done in August, 2015 in Kumamoto Prefecture conforming to the Declaration of Helsinki. Inclusion criteria were free-living subjects aged 20–60 years old. Exclusion criteria were routine medication that may potentially interfere with vitamin D or bone metabolism, or the current or past history of renal or liver disease, or osteoporosis.

The number of subjects needed in the current study was calculated as follows. From our preliminary data, at least 25 and 6 subjects were considered necessary in the vitamin D insufficiency/deficiency and vitamin D sufficiency group, respectively, in order to detect a kilogram per body weight (kg/BW) kg difference in the lower limb muscle strength between these groups with a two-sided statistical power of 95%. Similarly, according to the previous reports [12], at least 9 and 2 subjects were considered necessary in the vitamin D insufficiency/deficiency and vitamin D sufficiency group in order to detect a 0.15 kg/m^2 kg difference in ASMI between these groups with the same statistical power.

2.2. Methods

2.2.1. Nutritional intakes

Nutritional intakes were estimated using brief-type self-administered diet history (BDHQ) [13], which has been validated against 16-day dietary records. BDHQ is a structured questionnaire, which assesses dietary intake based on the reported consumption frequency of 58 different food and beverage items.

2.2.2. Examination of chance to sun exposure, use of sunscreen and vitamin D supplements

We have measured the subjects' sun exposure time and evaluated the use of sunscreen and vitamin D supplements using Vitamin D & Sun (VIDSUN) questionnaire [14].

2.2.3. Laboratory data

Blood was drawn after overnight fasting. After centrifugation, serum was kept frozen at −80 °C until analysis. Serum concentration of the following parameters were measured; serum albumin, triglyceride, total cholesterol, HDL-cholesterol, triglyceride, C-reactive protein, calcium, and intact parathyroid hormone (iPTH) at a central laboratory (SRL, Inc., Tokyo, Japan). LDL-cholesterol level was calculated by Friedewald's equation as total cholesterol − HDL-cholesterol − triglyceride/5.

2.2.4. Measurement of serum vitamin D_3 metabolites levels

Serum vitamin D_3 metabolites were measured by liquid chromatography tandem mass spectrometry (LC-APCI-MS/MS) [15], which is capable of measuring 25$(OH)D_3$ and 24,25$(OH)_2D_3$ separately. This method involves the use of deuterated 25$(OH)D_3$ (d6-25$(OH)D_3$) as an internal standard and the selection of a precursor and product ion with a MS/MS multiple reaction monitoring (MRM) method. Separation was carried out using a reversed-phase C18 analytical column (CAPCELL PAK C18 UG120, 5 μm; (4.6 I.D. × 250 mm) (SHISEIDO, Tokyo, Japan). The values of coefficient of variation (CV) for intra-assay and inter-assay were 3.4–9.2% and 11.9% in measurement of 25$(OH)D_3$, and 13.1–19.3% and 14.7% in measurement of 24,25$(OH)_2D_3$, respectively.

Total serum 25(OH)D level was calculated by the summation of these two metabolites levels.

2.2.5. Muscle mass measurement by dual-energy X-ray absorptiometry (DXA)

Lean body mass was measured by DXA (Discovery, Hologic Inc, Madison, Wisconsin, USA) at upper and lower limbs, and trunk. Appendicular skeletal mass index (ASMI), arm ASMI, and leg ASMI were calculated as skeletal muscle mass/squared height, upper limbs muscle mass/squared height, and lower limbs muscle mass/squared height, respectively.

2.2.6. Measurement of lower limb muscle strength

Lower limb muscle mass was measured by Quadriceps Training Machine (QTM) (Locomo Scan®, Alcare Co., Ltd. Tokyo, Japan), which was developed to measure quadriceps muscle strength [16]. Quadriceps muscle strength at the right and left knee was measured by the QTM, and muscle strength adjusted by body weight was calculated as average lower limb muscle strength/body weight.

2.2.7. Statistical analysis

Comparison between the two independent groups was made by Student's t-test or Mann–Whitney test depending on normality. Contingency table was analyzed by χ^2 test in complex sample analysis. Multiple regression analysis was employed to determine the significant predictor(s) for ASMI and lower limb muscle strength.

3. Results

3.1. Characteristics of subjects

As shown in Table 1, male subjects had significantly higher serum total 25(OH)D levels than female subjects. Although vitamin D intake in 77.5% of the subjects exceeded the Adequate Intake (AI) in Dietary Intake reference for Japanese, 2015, their serum total 25(OH)D level was below 20 ng/mL in 70% of them. The prevalence of vitamin D insufficiency and deficiency was significantly higher in female subjects compared with male. None of subjects were using supplement containing vitamin D.

3.2. Comparison of the VIDSUN questionnaire responses according to their vitamin D status

There were no significant differences between the two groups dichotomized according to their vitamin D status (Table 2). Borderline significant difference was shown in the average sun exposure in the past week, but serum total 25(OH)D level was not significantly associated with the average sun exposure time in multivariate analysis adjusted by age and sex (data not shown).

Table 1
Characteristics of subjects.

	All (n = 40)	Male (n = 16)	Female (n = 24)	p value
Age (y)	42.0 ± 10.6	38.1 ± 11.6	44.5 ± 9.2	0.059
Body height (cm)	163.1 ± 8.2	170.4 ± 6.4	158.1 ± 5.1	<0.001
Body weight (kg)	61.6 ± 14.5	73.1 ± 15.2	54.0 ± 7.1	<0.001
BMI(kg/m^2)	23.1 ± 4.4	25.2 ± 5.2	21.6 ± 3.2	0.011
Serum albumin (g/dL)	4.6 ± 0.3	4.6 ± 0.3	4.5 ± 0.3	0.311
Serum triglyceride (mg/dL)	114 (51,181)	131 (78,181)	93 (49,180)	0.180
Total cholesterol (mg/dL)	183 ± 38	165 ± 32	196 ± 37	0.009
HDL-cholesterol (mg/dL)	59 ± 16	48 ± 9	67 ± 14	<0.001
LDL-cholesterol (mg/dL)	98 ± 26	90 ± 21	103 ± 29	0.128
C-reactive protein (mg/dL)	0.02 (0.02,0.05)	0.04 (0.02,0.09)	0.02 (0.02,0.05)	0.100
Serum calcium (mg/dL)	9.2 ± 0.4	9.2 ± 0.3	9.1 ± 0.4	0.731
Serum 25(OH)D_3 (ng/mL)	15.2 ± 5.4	17.4 ± 4.6	13.7 ± 5.4	0.030
Serum 24,25$(OH)_2D_3$ (ng/mL)	1.4 ± 0.9	1.7 ± 1.0	1.2 ± 0.7	0.095
Serum total 25(OH)D (ng/mL) [25(OH)D+ 24,25$(OH)_2D_3$]	16.6 ± 6.0	19.1 ± 5.3	15.0 ± 6.0	0.030
Vitamin D status Sufficiency/insufficiency/deficiency (n)	12/23/5 (30.0/57.5/12.5)%	10/5/1 (62.5/31.3/6.2)%	2/18/4 (8.3/75.0/16.7)%	0.001[a]
Intact-PTH (pg/mL)	41 ± 19	38 ± 12	43 ± 23	0.503
Energy intake (kcal/day)	1853 ± 516	2065 ± 586	1712 ± 420	0.032
Protein intake (g/day)	65.9 ± 21.3	71.6 ± 24.6	62.2 ± 18.4	0.176
Fat intake (g/day)	58.4 ± 21.0	61.6 ± 27.0	56.2 ± 16.2	0.427
Calcium intake (mg/day)	457 ± 210	429 ± 238	475 ± 192	0.499
Vitamin D (μg/day)	10.3 (7.3,15.1)	13.6 (8.4, 18.8)	9.7 (5.6, 12.9)	0.107
Number of subject with taking vitamin D above the adequate intake of DRI (n)	31 (77.5%)	13 (81.3%)	18 (75.0%)	0.643[a]

Average ± standard deviation for Student t-test; Median (Q1, Q3) for Mann–Whitney U test.
Student t-test or Mann–Whitney U test depending on normality.
Vitamin D sufficiency; Total 25(OH)D level≧20 ng/mL, insufficiency: 10–19.9 ng/mL, deficiency: <10 ng/mL.
[a] Chi-squared test.

Table 2
Comparison of the VIDSUN questionnaire responses according to their vitamin D status.

	All (n = 40)	Vitamin D insufficiency/ deficiency total 25(OH)D <20 ng/mL (n = 28)	Vitamin D sufficiency total 25(OH)D ≧20 ng/mL (n = 12)	p value
Gender M/F	16/24	6/22	10/2	<0.001
Age (y)	42.0 ± 10.6	43.0 ± 10.0	39.6 ± 11.9	0.396
Current smoking status: yes (n)	13 (33%)	7 (25%)	6 (50%)	0.154
Sun tan in last 12 months, yes	25 (63%)	16 (57%)	9 (75%)	0.477
In sunlight lightly dressed in last 3 months Regularly/Occasionally/Never	8/31/1	6/21/1	2/10/0	0.938
Sunscreen use when going outside Always/More often than not/Sometimes/Infrequently/Never	3/4/5/11/17	2/4/4/8/10	1/0/1/3/7	0.555
Vitamin D supplement: yes	0	0	0	–
Average sun exposure in past week (min) ≥30/15–30/5–15/<5	18/10/10/2	9/9/9/1	9/1/1/1	0.055

Chi-squared test.

Table 3
Comparison of the anthropometry data and body composition according to their vitamin D status.

	All (n = 40)	Vitamin D insufficiency/ deficiency total 25(OH)D <20 ng/mL (n = 28)	Vitamin D sufficiency total 25(OH)D ≧20 ng/mL (n = 12)	p value
BMI (kg/m^2)	23.1 ± 4.4	22.4 ± 4.3	24.6 ± 4.4	0.163
Total body fat (%)	27.1 ± 6.7	29.2 ± 4.6	22.2 ± 8.2	0.015
Trunk fat (%)	26.6 ± 7.1	28.0 ± 5.7	23.3 ± 8.9	0.117
ASMI (kg/m^2)	6.46 (5.43, 7.61)	5.68 (5.23, 6.88)	7.73 (7.39, 8.43)	<0.001
Arm ASMI (kg/m^2)	1.54 (1.17, 1.96)	1.31 (1.14, 1.66)	1.98 (1.79, 2.19)	<0.001
Leg ASMI (kg/m^2)	4.87 (4.28, 5.60)	4.40 (4.04, 5.34)	5.83 (5.44, 6.32)	<0.001
Lower limb muscle adjusted by BW (kg/BW)	0.64 ± 0.19	0.58 ± 0.18	0.76 ± 0.15	0.004

Average ± standard deviation for Student t-test; Median (Q1, Q3) for Mann–Whitney U test.
Student t-test or Mann–Whitney U test depending on normality.
BW: body weight.

3.3. Comparison of the anthropometrical data and body composition according to their vitamin D status

Table 3 shows that vitamin D insufficiency/deficiency group has significantly higher body fat, lower SMI and muscle strength, which, however, probably reflects higher percentage of female subjects in this group.

3.4. The correlation between serum vitamin D_3 metabolites levels and skeletal mass index, lower limbs muscle strength

Table 4 shows that all serum vitamin D_3 metabolites levels were significantly correlated with all parts of ASMI examined here and lower limb muscle strength, except for the correlation between serum 24,25$(OH)_2D_3$ concentration and lower limb muscle strength. However, these significant correlations between serum total 25(OH)D level and whole and site-specific ASMI disappeared in an age and sex adjusted model.

3.5. Independent predictors for ASMI and lower limb muscle strength

As shown in Table 5, serum 25$(OH)D_3$ level was a positive significant predictor for ASMI. Serum 25$(OH)D_3$ level was also significantly positive associated with lower limb muscle strength, while serum 24,25$(OH)_2D_3$ level was a negative predictor for borderline significance.

4. Discussion

We have studied the relationships between serum concentrations of vitamin D_3 metabolites and lower muscle mass and strength in middle-aged Japanese subjects. Vitamin D

Table 4
The correlation between serum vitamin D_3 metabolites levels and ASMI, lower limbs muscle strength adjusted by BW (unadjusted correlation).

	25$(OH)D_3$	24,25$(OH)_2D_3$	Total 25(OH)D
ASMI (kg/m^2)	r = 0.455**	r = 0.331*	r = 0.453**
Arm ASMI (kg/m^2)	r = 0.422**	r = 0.340*	r = 0.424**
Leg ASMI (kg/m^2)	r = 0.458**	r = 0.318*	r = 0.453**
Lower limb muscle adjusted by BW (kg/BW)	r = 0.388*	r = 0.140	r = 0.366*

Pearson's correlation. *; $p < 0.05$, **; $p < 0.01$.
BW: body weight.

Table 5
Independent factor(s) for ASMI and lower limb muscle strength.

Variable	β coefficient	95% CI	p value	R^2
ASMI				
Sex (M = 1, F = 2)	−1.394	−1.736 to −1.053	<0.001	0.920
Age	−0.015	−0.029 to −0.001	0.039	
BMI	0.199	0.164 to 0.234	<0.001	
$25(OH)D_3$	0.046	0.007 to 0.085	0.007	
$24,25(OH)_2D_3$	0.002	−0.236 to 0.240	0.984	
Lower limb muscle strength				
Sex (M = 1, F = 2)	−0.070	−0.239 to 0.099	0.403	0.265
Age	−0.007	−0.012 to −0.001	0.016	
Leg ASMI	−0.272	−0.708 to 0.164	0.213	
$25(OH)D_3$	0.027	0.011 to 0.043	0.001	
$24,25(OH)_2D_3$	−0.091	−0.184 to 0.002	0.054	

Multiple regression model by forced entry method.

insufficiency/deficiency (total serum 25(OH)D < 20 ng/mL) was present in 70% of our subjects, and female subjects had significantly lower serum 25(OH)D level compared with male subjects. A recent study has described that the prevalence of vitamin D sufficiency (plasma 25(OH)D concentration ≥ 30 ng/mL) was extremely low (9.1%) in 9084 Japanese adults, and male gender was a significant positive predictor for vitamin D sufficiency [17]. Other reports have also described higher prevalence of vitamin D deficiency among female subjects than male subjects [18–20]. Our result is almost consistent with these reports.

Our study has suggested that serum $25(OH)D_3$ level was significantly correlated with both ASMI and lower limb muscle strength. In a previous cross-sectional study, ASMI values were significantly lower in male subjects aged 40 years or older with hypovitaminosis D, but there was no difference in ASMI by 25(OH)D status in female subjects regardless of age [12]. Although a meta-analysis revealed that vitamin D supplementation had no significant effect on muscle mass in a pooled analysis, positive effect of vitamin D supplementation on muscle mass was seen only in schoolchildren's study [21]. From these results, vitamin D seems to have a weak association with muscle mass in adults.

We have measured lower limb muscle mass by QTM which mainly reflects quadriceps muscle strength. Since quadriceps muscle strength is a significant predictor of incident falling [22], we believe that the muscle strength measured by QTM is of clinically important information. In a cross-sectional study of postmenopausal women, subjects with hypovitaminosis D had worse upper and lower limb muscle strength and physical performance than subjects with normal levels of $25(OH)D_3$ [23]. Another observational studies have also reported the relationships between serum 25(OH)D level and muscle strength [6,7]. In another study, however, serum 25(OH)D concentration was not associated with lean body mass, muscle strength, and physical function in men aged 30–79 years [24]. These results suggest that serum 25(OH)D level is more strongly related to muscle strength in female subjects than in male subjects. The significant relation between serum 25(OH)D level and muscle strength in the current study may be due to the high percentage of women in the study subjects. A meta-analysis of intervention studies has suggested that vitamin D supplementation has a small positive effect on muscle strength, which is more prominent in those with their baseline 25(OH)D concentration lower than 12 ng/mL. These results, together with the higher prevalence of vitamin D insufficiency/deficiency in women, would be the basis for that positive association between serum 25(OH)D level and muscle strength observed in women.

A recent study of middle-aged women has reported a threshold of serum 25(OH)D concentration that at least 12–13 ng/mL of serum 25(OH)D level is required for optimal musculoskeletal health [25]. Then, we have compared skeletal muscle mass and strength in subjects with their serum 25(OH)D concentration above 13 ng/mL and those below it, but there were no significant differences in these parameters between the two groups (data not shown). This discrepancy might at least partly be due to the inclusion of male subjects in the present study.

It is established that loss of lean muscle mass dose not directly translate into a loss of strength in the older subjects [26]. Of the possible mechanisms, adipose tissue infiltration in muscle may be one of the responsible factors. In a study involving young women, serum 25(OH)D level had strong negative association with thigh muscle fat, whereas no relationship was observed between 25(OH)D level and thigh muscle area [27]. Thus, additional studies of possible clinical interest are needed whether adipose infiltration in the legs is associated with lower limb muscle strength, and also with serum 25(OH)D concentration.

Finally, we have to mention some limitations of this study. First, the number of subjects studied remained only modest, although the number of subjects needed was calculated before initiating the study. The second one is the lack of data on physical activity. Muscle mass and strength constitute the basis for physical activity, and physical activity could be a good reflection of actual muscle power. Unfortunately, physical activity could not be examined in the present study. Finally, muscle mass does not necessarily parallel with muscle strength. For example, increased fat infiltration with advanced age impairs the muscle strength, Additional information on muscle quality by use of such instruments as magnetic resonance imaging (MRI) would have shed more light on muscle quality.

In conclusion, our data show that vitamin D status is significantly and positively associated with skeletal muscle mass and strength in middle-aged subjects.

Conflict of interest

The authors declare no conflict of interest.

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