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ORIGINAL ARTICLE

The vitamin D receptor expression in skeletal muscle of women with distal radius fracture

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Abstract

Summary We evaluated the vitamin D receptor (VDR) expression in the forearm flexor muscle of women with distal radius fracture. High VDR expression was associated with low appendicular lean mass index.

Introduction We aimed to evaluate the relationship between the VDR expression in the muscle cell and the muscle mass in women with a distal radius fracture (DRF).

Methods We prospectively recruited 45 women over 50 years of age (mean age, 66 years) with DRF and acquired biopsy of the forearm flexor muscle. The muscle cross-sectional area (CSA) and VDR expression were measured using immunohistochemistry staining. The clinical parameters including grip strength, gait speed, body mass index (BMI), bone mineral density (BMD), and serum vitamin D levels were compared between patients grouped by appendicular lean mass index and were correlated with the VDR expression.

Results Twelve patients (27%) showed a decreased appendicular lean mass index, less than the cut-off value of 5.4 kg/m^2 which was suggested by the Asian Working Group for Sarcopenia. Patients with a low appendicular lean mass index had significantly lower muscle CSA ($p = 0.037$), but a higher VDR expression ($p = 0.045$) than those with higher indices. VDR expression was negatively correlated with BMI ($r = -0.417$, $p = 0.004$) and appendicular lean mass index ($r = -0.316$, $p = 0.044$).

Conclusions DRF patients with low appendicular lean mass index presented high VDR expression and low CSA in forearm muscle cells. This suggests that the VDR expression might be upregulated in the attempt to compensate for the decreasing muscle mass. Further studies are necessary to explore the role of VDR in the progression of sarcopenia.

Keywords Vitamin D · Vitamin D receptor · Distal radius fracture · Sarcopenia · Skeletal muscle

Introduction

Skeletal muscle tissue accounts for the largest component of adipose tissue-free body mass in the human body mass and plays a central role in mobility and metabolic functions [1, 2]. A loss of muscle mass and muscle strength becomes pronounced around the age of 50 [3] and progresses rapidly 10 years later [4]. Muscle mass and strength reductions with decreased physical performance, as well as the consequent frailty in mature adults, are known by the term "sarcopenia." The underlying cellular changes involve the weakening of factors that otherwise promote muscle anabolism and increase the expression of inflammatory factors and agents contributing to muscle catabolism [5].

A distal radius fracture (DRF) is the most common upper extremity fracture in old women [6]. Patients with DRF display a high incidence of underlying osteoporosis [7], a low serum vitamin D level [8], subtle early physical performance

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changes [9], and a high prevalence of sarcopenia [10]. Since DRFs typically occur earlier than hip fractures by an average of 15 years [11], they can reflect early changes of the bone such as osteoporosis and muscle frailty for instance, the loss of muscle mass.

Some studies suggest a positive association between serum vitamin D levels and muscle strength as well as physical performance in older adults [12, 13]. It is known that individuals with a low vitamin D status improve in both muscle strength and performance through vitamin D supplements [14]. The identification of the vitamin D receptor (VDR) in skeletal muscle cells [15, 16] provided evidence how vitamin D affects skeletal muscles. VDR is a member of the nuclear receptor superfamily that regulates the expression of many genes and the vitamin D-VDR complex exerts non-genomic effects on intracellular signaling and calcium influx [17]. It has also been demonstrated that VDR-null mice exhibited impaired muscle maturation and reduced strength [18]. However, the relationship between VDR expressions and muscle mass has not been well studied. Hence, the purpose of this study was to evaluate the relationship between the VDR expression in the muscle cell and the muscle mass in women with a DRF.

Patients and methods

Subjects

This research was conducted as a part of the Study on Aging Radial fracture Cohort (SARCO) which is an ongoing longitudinal, population-based cohort investigation of patients with a DRF which began in November 2015. For the current study, we prospectively recruited 45 women who sustained DRF from a minor trauma, such as a fall on an outstretched hand, undergoing surgical treatment with an open reduction and internal fixation. The inclusion criteria were an acute DRF treated within 2 weeks after the injury, an age above 50 years, and the voluntary agreement to participate in this study. We excluded patients with cognitive disorders, neuromuscular diseases, or chronic debilitating disease that was considered to affect muscle function, such as Parkinson's disease, rheumatoid arthritis, and renal insufficiency. The participation of males was excluded due to their insufficient number for statistical analysis. Finally, the data of 45 women with the mean age 66 years (SD 8 years, range 51–84 years) were analyzed.

Evaluation of muscle mass, bone mineral density, and physical performance

The subjects underwent whole-body dual-energy X-ray absorptiometry (DXA) (GE Medical Systems Lunar Corp., Madison, WI, USA) to assess the bone mineral density (BMD) and body composition such as bone mass and lean soft tissue mass. The appendicular skeletal muscle mass (ASM) was calculated as the sum of the lean soft tissue mass in both arms and legs. A low lean mass was defined after adjusting ASM for height (ASM/ht^2). The definitions of both low lean mass and sarcopenia followed the Asian Working Group for Sarcopenia (AWGS) [19], suggesting an ASM/Ht^2 cutoff value of 5.4 kg/m^2 in women of Asian ethnicity [19]. The participants were classified as sarcopenic if they had a low lean mass in addition to weakness (assessed by the grip strength) or slowness (classified by the gait speed).

The grip strength of the unaffected hand was measured with use of a Jamar dynamometer (Asimow Engineering, Los Angeles, CA, USA) with the elbow flexed at 90° and the forearm in neutral rotation. The mean values of three trials were recorded in kilograms. For the adjustment of hand dominance, the grip strength of the left hand was multiplied by 1.1 according to the simple rule that the dominant hand is approximately 10% stronger than the non-dominant hand for right-handed subjects. The rule was not applied to left-handed subjects [20]. A weak hand grip strength was defined as < 18 kg for women according to the AWGS [19].

Gait speed was measured by having each subject walk a 2.4-m (8-ft) straight course with a self-selected normal walking speed. This was done as a part of physical performance evaluation using the short physical performance battery (SPPB). A gait speed ≤ 0.8 m/s was defined as the cutoff for low physical performance according to the AWGS [19]. The SPPB, which mainly assesses lower extremity functions, is composed of three components: standing balance, walking speed, and the ability to rise from a chair (chair stand). The test of standing balance included tandem, semi-tandem, and side-by-side stands. To perform the chair stand, the subject is asked to stand up and to sit down for five times as quickly as possible and timed from the initial sitting position until the final standing one. A summary of performance score was created by adding all scores, with the higher values indicating the better performance.

Measurement of VDR and CSA

A single surgeon performed the standard open reduction and internal fixation of the distal radius fractures using volar approach. A small part of flexor digitorum superficialis muscle (1 cm^3) was collected from the surgical field during operation, immediately fixed in formalin, and paraffin-embedded. Four-micrometer serial sections were cut and the slides were incubated with a primary antibody (Rat monoclonal antibody to Vitamin D Receptor, Abcam plc, Cambridge, MA, USA), and a secondary antibody (Omimap anti-rat HRP, Ventana Medical Systems Inc., Tucson, AZ, USA). Slides were incubated in a DAB Map Kit (Ventana Medical Systems) and the H_2O_2 substrate was treated with a hematoxylin and bluing reagent for counterstaining.

For quantitative analysis, tissue sections were evaluated with regard to both staining intensity and the percentage of VDR-positive nuclei, according to a previously described scoring method [21, 22]. Out of at least 500 cells, in minimum of eight fields of × 400 objective, positive myonuclei were counted and the percentage of immunoreactive myonuclei in each field was calculated (Fig. 1). The staining intensity was classified as 0 (negative), 0.5 (intermediate), and 1 (strong). The staining intensity and percentage of stained myonuclei were then multiplied to generate a staining index (SI) for each case. Two physicians blinded to the clinical information examined each sample. The complete scoring procedure was repeated three times and the average SI value calculated. We evaluated the inter-rater reliability with intraclass correlation coefficients (ICCs) and the value was 0.85. The cross-sectional areas of single muscle fibers were measured with the ImageJ Software (NIH, USA). The criteria used in the selection of muscle fibers to measure the CSA have been described previously [23].

Measurement of serum vitamin D levels

Serum 25(OH)D (25-hydroxyvitamin D) levels were assessed in all patients preoperatively using Diels-Alder derivatization and ultrahigh-performance liquid chromatography-tandem mass spectrometry (Waters Corp, Milford, MA, USA), which constitute the gold standard for this measurement. The calibration was performed with the standard reference material 972 from the National Institute of Standards and Technology. The intra-assay and inter-assay coefficients of variation at 29 ng/mL were 4.0 and 7.7%, respectively. All sampling was performed during daytime.

Statistical analysis

The subjects were divided into two groups by the lean mass index with the cutoff value of 5.4 kg/m^2, following the AWGS definition. Patients with and without low muscle mass were compared regarding age, the body mass index (BMI), grip strength, gait speed, the SPPB score, serum vitamin D levels, the VDR expression, muscle CSA, and the femur neck bone mineral density (BMD), using independent sample *t* tests. The association of the VDR with the assessed parameters was examined using Pearson correlation coefficients. All statistical tests were two-sided and *p* values of less than 0.05 were considered significant.

In a previous study, the mean of VDR-positive myonuclei ratio was 0.60 with standard deviation of 0.04 [24]. Based on that study, we designed to determine differences of 1 standard deviation in VDR expression between patients with and without low muscle mass index. With the prevalence of sarcopenia varying between 1 and 29% [25], and the prevalence of low lean mass reported 20.2% in Korean women older than 50 years [26], we assumed that 20% of the total patients would show decreased lean mass. Power analysis indicated that a sample size of 8 and 32 patients in each group would provide 80% statistical power (alpha = 0.1, beta = 0.8) with the use of Student's *t* test. With estimation of 10% to have inadequate data or variations on muscle mass, we recruited 45 patients.

Results

Comparison of parameters according to the appendicular lean mass index

Twelve patients (26%) of the total sample had an appendicular lean mass index lower than 5.4 kg/m^2. Patients with lower muscle mass showed significantly lower cross-sectional area of a single muscle fiber ($p = 0.037$), but higher level of VDR expression ($p = 0.045$) (Table 1). Age, grip strength, gait speed, the SPPB score, the serum vitamin D level, and the femur neck BMD did not differ between the two groups. Only two out of the 12 patients with low muscle mass had weak grip strength and were defined as sarcopenic. The gait speed was greater than 0.8 m/s in all studied patients.

Correlations among the VDR and the assessed parameters

Diverse VDR expression levels were observed in the skeletal muscles of the forearm. The mean staining index (SI) was 0.78 (SD = 0.07, range 0.60–0.92) for the total sample. The VDR expression was significantly correlated with a low BMI ($r = -0.417$, $p = 0.004$) and a low appendicular lean body mass adjusted by height ($r = -0.316$, $p = 0.044$), but no associations with age, serum vitamin D, and the femoral neck BMD were detected (Table 2).

Discussion

Prior studies have shown that vitamin D affects skeletal muscles through their vitamin D receptor. However, the relationship between the expression of VDR and muscle mass has not been well established. Hence, we assessed the VDR expression in the forearm's skeletal muscles by immunohistochemistry to evaluate its association with the muscle mass and clinical parameters in patients with DRF. It was found that subjects with a low appendicular lean mass index had a significantly lower muscle fiber cross-sectional area, but an elevated VDR expression compared to those with a higher index.

In this study, 4% of the patients were sarcopenic, which is lower than in a prior investigation on the prevalence of sarcopenia in patients with DRFs [10]. However, the prevalence of sarcopenia based on the definition of the European

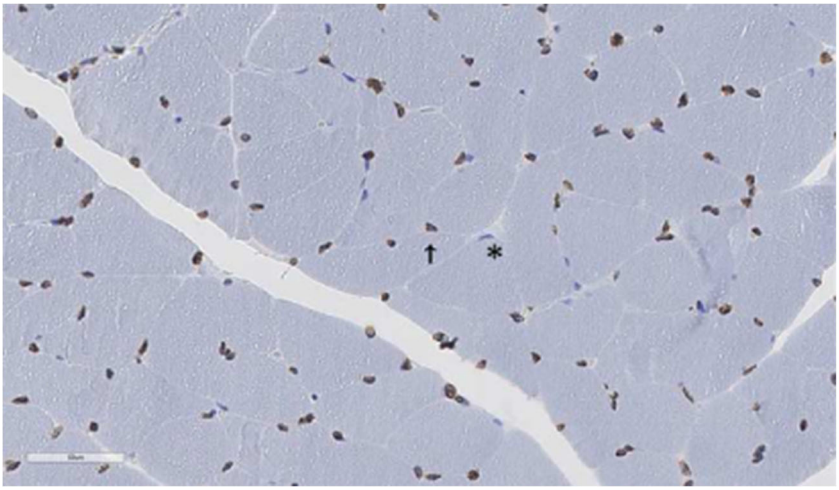

Fig. 1 Representative case showing VDR staining. VDR-positive nuclei is stained in dark brown color (↑) and VDR-negative nuclei shown in blue color (*)

Working Group on Sarcopenia in Older People (EWGSOP) varies between 1 and 29% in community-dwelling populations aged over 50 years [25]. Patients with a low appendicular mass index indeed had a lower muscle CSA. Nonetheless, there were no statistically significant group differences in grip strength, gait speed, or other physical performances. This is consistent with previous study reporting that DRFs do not tend to occur in individuals exhibiting poor physical performance [27, 28].

The association of age with VDR expression was not significant which was an unpredicted result considering previous studies [29–31]. Simpson et al. found that young cultured skeletal myocytes expressed more VDR than old ones [29] and Horst et al. found an association of age with diminished expression of the VDR in rat intestines and bone tissues [30]. Likewise, Bischoff-Ferrari et al. reported that the VDR expression in human muscle tissue decreased with age [31]. In our study, however, relatively younger adults were recruited. Further studies with older patients are necessary to ascertain clinical relevance of age on VDR expression with respect to progression of muscle mass decrement.

Table 1 Comparison of parameters according to appendicular lean mass index

	Appendicular lean mass index (kg/m^2)		*p* value
	ALMI ≤ 5.4	ALMI > 5.4	
Age (years)	66.8	65.3	0.638
BMI (kg/m^2)	22.1	24.0	0.063
Grip strength (kg)	20.4	22.3	0.309
SPPB	10.3	10.8	0.514
Gait speed (m/s)	1.55	1.41	0.274
Vit D (ng/mL)	20.5	22.2	0.635
VDR index	0.804	0.769	0.045*
CSA (μm^2)	1218	1561	0.037*
FN BMD (g/cm^2)	0.598	0.615	0.626

BMI body mass index, *SPPB* short physical performance battery, *VDR* vitamin D receptor, *CSA* cross-sectional area, *FN BMD* femoral neck bone mineral density, *Vit D* serum vitamin D concentration

*$p < 0.05$

The association of the VDR expression and serum vitamin D status was not statistically significant in our findings, which is consistent with previous studies [31, 32]. Bischoff-Ferrari et al. were unable to identify a relationship between serum vitamin D and the VDR expression in human muscles [31]. Additionally, Kinyamu et al. did not find a relationship between serum vitamin D and mucosal VDR levels in the intestines [32]. On the contrary, Pojednic et al. reported that vitamin D positively correlated with the intramuscular VDR protein concentration [33].

In this study, patients with a low appendicular muscle mass index had a higher VDR expression than those with a higher index, which was an unexpected finding. A limited number of studies investigating the impact of the VDR expression on muscle fiber size or lean mass exist, but most of them suggest an incremental effect of VDR on muscle fibers [17, 33–36]. VDR-null mice exhibited a clear muscle phenotype, with a small fiber size and an abnormal expression of all major muscle-specific genes [18]. Genetic variants of VDR have been shown to have a direct effect on muscle strength [34]. Mouse studies reported correlations between both vitamin D signaling and the VDR expression with grip strength, fiber quality, and myostatin expression which is an antagonist of myogenesis or muscle fiber development and growth [17, 35–37].

One supposition for our result of the inverse correlation between VDR expression and muscle mass index is that VDR may be upregulated in the attempt to compensate for the decreasing muscle mass during the progression to sarcopenia. The muscle CSA reflects muscle strength [38]. In this study, however, the low lean mass group showed no difference in grip strength or physical function. Therefore, one possible explanation could be that patients with a low lean

Table 2 Correlation coefficient (r) between clinical parameters

	Age	BMI	Grip Str.	ASM/Ht^2	CSA	FN BMD	Vit D
VDR	− 0.150	− 0.417* ($p = 0.004$)	0.049	− 0.316* ($p = 0.044$)	− 0.158	− 0.023	− 0.084
Age		0.123	− 0.335*($p = 0.024$)	0.184	− 0.059	− 0.416* ($p = 0.008$)	0.068
BMI			0.065	0.660* ($p < 0.0001$)	0.374* ($p = 0.035$)	− 0.068	0.050
Grip Str				0.076	0.467* ($p = 0.007$)	0.024	−0.188
ASM/Ht^2					0.453* ($p = 0.010$)	− 0.033	− 0.014
CSA						− 0.136	− 0.134
FN BMD							− 0.168

BMI body mass index, *Grip Str* grip strength, *ASM/Ht^2* appendicular skeletal mass adjusted by height, *CSA* cross-sectional area, *FN BMD* femoral neck BMD, *Vit D* serum vitamin D concentration

*$p < 0.05$

mass may increase the VDR expression and maximize the use of vitamin D to compensate for reduced muscle mass. Brennan-Speranza et al. reported that the quadriceps muscles' VDR expression was significantly higher in biopsies from patients with end-stage osteoarthritis of the knee compared to controls, which suggests that the vitamin D pathway plays a part in compensating for this reduced muscle strength [39]. Frontera et al. studied the muscle fiber size and function in a longitudinal study of mature adults and stated that surviving fibers may compensate to partially correct muscle size deficits to maintain an optimal force-generating capacity [38].

This study has several limitations. First, the VDR evaluation was cross-sectional, so a causal relationship between the VDR and changes in skeletal muscles could not be determined. Further longitudinal studies on changes of VDR expression are necessary. Second, the DRF patients were relatively young to represent the typical characteristics of sarcopenia such as decreased activities of daily living and increased frailty. However, the study sample can be a good model to observe early muscle mass changes. Further studies including subjects with an advanced age and sarcopenic patients are necessary. Third, one of the disadvantages associated with immunohistochemistry is that the outcome depends on the perception of examiner who interprets the results. However, in this study, two physicians independently examined the stained slides and the ICC = 0.85 indicates an excellent inter-rater reliability.

In conclusion, this study of patients with DRF found that those with low appendicular lean mass had high VDR expression and low CSA in the forearm's muscle cells. This suggests that the VDR expression might be upregulated in patients with an ongoing decrease in muscle mass. Further studies are necessary to explore the role of VDR in the progression of sarcopenia.

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Compliance with ethical standards

Conflicts of interest None.

Ethics approval and consent to participate The Seoul National University Bundang Hospital Institutional Review Board (SNUBH IRB) reviewed the protocol and approved the study (B-1501-282-002). All participants provided informed written consents.

References

1. Janssen I, Heymsfield SB, Wang Z, Ross R (2000) Skeletal muscle mass and distribution in 468 men and women aged 18–88 yr. J Appl Physiol 89(1):81–88
2. Lukaski HC (1996) Estimation of muscle mass; in Roche AF, Heymsfield SB, Lohman TG(eds): Human body composition. Human Kinetics, Champaign, pp 109–128
3. Lexell J, Taylor CC, Sjöström M (1988) What is the cause of the ageing atrophy?: total number, size and proportion of different fiber types studied in whole vastus lateralis muscle from 15-to 83-year-old men. J Neurol Sci 84(2):275–294
4. Frontera WR, Hughes VA, Fielding RA, Fiatarone MA, Evans WJ, Roubenoff R (2000) Aging of skeletal muscle: a 12-yr longitudinal study. J Appl Physiol 88(4):1321–1326
5. Lang T, Streeper T, Cawthon P, Baldwin K, Taaffe DR, Harris TB (2010) Sarcopenia: etiology, clinical consequences, intervention, and assessment. Osteoporos Int 21(4):543–559. https://doi.org/10.1007/s00198-009-1059-y
6. O'neill T, Marsden D, Adams J, Silman A (1996) Risk factors, falls, and fracture of the distal forearm in Manchester, UK. J Epidemiol Community Health 50(3):288–292
7. Mallmin H, Ljunghall S (1994) Distal radius fracture is an early sign of general osteoporosis: bone mass measurements in a population-based study. Osteoporos Int 4(6):357–361. https://doi.org/10.1007/bf01622198
8. Jang WY, Chung MS, Baek GH, Song CH, Cho HE, Gong HS (2012) Vitamin D levels in post-menopausal Korean women with a distal radius fracture. Injury 43(2):237–241. https://doi.org/10.1016/j.injury.2011.10.020
9. Cho YJ, Gong HS, Song CH, Lee YH, Baek GH (2014) Evaluation of physical performance level as a fall risk factor in women with a distal radial fracture. J Bone Joint Surg Am 96(5):361–365. https://doi.org/10.2106/jbjs.l.01359

10. Roh YH, Koh YD, Noh JH, Gong HS, Baek GH (2017) Evaluation of sarcopenia in patients with distal radius fractures. Arch Osteoporos 12(1):5. https://doi.org/10.1007/s11657-016-0303-2
11. Owen R, MELTON III L, Ilstrup D, Johnson K, Riggs B (1982) Colles' fracture and subsequent hip fracture risk. Clin Orthop Relat Res (171):37-43
12. Visser M, Deeg DJ, Lips P, Longitudinal Aging Study A (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. https://doi.org/10.1210/jc.2003-030604
13. Snijder MB, van Schoor NM, Pluijm 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. https://doi.org/10.1210/jc.2006-0510
14. Ceglia L, Harris SS (2013) Vitamin D and its role in skeletal muscle. Calcif Tissue Int 92(2):151–162. https://doi.org/10.1007/s00223-012-9645-y
15. Simpson RU, Thomas GA, Arnold AJ (1985) Identification of 1,25 dihydroxyvitamin D3 receptors and activities in muscle. J Biol Chem 260(July 25):8882–8891
16. Bischoff HA, Borchers M, Gudat F, Duermueller U, Theiler R, HB S¨a, Dick W (2001) In situ detection of 1,25dihydroxycitamin D3 receptor in human skeletal muscle tissue. Histochem J 33(1):19–24
17. Girgis CM, Clifton-Bligh RJ, Hamrick MW, Holick MF, Gunton JE (2013) The roles of vitamin D in skeletal muscle: form, function, and metabolism. Endocr Rev 34(1):33–83. https://doi.org/10.1210/er.2012-1012
18. Endo I, Inoue D, Mitsui T, Umaki Y, Akaike M, Yoshizawa T, Kato S, Matsumoto T (2003) Deletion of vitamin D receptor gene in mice results in abnormal skeletal muscle development with deregulated expression of myoregulatory transcription factors. Endocrinology 144(12):5138–5144
19. Chen LK, Liu LK, Woo J, Assantachai P, Auyeung TW, Bahyah KS, Chou MY, Chen LY, Hsu PS, Krairit O (2014) Sarcopenia in Asia: consensus report of the Asian Working Group for Sarcopenia. J Am Med Dir Assoc 15(2):95–101
20. Petersen P, Petrick M, Connor H, Conklin D (1989) Grip strength and hand dominance: challenging the 10% rule. Am J Occup Ther 43(7):444–447
21. Wang D, Li T, Ye G, Shen Z, Hu Y, Mou T, Yu J, Li S, Liu H, Li G (2015) Overexpression of the receptor for advanced glycation endproducts (RAGE) is associated with poor prognosis in gastric cancer. PLoS One 10(4):e0122697. https://doi.org/10.1371/journal.pone.0122697
22. Remmele W, Hildebrand U, Hienz HA, Klein P-J, Vierbuchen M, Behnken LJ, Heicke B, Scheidt E (1986) Comparative histological, histochemical, immunohistochemical and biochemical studies on oestrogen receptors, lectin receptors, and Barr bodies in human breast cancer. Virchows Archiv A 409(2):127–147
23. Ceglia L, Niramitmahapanya S, Price LL, Harris SS, Fielding RA, Dawson-Hughes B (2013) An evaluation of the reliability of muscle fiber cross-sectional area and fiber number measurements in rat skeletal muscle. Biol Proced Online 15(1):6
24. Ceglia L, Niramitmahapanya S, da Silva Morais M, Rivas DA, Harris SS, Bischoff-Ferrari H, Fielding RA, Dawson-Hughes B (2013) A randomized study on the effect of vitamin D_3supplementation on skeletal muscle morphology and vitamin D receptor concentration in older women. J Clin Endocrinol Metab 98(12):E1927–E1935. https://doi.org/10.1210/jc.2013-2820
25. Cruz-Jentoft AJ, Landi F, Schneider SM, Zúñiga C, Arai H, Boirie Y, Chen L-K, Fielding RA, Martin FC, Michel J-P (2014) Prevalence of and interventions for sarcopenia in ageing adults: a systematic review. Report of the International Sarcopenia Initiative (EWGSOP and IWGS). Age Ageing 43(6):748–759
26. Kwon HJ, Ha YC, Park HM (2016) Prevalence of sarcopenia in the Korean woman based on the Korean National Health and Nutritional Examination Surveys. J Bone Metab 23(1):23–26
27. Silman A (2003) Risk factors for Colles' fracture in men and women: results from the European Prospective Osteoporosis Study. Osteoporos Int 14(3):213–218
28. Kelsey JL, Prill MM, Keegan TH, Tanner HE, Bernstein AL, Quesenberry CP, Sidney S (2005) Reducing the risk for distal forearm fracture: preserve bone mass, slow down, and don't fall! Osteoporos Int 16(6):681–690
29. Simpson R, Thomas G, Arnold A (1985) Identification of 1, 25-dihydroxyvitamin D3 receptors and activities in muscle. J Biol Chem 260(15):8882–8891
30. Horst R, Goff J, Reinhardt T (1990) Advancing age results in reduction of intestinal and bone 1,25-dihydroxyvitamin D receptor. Endocrinology 126(2):1053–1057
31. Bischoff-Ferrari H, Borchers M, Gudat F, Dürmüller U, Stähelin H, Dick W (2004) Vitamin D receptor expression in human muscle tissue decreases with age. J Bone Miner Res 19(2):265–269
32. Kinyamu HK, Gallagher JC, Prahl JM, Deluca HF, Petranick KM, Lanspa SJ (1997) Association between intestinal vitamin D receptor, calcium absorption, and serum 1,25 dihydroxyvitamin D in normal young and elderly women. J Bone Miner Res 12(6):922–928. https://doi.org/10.1359/jbmr.1997.12.6.922
33. Pojednic RM, Ceglia L, Olsson K, Gustafsson T, Lichtenstein AH, Dawson-Hughes B, Fielding RA (2015) Effects of 1,25-dihydroxyvitamin D3 and vitamin D3 on the expression of the vitamin d receptor in human skeletal muscle cells. Calcif Tissue Int 96(3):256–263. https://doi.org/10.1007/s00223-014-9932-x
34. Bozsodi A, Boja S, Szilagyi A, Somhegyi A, Varga PP, Lazary A (2016) Muscle strength is associated with vitamin D receptor gene variants. J Orthop Res 34(11):2031–2037. https://doi.org/10.1002/jor.23220
35. Girgis CM, Cha KM, Houweling PJ, Rao R, Mokbel N, Lin M, Clifton-Bligh RJ, Gunton JE (2015) Vitamin D receptor ablation and vitamin D deficiency result in reduced grip strength, altered muscle fibers, and increased myostatin in mice. Calcif Tissue Int 97(6):602–610. https://doi.org/10.1007/s00223-015-0054-x
36. Garcia LA, King KK, Ferrini MG, Norris KC, Artaza JN (2011) 1, 25(OH)2vitamin D3 stimulates myogenic differentiation by inhibiting cell proliferation and modulating the expression of promyogenic growth factors and myostatin in C2C12 skeletal muscle cells. Endocrinology 152(8):2976–2986
37. Perez-Siles G, Grant A, Ellis M, Ly C, Kidambi A, Khalil M, Llanos RM, La Fontaine S, Strickland AV, Züchner S (2016) Characterizing the molecular phenotype of an Atp7a T985I conditional knock in mouse model for X-linked distal hereditary motor neuropathy (dHMNX). Metallomics 8(9):981–992
38. Frontera WR, Reid KF, Phillips EM, Krivickas LS, Hughes VA, Roubenoff R, Fielding RA (2008) Muscle fiber size and function in elderly humans: a longitudinal study. J Appl Physiol (1985) 105(2):637–642. https://doi.org/10.1152/japplphysiol.90332.2008
39. Brennan-Speranza TC, Mor D, Mason RS, Bartlett JR, Duque G, Levinger I, Levinger P (2017) Skeletal muscle vitamin D in patients with end stage osteoarthritis of the knee. J Steroid Biochem Mol Biol 173:180–184. https://doi.org/10.1016/j.jsbmb.2017.01.022