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ORIGINAL ARTICLE

25(OH) vitamin D and functional outcomes in older adults admitted to rehabilitation units: the safari study

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Abstract

Summary Vitamin D (25(OH)D) deficiency is associated with poor physical performance; little is known about its impact on geriatric rehabilitation. We found a positive non-linear relationship between 25(OH)D and functional gain, stronger in levels < 16 ng/ml (below the cutoff for "deficiency"). An early 25(OH)D dosage may be advisable for this population.

Introduction Vitamin D (25(OH)D) deficiency is highly prevalent in older people, and it is associated with poor muscular strength and physical performance. Its impact on functional outcomes during geriatric rehabilitation has been poorly studied. We aim to analyze the association between 25(OH)D and functional recovery in geriatric rehabilitation units.

Methods We conducted a prospective multi-center cohort study including patients ≥ 65 years old admitted to 3 geriatric rehabilitation units in Italy and Spain, after orthopedic events or stroke. Outcomes were absolute functional gain (AFG, discharge-admission Barthel index) and ability to walk (AW) at 3 months after admission. The association between 25(OH)D quartiles (Q1-Q2-Q3-Q4) and outcomes was explored using linear or logistic regression models.

Results We included 420 patients (mean age = 81.2 years [SD = 7.7], 66.4% females, mean 25(OH)D concentration = 13.5 ng/ml [SD = 8.7]) (to convert to nmol/l multiply by 2.496). A non-linear relationship between 25(OH)D and AFG was found, with a stronger association for 25(OH)D levels < 16 ng/ml. Compared to Q1 (25(OH)D ≤ 6 ng/ml), participants in Q3 (25(OH)D 11.5–18.2 ng/ml) had the best AFG and AW (mean AFG [SD], Q1 = 28.9 [27.8], Q2 = 32.5 [23.5], Q3 = 43.1 [21.9], Q4 = 34.5 [29.3], R^2 = 7.3%; AW, Q1-Q2 = 80%, Q3 = 91%, Q4 = 86%). Regression models adjusted for potential confounders confirmed these results (AGF Q2, β = 2.614, p = 0.49; Q3, β = 9.723, p < 0.01; Q4, β = 4.406, p = 0.22; AW Q2, OR [95% CI] = 1.84 [0.67–5.33]; Q3, OR [95% CI] = 4.01 [1.35–13.48]; Q4, OR [95% CI] = 2.18 [0.81–6.21]).

Conclusions In our study, 25(OH)D concentration showed a positive association with functional outcomes at 3 months. The association is stronger below the usual cutoff for "deficiency." Dosage of 25(OH)D concentration may help identify geriatric rehabilitation patients at risk for a worse functional recovery.

Keywords Aged · Barthel index · Functional recovery · Rehabilitation · Vitamin D

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Introduction

Vitamin D insufficiency (usually defined as 25(OH)D serum concentration between 21 and 29 ng/ml) is a highly prevalent condition worldwide, regardless of age and latitude. Prevalence has been reported at around 40% of healthy adults, increasing up to 70–100% when hospitalized [1]. Vitamin D deficiency (usually defined as 25(OH)D serum concentration ≤ 20 ng/ml) is also very common, with a prevalence of around 35% in hospitalized patients [1]. Older adults are at a higher risk of vitamin D deficiency and insufficiency due to dietary deficiencies, lower sun exposure, and a physiological age-related decrease of vitamin D3 cutaneous synthesis [2]. In community-dwelling older adults, vitamin D deficiency and insufficiency have a prevalence of about 30% and 75%, respectively [3, 4], while in rehabilitation settings insufficiency may result in more than 90% of patients [5].

In addition to the well-known role of vitamin D in improving bone mineral density [6], recent evidence documented that vitamin D contributes both to muscular health [7] and strength [8–10]. Furthermore, low 25(OH)D levels are associated with higher risk of incident disability, likely through the association with poor physical performance [11, 12] and neuromuscular disorders [13, 14]. However, a recent meta-analysis has raised controversy regarding the impact of vitamin D supplementation combined with resistance exercise training on musculoskeletal health, although confirming the association with muscular strength. This meta-analysis pointed out that few studies are available on this topic in older adults, and that further evidence is required to draw any final conclusions of the role of vitamin D on muscular health [15].

Due to the close relationship between vitamin D deficiency and physical performance, it is hypothesized that vitamin D deficiency might affect rehabilitation outcomes and physical function in older adults. However, limited and discordant evidence is available about the association between 25(OH)D and rehabilitation outcomes in this population: most of the studies examining this topic have a relatively small sample size and are not focused on older adults [5, 16, 17], a population in which the consequence of vitamin D deficiency may be even more evident, due to age-related body and muscle composition change [18].

Our hypothesis is that there is a positive association between 25(OH)D serum concentration and functional recovery. The objective of our study was to analyze the association between 25(OH)D levels and functional recovery in an older population admitted to geriatric rehabilitation units for orthopedic conditions or stroke, the most prevalent conditions in this setting.

Methods

Study design and setting

We analyzed data from the Sarcopenia and Function in Aging Rehabilitation (SAFARI) study, a multi-center international collaboration project on the identification of the frailty-related factors associated with functional improvement in older patients admitted to geriatric rehabilitation units. This was a prospective multi-center cohort study conducted on patients aged 65 years or older and admitted after an orthopedic surgery (hip fracture and hip or knee replacement) or stroke in the rehabilitation departments of Gemelli Hospital, Rome (Italy), Ancelle Hospital, Cremona (Italy), and Parc Sanitari Pere Virgili, Barcelona (Spain) between December 2014 and May 2016. Exclusion criteria included unstable medical conditions that may influence the rehabilitative program, terminal diseases, previous severe dementia (Global Deterioration Scale 6–7), and severe functional impairment before the event (i.e., total Barthel index ≤ 40).

At admission, patients underwent a multidimensional geriatric assessment to develop an individualized treatment plan that included a rehabilitation program aimed to improve functional outcomes. The rehabilitation units were staffed by full-time geriatricians, nurses, and nursing assistants, and also by physical, speech, and occupational therapists.

The study was approved by the Animal and Human Ethics Committee from each Institution. Informed consent was obtained from all individual participants included in the study.

Measurements and outcomes

Baseline evaluation was performed within 72 h of admission by geriatricians and trained nurses or physiotherapists. It included demographic characteristics, main diagnosis at admission (hip fracture, orthopedic elective surgery, or stroke), body mass index (BMI), comorbidities (Charlson index), cognitive function (Mini-Mental State Examination [MMSE]), and nutritional status (Mini-Nutritional Assessment-Short Form [MNA-SF]). Muscle strength was assessed by measuring the grip strength in the dominant hand (or in the preserved hand in post-stroke patients) with a Jamar® hydraulic dynamometer, and functional status was evaluated with the Barthel index (BI, which rates 0–100, from complete dependence to independence in the basic activities of daily living), collected before the acute event (self-reported by the patient or the caregiver at admission), at admission, at 30 days and at 3 months after admission (via telephone interviews). BI has been validated for use with patients or proxies, and as well as for telephone interviews [19]. Length of stay (LOS) was also recorded.

25(OH)D concentration was determined at the time of admission to the rehabilitation units with the same technique, chemiluminescent immunoassay (CLIA), at each of the three

local laboratories, with normal reference values ≥ 30 ng/ml. All centers participated in the DEQAS. The mean precision and accuracy of the centers were 8% and 4%, respectively. In all centers, vitamin D supplementation was administrated according to local protocols. This information, however, was collected by one center only.

The functional outcomes evaluated were the ability to walk and the absolute functional gain (AFG), both at 30 days and at 3 months. The ability to walk was a dichotomous variable, defined by a cutoff of ten from the walking BI item (15-point item): patients with a walking BI ≥ 10 (independent for indoor walking) were defined as able to walk. The AFG was defined as the difference between the total BI at 30 days or 3 months minus the total BI at admission.

Statistical analysis

We explored the relationship between 25(OH)D and AFG using graphic methods (scatterplot with spline interpolation). This exploratory analysis revealed a non-linear relationship between the two variables, with a positive association for 25(OH)D concentration below 16 ng/ml, and an inversion of the trend for concentrations above this value. Therefore, we decided to analyze data according to 25(OH)D quartiles (Q) (Q1, 3–6 ng/ml; Q2, 6.1–11.4 ng/ml; Q3, 11.5–18.2 ng/ml; Q4, 18.3–50.5 ng/ml). We performed supplementary analysis using the cutoffs of severe vitamin D deficiency (25(OH)D < 12 ng/ml) [20], deficiency (25(OH)D 12–20 ng/ml), insufficiency (25(OH)D 20.1–29.9 ng/ml), and normal 25(OH)D concentration (≥ 30 ng/ml) [21].

We analyzed baseline characteristics of the study sample using descriptive statistics (mean and standard deviation for continuous variables, proportion for categorical variables), according to quartiles of 25(OH)D serum concentration. We evaluated the association between 25(OH)D and AFG and the ability to walk using linear or logistic regression models, as appropriate, crude and adjusted for potential confounders, using the first quartile as a reference. The relationship between 25(OH)D concentration and AFG was further explored with linear regression models performed separately for 25(OH)D values below and above 16 ng/ml, both crude and adjusted for potential confounders. Finally, the association between 25(OH)D and functional gain was studied through a linear mixed model, using BI as outcome over the time, both crude and adjusted for potential confounders, using the first quartile as a reference.

We selected the potential confounders included in the analyses on the basis of clinical significance, prior knowledge, and results of the univariate analysis. To explore the different roles of demographic and clinical variables, we first adjusted for age and sex, and then for the other potential confounders (i.e., Charlson index, MMSE, length of stay, BI at admission, handgrip strength at admission, eGFR, BMI at admission, study site, diagnosis at admission). All analyses were performed using R version 3.3.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Mean age of the 420 study participants was 81.2 years (SD = 7.7), 66.4% were female. Diagnosis at admission was hip fracture for 175 patients, elective orthopedic surgery for 136, and stroke for 138. Mean 25(OH)D concentration was 13.5 ng/ml (SD = 8.7), with no difference in the periods of April–September (13.1 ng/ml) and October–March (13.8 ng/ml); 81.2% of the samples had 25(OH)D concentration < 20 ng/ml and 93.8% 25(OH)D < 30 ng/ml (to convert ng/ml in nmol/l multiply values by 2.496). The mean length of stay was 29 days (SD = 9.7).

Patients in the first quartile of 25(OH)D serum concentration were older (mean age [SD] 84.2 [7.3] years, 81.7 [7.2], 79.9 [7.8], 79.7 [7.6] across increasing quartiles, p for trend < 0.01). There was no difference across quartiles in sex, diagnosis at admission, Charlson index, MMSE, BMI, eGFR estimated using the CKD-EPI formula, and albumin. Muscle strength was lower in the first 25(OH)D quartile (mean handgrip strength [SD] Q1, 12.3 [8.3] kg; Q2, 15.2 [10]; Q3, 15.8 [9.2]; Q4, 14.1 [8.4]; p for trend = 0.03). BI pre-event and at admission did not change throughout quartiles, while both BI at 30 days and 3 months increased across quartiles (Table 1). Information on vitamin D supplementation was available for one center only (200 participants) and only 29 participants received supplementation. In this subgroup, supplementation did not significantly affect AFG at 30 days (21.2 vs 16.9, p = 0.29), AFG at 3 months (22.1 vs 26.6, p = 0.50), the ability to walk at 30 days (90% vs 78%, p = 0.22), and the ability to walk at 3 months (88% vs 84%, p = 0.74).

Figure 1 shows the relationship between 25(OH)D concentration and AFG at 30 days after admission. There was a non-linear relationship, with a positive association for 25(OH)D concentration values up to 16 ng/ml, however not confirmed by a linear regression model adjusted for the potential confounders (β 0.136, p = 0.71), and no association when values where higher than 16 ng/ml. Splitting up the curve according to 25(OH)D quartiles, a positive association between 25(OH)D and AFG at 30 days was evident within the first three quartiles, while within the fourth quartile there was no further improvement in AFG (Fig. 1). The mean AFG at 30 days (SD) according to 25(OH)D quartiles was Q1, 23.8 (18.7); Q2, 22.1 (19); Q3, 29.2 (17.1); and Q4, 28.1 (18.2) (Table 1). Linear regression models, both crude and adjusted for potential confounders, did not show a statistically significant association between 25(OH)D quartiles and AFG at 30 days (Table 2).

Table 1 General characteristics of the population distributed by quartiles of 25(OH)D concentration

Characteristics	I quartile (3–6 ng/ml) N105	II quartile (6.1–11.4 ng/ml) N105	III quartile (11.5–18.2 ng/ml) N105	IV quartile (18.3–50.5 ng/ml) N105	*p*
Age (years), mean (SD)	84.2 (7.3)	81.7 (7.2)	79.9 (7.8)	79.7 (7.6)	< 0.01
Female sex, (%)	71	67	63	65	0.59
Hip fracture, (%)	30	25	23	22	0.12
Elective orthopedic surgery, (%)	19	23	33	26	
Stroke, (%)	25	28	20	28	
BMI (kg/m^2), mean (SD)	25.1 (5.3)	25.6 (4.3)	25.9 (4.2)	25.7 (4.1)	0.69
eGFR (ml/min1.73m^2), mean (SD)	67.1 (22.5)	64.6 (22)	69.3 (21)	71.8 (20.3)	0.20
Charlson Index, mean (SD)	3.3 (2.6)	3.6 (2.5)	4.1 (2.6)	3.7 (2.7)	0.22
MMSE, mean (SD)	22.7 (5.6)	22 (6.1)	23.8 (5.1)	22.9 (5.6)	0.14
Handgrip strength at admission (kg), mean (SD)	12.3 (8.3)	15.2 (10)	15.8 (9.2)	14.1 (8.4)	0.03
Length of stay, mean (SD)	29.6 (9.8)	29.5 (9.6)	27.4 (9)	29.4 (10.3)	0.30
BI before event, mean (SD)	87.9 (16.6)	88.9 (16.7)	92.3 (13.7)	90.7 (16.4)	0.19
BI at admission, mean (SD)	43.4 (19.1)	41.3 (22.5)	43.8 (22.3)	41.9 (20.1)	0.79
BI at 30 days, mean (SD)	67.7 (21.4)	63.5 (28)	73.2 (21.4)	70.4 (24.6)	0.03
BI at 3 months, mean (SD)	71.1 (29.3)	72.3 (28.3)	86.4 (19)	76.4 (29.5)	< 0.01
AFG at 30 days, mean (SD)	23.8 (18.7)	22.1 (19)	29.2 (17.1)	28.1 (18.2)	0.01
AFG at 3 months, mean (SD)	28.9 (27.8)	32.5 (23.5)	43.1 (21.9)	34.5 (29.3)	< 0.01
AW at 30 days (%)	71	66	68	72	0.80
AW at 3 months (%)	80	80	91	86	0.10

BMI, body mass index; *MMSE*, mini-mental state examination; *eGFR*, estimated glomerular filtration rate; *BI*, Barthel index; *AW*, ability to walk

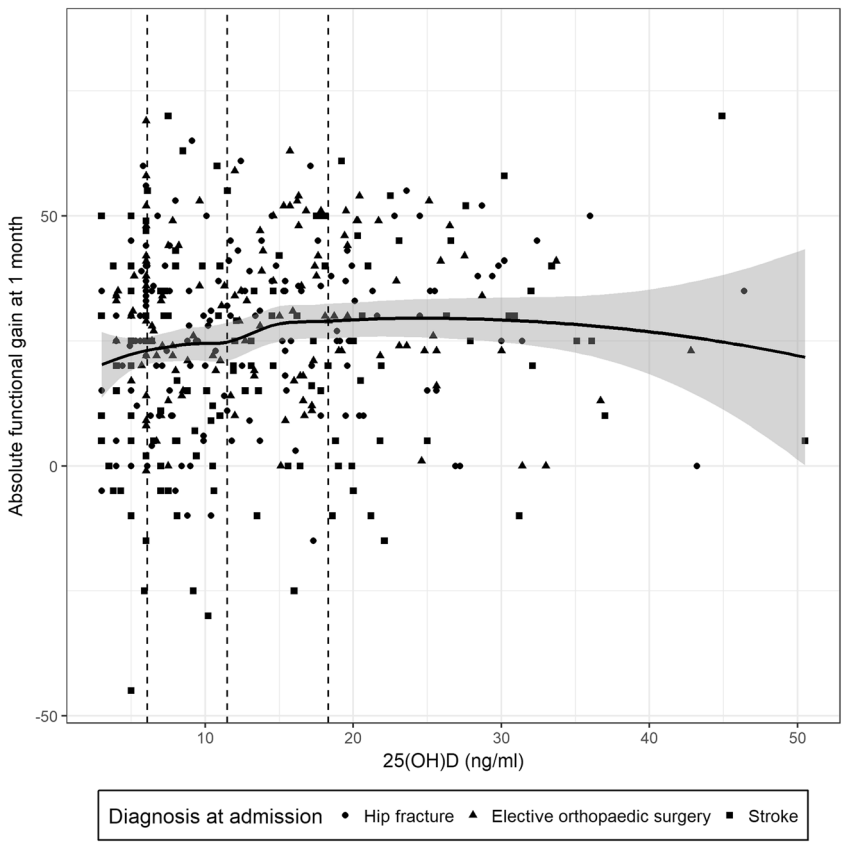

Fig. 1 Association between 25(OH)D and absolute functional gain at 30 days from admission. There is a non-linear relationship between 25(OH)D and absolute functional gain, with a weak positive association for 25(OH)D concentration values up to 16 ng/ml, and no association when values where higher than 16 ng/ml. Patients with different diagnosis at admission are equally distributed in the graph

Table 2 Linear regression models of the association between 25(OH)D quartiles and absolute functional gain

Quartiles	30 days		3 months	
	β crude (P)	β adjusted*(P)	β crude (P)	β adjusted* (P)
I quartile	Reference	Reference	Reference	Reference
II quartile	− 1.712 (0.51)	− 0.536 (0.85)	3.63 (0.36)	2.614 (0.49)
III quartile	5.383 (0.04)	3.025 (0.28)	14.205 (< 0.01)	9.723 (< 0.01)
IV quartile	4.337 (0.09)	3.802 (0.18)	5.661 (0.14)	4.406 (0.22)

*Models adjusted for age, sex, MMSE, Charlson index, length of stay, Barthel index at admission, eGFR (CKD-EPI), BMI at admission, handgrip strength at admission, study site, diagnosis at admission

Regarding the relationship between 25(OH)D concentration and AFG at 3 months (Fig. 2), we found a positive relationship for values below 16 ng/ml, that was confirmed by a linear regression model, both crude (β 1.89, $P < 0.01$) and adjusted for the complete set of confounders (β 1.20, $p < 0.01$). Instead, a weak inverse relationship was evident for 25(OH)D values over 16 ng/ml, that was not statistically significant in linear regression analyses (crude β − 0.58, $p = 0.13$; adjusted β − 0.22, $p = 0.55$, respectively). Dividing the curve according to 25(OH)D quartiles, a positive association between 25(OH)D and AFG at 3 months was evident within the first three quartiles, while within the fourth quartile, there was no further improvement of AFG when increasing values of 25(OH)D (Fig. 2). There was an improvement in mean AFG across 25(OH)D quartiles, less evident in the fourth quartile (mean [SD] Q1, 28.9 [27.8]; Q2, 32.5 [23.5]; Q3, 43.1 [21.9]; and Q4, 34.5 [29.3], $p < 0.01$, $R^2 = 7.3\%$) (Table 1). This data was confirmed in a crude and adjusted linear regression model, where improvement was statistically significant in the third 25(OH)D quartile, compared to the first one (crude model: Q2, β 3.63, $p = 0.36$; Q3, β 14.21, $p < 0.01$; Q4, β 5.66, $p = 0.14$; adjusted model: Q2, β 2.61, $p = 0.49$; Q3, β 9.72, $p < 0.01$; Q4, β 4.41, $p = 0.22$) (Table 2).

In relation to the ability to walk, there was no difference across 25(OH)D quartiles in the proportion of patients able to ambulate at 30 days after admission (Table 1). These results were confirmed both in a crude logistic regression model (OR [95% CI] Q2 0.79 [0.44–1.44],Q3 0.88 [0.48–1.60], and Q4

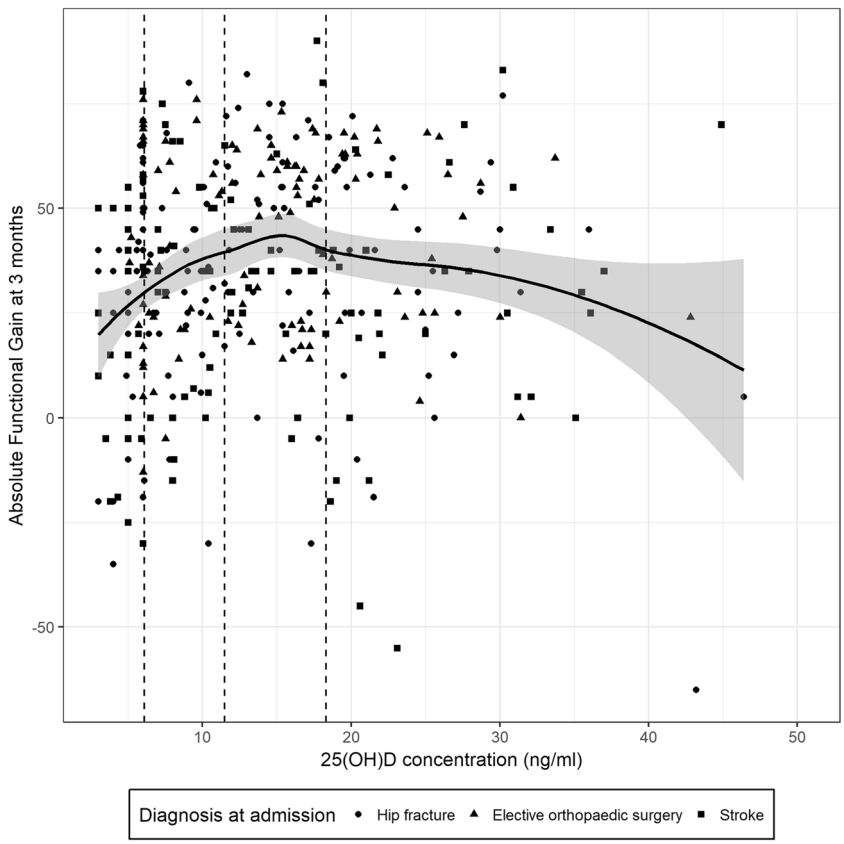

Fig. 2 Association between 25(OH)D and absolute functional gain at 3 months from admission. A non-linear relationship between 25(OH)D and absolute functional gain is evident for 25(OH)D values up to 16 ng/ml, and a weak inverse association for values higher than 16 ng/ml. Patients with different diagnosis at admission are equally distributed in the graph

1.04 [0.57–1.92]), and after adjustment for potential confounders (OR [95% CI] Q2 0.86 [0.35–2.10], Q3 0.89 [0.37–2.13], and Q4 0.90 [0.38–2.13]) (Table 3).

At 3 months, there was an increased proportion of patients able to walk across 25(OH)D quartiles, improvement, again, less evident in the fourth quartile: Q1, 80%; Q2, 80%; Q3, 91%; and Q4, 86% (p for trend = 0.095) (Table 1). In logistic regression models, compared to Q1, patients in Q3 had a significant improvement of the outcome, both in the crude (OR [95% CI] Q2, 1.00 [0.47–2.11]; Q3, 2.56 [1.11–6.30]; Q4, 1.58 [0.73–3.51]) and in the adjusted model (OR [95% CI] Q2, 1.84 [0.67–5.33]; Q3, 4.01 [1.35–13.48]; Q4, 2.18 [0.81–6.21]) (Table 3).

Similar results were found when 25(OH)D was categorized according to the clinical 25(OH)D cutoffs (Supplementary Tables 1 and 2).

Figure 3 shows BI changes over time across 25(OH)D quartiles: participants in quartile III resulted in better improvement in BI over time in respect to the other quartiles. Adjusted linear mixed models confirmed these results: participants in the III 25(OH)D quartile have a 7.52-point improvement in BI respect to I quartile at 30 days ($p = 0.03$) and of 16.98 points at 3 months ($p < 0.01$). An improvement in the Barthel index was also observed for IV quartile but reached the statistical significance only at the 3-months follow-up (β 8.63, $p = 0.02$) (Supplementary Table 3).

Discussion

Our study documented a high prevalence of vitamin D insufficiency (81.2%) and deficiency (94.3%) in an older population admitted to the rehabilitation units. Despite our hypothesis, we did not find a statistically significant association with outcomes measured at 30 days from admission, with the exception of changes in Barthel index over the time, for which a non-linear relationship and a statistically significant improvement in the third 25(OH)D quartile respect to the first one was evident already at 30 days. At 3 months from admission, we found a non-linear association between 25(OH)D quartiles and functional outcomes, with an association that was weaker in the fourth quartile.

Our results at 30 days from admission confirmed the precedent findings of Pellicane et al. that in a sample of patients with a mean age of 71 years admitted to an inpatient rehabilitation unit did not find differences in functional independence between those with 25(OH)D levels below or above 30 ng/ml [16]. Similar results were documented by Kiebzak et al. comparing patients with 25(OH)D levels lower and higher than the median 25(OH)D value (16.6 ng/ml) in a sample with a mean age of 70 years old admitted to an ambulatory rehabilitation [5]. However, these two studies were not focused on older people, and had a relatively small sample size (about 100 patients). Another study on 456 older patients admitted after a hip fracture found a positive association between 25(OH)D concentration and BI at discharge [17]. However, this study was not comparable to the others, because it took into account only the BI at discharge (mean LOS about 37 days) and not the functional improvement after rehabilitation. Few and contrasting data is available for a longer and more thorough follow-up; in a post-stroke population of 50 patients with a mean age of 72 years, 25(OH)D concentration was not associated with BI and modified Rankin Scale (mRS) both at 3 and 6 months [22]. On the other hand, poor functional outcomes (evaluated with mRS) were observed in 266 non diabetic-patients with vitamin D insufficiency 1 year after stroke [23], and at 3 months after thrombolysis due to an ischemic stroke [24]. However, none of these studies were focused on older adults, nor took into account the modification of functional outcomes over time, or if the patients performed rehabilitation shortly after the acute event and for how long. To our knowledge, only one study analyzed improvement in functional outcomes both at discharge and after discharge from a rehabilitation setting; in a sample of 171 older patients surgically treated for inter-trochanteric hip fracture, Seng et al. did not find differences in the improvement of modified BI either at discharge, or at 6 and 12 months, between patients with 25(OH)D below or above 20 ng/ml [25].

The lack of association between 25(OH)D and functional outcomes documented in many studies might be explained by the non-linear relationship between these two variables that

Table 3 OR for ability to walk according to 25(OH)D quartiles

Quartiles	30 days		3 months	
	Crude (95% CI)	Adjusted* (95% CI)	Crude (95% CI)	Adjusted* (95% CI)
I quartile	Reference	Reference	Reference	Reference
II quartile	0.79 (0.44–1.44)	0.86 (0.35–2.10)	1.00 (0.47–2.11)	1.84 (0.67–5.33)
III quartile	0.88 (0.48–1.60)	0.89 (0.37–2.13)	2.56 (1.11–6.30)	4.01 (1.35–13.48)
IV quartile	1.04 (0.57–1.92)	0.90 (0.38–2.13)	1.58 (0.73–3.51)	2.18 (0.81–6.21)

*Models adjusted for age, sex, MMSE, Charlson index, length of stay, Barthel index at admission, eGFR (CKD-EPI), BMI at admission, handgrip strength at admission, study site, diagnosis at admission

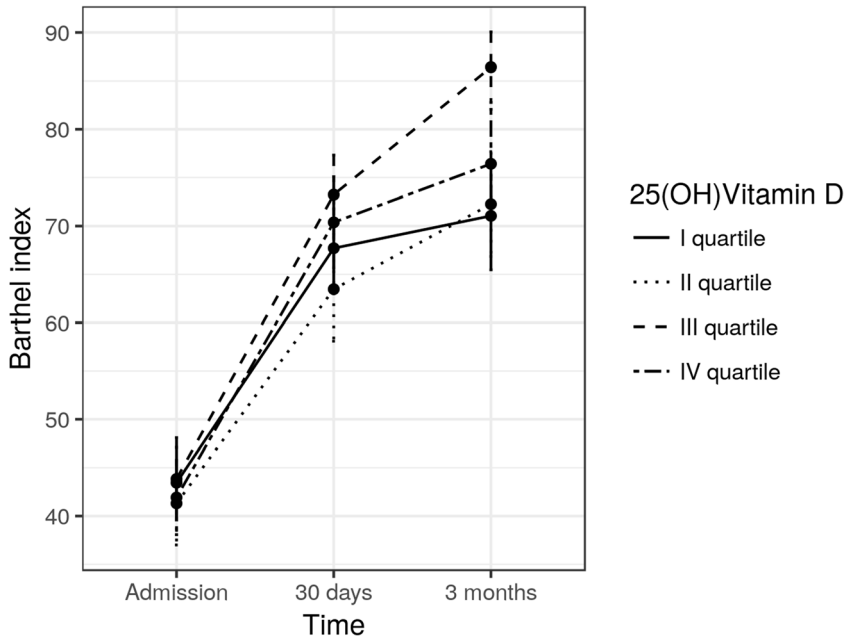

Fig. 3 Changes in the Barthel Index over time. Participants in the III 25(OH)D quartile had a better improvement in the Barthel index in respect to the other quartiles

we proved in our study; a dichotomization of 25(OH)D or its analysis using linear models as a continuous variable may therefore not be representative of this relationship. This non-linear association was already documented in community dwelling older people; in a cohort of 4100 persons aged ≥ 60 years, there was a more evident improvement in walking time and time to stand for 25(OH)D concentration above 16 ng/ml [26], and of physical performance for 25(OH)D concentration < 20 ng/ml [12]. Instead, the lack of association between 25(OH)D and functional outcomes at 30 days, with the exception of an improvement in Barthel index over the time, observed in our study might be explained by a longer recovery time after an acute event needed for older adults [27].

The association between 25(OH)D levels and muscular strength [15], which might partly justify the relationship between 25(OH)D and functional outcomes, may be explained by the important role played by vitamin D in the skeletal muscle. In this tissue, vitamin D receptors (VDR) are well represented, and vitamin D contributed to the regulation of ATP-dependent calcium uptake by sarcoplasmic reticulum and in the production of actin and myosin [28]. Furthermore, vitamin D supplementation increases VDR intra-myonuclear concentration in type II fibers, type II muscle diameter, and representation in rats [29]. VDR activation may be significantly reduced for 25(OH)D serum concentration below a critical value, thus explaining why in our sample, the association between 25(OH)D and functional outcomes is evident for 25(OH)D concentration values below about 16 ng/ml. After this threshold, 25(OH)D concentration may not significantly influence VDR activation, thus explaining the lack of further improvement of functional outcomes for 25(OH)D values above 16 ng/ml. This value is included in the third 25(OH)D quartile; it might explain the lack of further improvement in the fourth quartile documented in our population.

The reference value for 25(OH)D insufficiency of 20 ng/ml was established by assessing the point where serum parathyroid hormone starts to rise [30]; however, according to our results, and to the previously mentioned studies, this cutoff could not be representative of vitamin D effects on clinical and functional outcomes, especially in older adults. Considering the non-linear relationship between 25(OH)D and functional outcomes found in our study and previously reported by other authors, further studies in larger cohorts could work to propose new 25(OH)D cutoffs for older adults.

Among the strengths of our study, we include the relatively large sample size compared to the majority of previous studies in the same setting. Second, it placed focus on older adults, a population in which vitamin D deficiency may be more evident also because of age-related modification of the body composition [31]. Thanks to its longitudinal design, this study provides information on functional outcomes both during rehabilitation and after discharge in the same sample, thus giving precious information on different steps after an acute event or an elective orthopedic surgery. We also acknowledge different limitations in our study; despite its longitudinal design, it had a relatively short follow-up, thus it may not accurately capture long-time effects of 25(OH)D. Data on vitamin D supplementation was available for one center only and we cannot exclude that data from the other two centers might influence our results. However, our analyses in this subsample suggest that supplementation did not significantly affect our outcomes. Finally, 25(OH)D dosage might be influenced by the different study site; in order to reduce this bias, we adjusted the models for the study site.

In conclusion, 25(OH)D concentration is positively associated with functional outcomes in older patients admitted to a rehabilitation setting. Testing for vitamin D insufficiency (perhaps using a lower cutoff compared to the one currently suggested) might contribute in estimating the chance of functional recovery after an acute event or an elective orthopedic surgery for knee or hip replacement. Further research should confirm these results, and possible intervention studies should assess the impact of interventions directed to increasing 25(OH)D levels in case of insufficient values in this population.

Compliance with ethical standards

Conflict of interest None.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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