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Vitamin D deficiency is associated with functional decline and falls in frail elderly women despite supplementation

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Abstract

Purpose—Institute of Medicine (IOM) guidelines recommend 800 IU vitamin D daily for older adults and maintaining serum 25-hydroxyvitamin D [25(OH)D] above 20 ng/ml for optimal skeletal health. The adequacy of IOM guidelines for sustaining function and reducing falls in frail elderly is unknown.

Methods—Female long-term care residents age ≥ 65 enrolled in an osteoporosis clinical trial were included in this analysis (n=137). Participants were classified based on baseline 25(OH)D levels as deficient (<20 ng/ml, n=26), insufficient (20–30 ng/ml, n=40), or sufficient (>30 ng/ml, n=71). Deficient women were provided initial vitamin D repletion (50,000 IU D_3 weekly for 8 weeks). All were supplemented with 800 IU vitamin D_3 daily for 24 months. Annual functional assessments included Activities of Daily Living (ADL), Instrumental ADL (IADL), Physical Performance Test (PPT), gait speed, cognition (SPMSQ), and mental health (PHQ-9). We used linear mixed models for analysis of functional measures and logistic regression for falls.

Results—Daily supplementation maintained 25(OH)D levels above 20 ng/ml in 95% of participants. All groups demonstrated functional decline. Women initially deficient had a greater decline in physical function at 12 (IADL: −2.0±0.4, PPT: −3.1±0.7, both p<0.01) and 24 months (IADL: −2.5±0.6, ADL: −2.5±0.6, both p<0.01), a larger increase in cognitive deficits at 12 months (1.7±0.4: p=0.01), and more fallers (88.5%, p=0.04) compared to those sufficient at baseline, despite supplementation to sufficient levels.

Conclusions—IOM guidelines may not be adequate for frail elderly. Further study of optimal 25(OH)D levels for maintaining function and preventing falls is needed.

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Keywords

Vitamin D; 25-hydroxyvitamin D; deficiency; frail elderly; long-term care; falls

Introduction

Vitamin D deficiency is a prevalent and often under-treated condition in the elderly [1–5]. Most deficiencies result from reduced sunlight exposure (one main source of vitamin D) and limited dietary intake of vitamin D [5]. Therefore, supplementation for long-term care residents is advised to prevent deficiency and maintain adequate serum 25-hydroxyvitamin D [25(OH)D] levels [6–9].

For community-dwelling elderly, the IOM recommends a daily intake of 800 IU vitamin D and a 25(OH)D level of at least 20 ng/ml [6], while the Endocrine Society and the American Geriatrics Society suggest a higher level of 30 ng/ml [7,9]. Although numerous studies have demonstrated a strong association between low 25(OH)D levels and poor outcomes [10–14], there is no consensus as to what supplemental dose and/or serum level may be adequate for optimal function in frail elderly.

We performed a secondary analysis of data from an osteoporosis trial to investigate the impact of vitamin D deficiency and supplementation on measures of physical activity, cognitive function, and falls in elderly women residing in long-term care. We sought to examine if supplementation at the IOM-recommended dosage of 800 IU/day was sufficient to maintain serum 25(OH)D levels above 20 ng/ml in a frail elderly cohort. Additionally, we examined the association of vitamin deficiency with functional changes and falls over two years.

Methods

Participants

Women age 65 years or older were recruited from long-term care facilities in the greater Pittsburgh area for enrollment in a clinical trial of zoledronic acid for osteoporosis [15]. From the primary cohort of 181 participants, 137 followed for 2 years were included in the current analysis. Participants included residents with cognitive impairment, impaired mobility, with multimorbidity [16], and with polypharmacy as previously described [15].

Serum Measures and Supplementation

Total serum 25(OH)D was assessed at baseline, 12, and 24 months by liquid chromatography with tandem mass spectroscopy. Intact parathyroid hormone (PTH) was measured at baseline by chemiluminesence immunoassay. Baseline 25(OH)D levels were used to classify subjects as vitamin D deficient (<20 ng/ml), insufficient (20–30 ng/ml), or sufficient (>30 ng/ml). A repletion dose of 50,000 IU vitamin D_3 (cholecalciferol) weekly was provided to deficient women for 8 weeks to bring serum levels >20 ng/ml. All participants were given oral vitamin D supplementation of 800 IU vitamin D_3 daily for 24 months.

Functional Assessments

Functional assessments were performed at 0 (baseline), 12, and 24 months. Measures included Katz's Activities of Daily Living (ADL) [17], Instrumental Activities of Daily Living (IADL) [18], the Nursing Home Physical Performance Test (PPT) [19] including a timed chair stand and gait speed measured via 6-meter walk. Cognition and mental health were assessed using the Short Portable Mental Status Questionnaire (SPMSQ) [20] and the Patient Health Questionnaire (PHQ-9) [21], respectively. Functional assessment measures have previously demonstrated reliability and validity [17–26]. Falls information was gathered from facility medical records, patient reports, and electronic medical record alerts.

Statistical analysis

We used appropriate descriptive statistics to summarize participant characteristics by whether they were vitamin D sufficient, insufficient and deficient, and compared them across groups using one-way analysis of variance and chi-square tests. To examine associations between serum 25(OH)D and PTH and graphically determine any thresholds for rising PTH, we constructed a display with locally weighted scatterplot smoothing (LOESS). For examining whether the 12- and 24-month change in measures of function significantly differed among the three groups, we fitted a series of linear mixed models with change in each functional measure as the dependent variable; participant group (baseline vitamin D sufficient/insufficient/deficient), follow-up time (12-/24-month) and their interaction as the main independent fixed effects of interest; baseline value of the measure as a covariate; and a participant random effect to account for multiple measures from the same participant. For falls, we fitted a logistic regression model with whether a participant was an incident faller as the dichotomous dependent variable, group based on 25(OH)D level at baseline as the independent variable and history of falls as a covariate. Due to some evidence that serum vitamin D levels below 45 ng/ml after repletion may be optimal [27], we performed a post hoc exploratory analysis further subdividing the insufficient group based on whether post-repletion level was ≤ 45 or >45 ng/ml. Also, we made an additional comparison between those continuously sufficient over the 2-year period to those replenished to sufficiency. SAS® version 9 was used for all statistical analyses (SAS Institute, Inc., Cary, North Carolina).

Results

Baseline characteristics

At baseline, 26 women (19%) were vitamin D deficient, 40 (29%) were insufficient, and 71 (52%) were sufficient (Table 1). Groups were similar in age, body mass index, dietary calcium and vitamin D intake, and presence of comorbidities. Women with vitamin D levels below 30 ng/ml exhibited slower gait speeds compared to those with sufficient levels as well as a tendency for a poorer IADL score. All other physical and cognitive functional measures were not significantly different between groups at baseline.

Serum PTH and 25(OH)D levels

Deficient women had significantly elevated PTH and lower serum calcium levels compared to those with sufficient vitamin D levels (p<0.0001 and p=0.0109, respectively). At baseline, the inverse association of serum 25(OH)D level with PTH appears to be stronger below levels of 37 ng/ml and even more so below 23 ng/ml (Fig. 1).

Vitamin D supplementation

Supplementation with 800 IU/d of vitamin D_3 was adequate to maintain serum 25(OH)D levels above the IOM recommended guideline of 20 ng/ml over the 24 months of follow-up in 95% of the women. Although we do not have daily compliance information, 25(OH)D levels at the 12-month time point suggest 2 women were non-compliant with the supplementation regimen during the first year. Three additional women had 25(OH)D levels below detectable limits at 24 months, two of whom transitioned to skilled nursing care during the follow-up period. Serum levels in initially deficient women rose from 13.8 ± 0.6 to 33.1 ± 1.7 ng/ml (mean ± standard error) after 12 months and 35.5 ± 1.9 ng/ml after 24 months of supplementation (both p<0.0001 compared to baseline). Similar results were achieved in insufficient women (36.8 ± 1.6 ng/ml at 12 months; 38.1 ± 1.5 ng/ml at 24 months, both p<0.0001 compared to baseline). Sufficient women maintained levels near baseline throughout the study (40.2 ± 1.2 ng/ml at 12 months; 43.1 ± 1.6 ng/ml at 24 months).

Changes in function

Despite reaching 25(OH)D levels above 20 ng/ml, women initially deficient in vitamin D exhibited a greater decline in physical function over 12 months with a decrease in IADL score of −2.0 ± 0.4 compared to −0.8 ± 0.3 (p=0.0211) and −0.5 ± 0.3 (p=0.0014) in the insufficient and sufficient groups, respectively (Fig. 2). PPT scores also declined to a greater extent in deficient women (−3.1 ± 0.7) compared to −0.5 ± 0.4 in sufficient women (p=0.0049, Fig. 2). Deficient women exhibited decline to a greater extent in the number of errors in cognition (1.7 ± 0.4) than insufficient (0.6 ± 0.2) and sufficient women (0.6 ± 0.2) as measured by the SPMSQ (p=0.0106 and p=0.0209, respectively, Fig. 2).

Functional scores continued to decline over 24 months in all groups with deficient women displaying the largest decline from baseline assessments. ADL scores declined by −2.5 ± 0.6, a greater extent in deficient women, compared to −1.2 ± 0.3 for the insufficient group and −1.0 ± 0.2 for sufficient women (p=0.0153 and p=0.0016, respectively). IADL scores also declined more in women initially deficient (−2.5 ± 0.6) compared to sufficient women (−1.2 ± 0.3, p=0.0038). Changes in gait speed, time to stand, and PHQ-9 were similar among the three groups at each time point.

A higher percentage of deficient women experienced falls (88.5%) compared to 65.0% of the insufficient group and 66.2% of sufficient women (Fig 3). Controlling for prior history of falls, those deficient were more likely to fall during the follow-up period compared to those insufficient (adjusted odds ratio (AOR)=4.11; p=0.0429) and sufficient (AOR=4.01; p=0.0365).

Exploratory Analyses

When descriptively comparing (due to small sample size) those who reached 25(OH)D levels ≤ 45 ng/ml (n=16; mean 32.7 ng/ml) to those with values >45 ng/ml (n=10; mean 53.0 ng/ml) after repletion, fall risk was slightly elevated among the latter (87.5 vs 90.0%). Further, the latter group exhibited greater decline in PPT (2.8 vs 4.7 points), ADL (1.6 vs 4.0) and SPMSQ (1.1 vs 2.8) over 24 months. When comparing those continuously sufficient (>30 ng/ml at all time points; n=57) and those replenished to sufficiency (<20 ng/ml at screening but >30 ng/ml after the repletion period; n=20), we found lesser decline in function (ADL −1.0 vs −2.9; IADL −1.2 vs −3.0; SPMSQ 0.9 vs 1.9; PPT −1.1 vs −4.1) and reduced fall incidence over the follow-up period.

Discussion

In our cohort of elderly women residing in long-term care facilities, vitamin D deficiency at baseline was associated with greater declines in function over 2 years, despite supplementation to restore 25(OH)D levels above 20 ng/ml. Women in the deficient group became more dependent on assistance for the completion of daily activities and had greater difficulty performing physical tasks. Women who were vitamin D deficient at baseline experienced greater cognitive decline. In addition to greater functional decline, more women in the vitamin D deficient group experienced falls during the study period.

The role of vitamin D in maintaining functional status is controversial. Both cross-sectional and longitudinal studies have demonstrated an association between vitamin D deficiency and reduced physical function in older adults [10,12–14,28–32]. While the link between D deficiency and physical performance is well-documented, the impact of supplementation on performance is less clear. Several studies support supplementation improving functional outcomes such as lower limb strength and balance [33–35]. Alternatively, others have shown no benefit of vitamin D supplementation on physical performance measures [27,36–38]. The seemingly contradictory findings surrounding vitamin D supplementation and function may stem from varied study designs including differences in cohort characteristics, length of follow-up, supplement dosage and formulations, and the functional outcomes measured. The ability of vitamin D supplementation to induce beneficial changes may also depend on the initial level of deficiency and sex of the study participants [29,39]. In addition to physical performance, emerging research has demonstrated a correlation between vitamin D deficiency and cognitive function [14,40–43]; however, the exact mechanism behind vitamin D's role in cognition remains to be fully elucidated. Our results are in agreement with the general consensus that vitamin D deficiency is related to decline in physical and cognitive function in older adults.

The usefulness of vitamin D supplementation for fall prevention is subject to similar controversy due to variations in populations studied, experimental designs, and reporting of falls. Indeed, even meta-analyses and systematic reviews examining the relationship between vitamin D and falls have varying results, finding either a decreased risk of falls [44–46] or no benefit [47,48] with vitamin D supplementation. A recent study of monthly vitamin D_3 supplementation found increased fall incidence with 60,000 IU compared to 24,000 IU [27]. While no definitive consensus has been reached, the U.S. Preventative Services Task Force

[8], American Geriatrics Society [9], and the Endocrine Society [7] recommend vitamin D supplementation in the range of 600 – 1000 IU/day in older adults at risk of falling. A meta-analysis of vitamin D supplementation trials found a dose of 700–1000 IU daily is needed to influence physical performance and falls [44]. Higher doses may be necessary than what is currently recommended by the IOM for adults over age 70 (800 IU) to achieve optimal functional benefits.

Clinical guidelines recommend vitamin D supplementation of at least 600–800 IU [6,9,7,8] in older adults; however, the 25(OH)D levels reached with the recommended doses can vary greatly. The IOM recommends a level of 20 ng/ml is adequate to maintain bone health and lessen fracture risk [6], but hesitates in recommending a level of "sufficiency" for preservation of physical function and reducing the risk of falling. A reference range for sufficient 25(OH)D levels relating to physical performance and falls has not been established, likely due to the difficulty in compiling findings of studies with varied dosing regimens, supplementation formulations, and outcome measures. While all groups had some measure of functional decline during the study period, sufficient women had lesser decline. Further, women continuously sufficient in vitamin D declined less than those deficient replenished to sufficiency. Our results suggest continuously maintaining 25(OH)D levels above 30 ng/ml and potentially closer to 40 ng/ml as observed in our sufficient group may be advantageous in reducing functional declines in elderly women. We believe based on functional outcomes and falls that 20ng/ml is not sufficient. Serum 25(OH)D levels closer to 30–40 ng/ml may be warranted in this population. Our results are in agreement with recommendations from other organizations supporting an optimal level of 30 ng/ml [9,7,8]. Furthermore, even at baseline, levels of PTH begin to climb as 25(OH)D levels fall below 37 ng/ml in our frail cohort.

Our study had several limitations. It is unknown how long women were deficient. The length of deficiency may impact the effectiveness of supplementation on functional outcomes, and women may require more than 2 years of adequate supplementation for maintenance or improvements in function. Deficient women showed greater functional decline, despite daily supplementation and maintenance of mean 25(OH)D levels above 20 ng/ml. Restoration of vitamin D in elderly women may not be adequate to overcome insults from prolonged periods of deficiency. Women deficient in vitamin D had lower IADL scores at baseline and may have been at a more advanced stage in the aging process. It is possible that supplementation alone would not be adequate to overcome the physical progression of frailty associated with aging. Ours was a sub-analysis of a clinical trial on osteoporosis prevention, and secondary analyses may have implicit biases. All participants were provided vitamin D supplementation according to the standard of care in these facilities. As such, we do not have a non-supplemented control group for comparisions. Finally our sample size was small.

However, our study also had several strengths. This is a neglected and frail population that is rarely included in clinical studies. In addition, the study design included a prospective follow-up of clinically relevant measures, and we utilized the newest IOM recommendations for vitamin D supplementation in this institutionalized group. Moreover, we used a state of the art vitamin D assay and included simultaneous serum calcium and parathyroid measures.

Furthermore, we were able to capture falls from several sources in these long-term care facilities to allow us to examine the association of vitamin D and falls.

In summary, we found that even after correction of vitamin D deficiency and maintenance of adequate levels (above 20 ng/ml) for two years, women who were deficient at baseline had the greatest functional declines and risk of falling. Aging is a dynamic process. As such, the influence of vitamin D deficiency is likely one aspect of a complex paradigm. Focus should be placed on prevention and early identification of deficiency, particularly in frail elderly women. Additionally, supplementation to maintain a serum 25(OH)D level of 30–40ng/ml may be most beneficial in this population in order to optimize functional performance; however, rigorous trials to ascertain 25(OH)D reference ranges for functional outcomes are warranted before preferred vitamin D supplementation regimens can be established.

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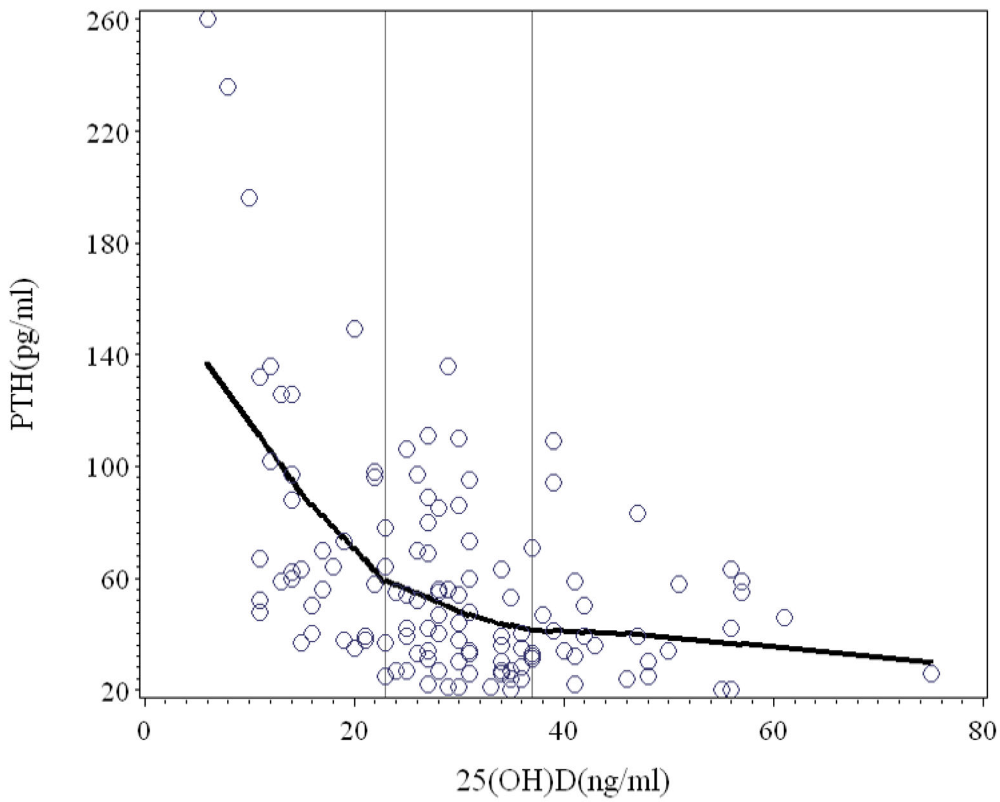

Fig. 1.

Association between 25-hydroxyvitamin D [25(OH)D] and parathyroid hormone (PTH) levels. PTH levels begin to rise at 25(OH)D levels below 37 ng/ml, with an even steeper rise occurring at 23 ng/ml

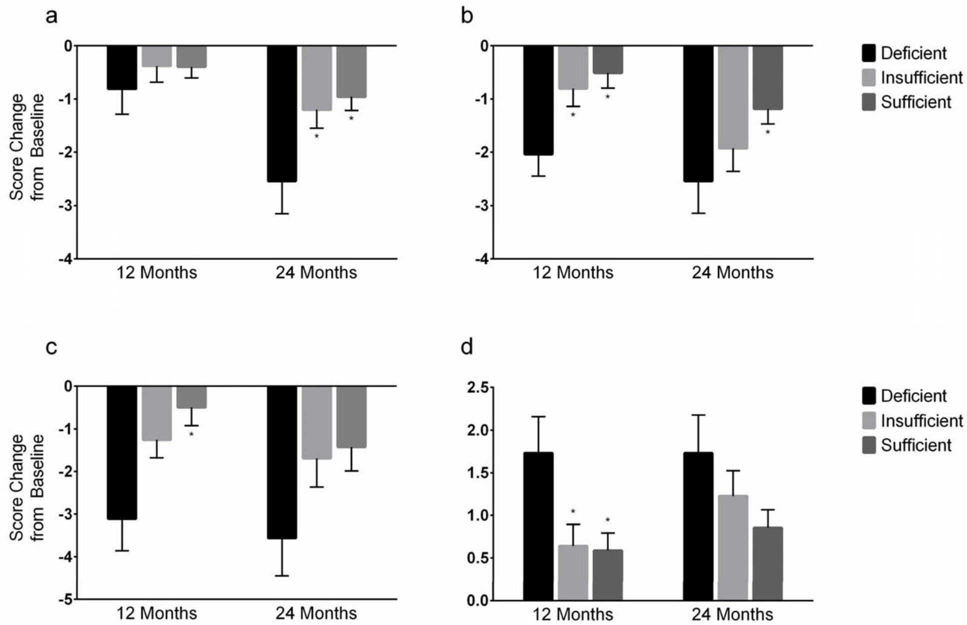

Fig. 2.

Change in functional measures over 24 months. Score changes from baseline (mean ± standard error) are presented for (a) Activities of Daily Living (ADL), (b) Instrumental Activities of Daily Living (IADL), (c) Physical Performance Test (PPT), and (d) Short Portable Mental Status Questionnaire (SPMSQ). * p<0.05 compared with deficient group

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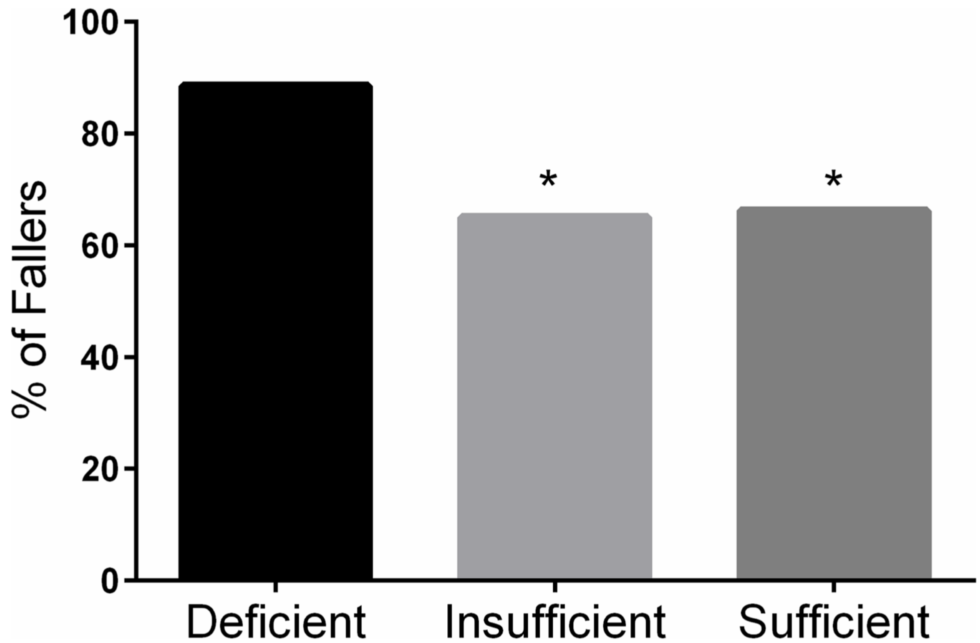

Fig. 3.
Percentage of fallers over 24 months. * $p<0.05$ compared with deficient group

Table 1

Baseline Group Characteristics

	Deficient (< 20 ng/ml) n=26	Insufficient (20–30 ng/ml) n=40	Sufficient (> 30 ng/ml) n=71	Overall p-value
25-hydroxyvitamin D_3 (ng/ml)	13.8 ± 0.6 *†	25.4 ± 0.4 *	40.2 ± 1.3	0.0001
Age (years)	85.8 ± 1.0	85.6 ± 0.8	84.9 ± 0.6	0.65
Height (in)	60.7 ± 0.5	62.2 ± 0.4	61.5 ± 0.3	0.06
Weight (kg)	69.3 ± 2.5	71.0 ± 2.2	67.2 ± 1.6	0.35
BMI (kg/m^2)	29.1 ± 0.9	28.4 ± 0.8	27.6 ± 0.7	0.48
Calcium intake (mg/d)	675.5 ± 63.5	739.1 ± 73.3	826.6 ± 50.5	0.25
Vitamin D intake (IU/d)	158.0 ± 28.1	181.3 ± 25.8	160.4 ± 15.6	0.73
Serum calcium (mg/dl)	9.2 ± 0.07 *	9.4 ± 0.06	9.4 ± 0.04	0.01
Serum PTH (pg/ml)	90.5 ± 11.9 *†	58.4 ± 5.1 *	40.7 ± 2.7	0.0001
Comorbidity index (0–8 scale)	3.2 ± 0.3	3.4 ± 0.2	3.3 ± 0.1	0.71
Functional Measures				
Gait speed (m/s)	0.5 ± 0.04 *	0.5 ± 0.04 *	0.6 ± 0.03	0.004
Time to stand (s)	3.1 ± 0.4	2.9 ± 0.3	2.8 ± 0.3	0.86
ADL (0–14 scale)	11.6 ± 0.4	11.7 ± 0.4	12.0 ± 0.3	0.70
IADL (0–14 scale)	6.7 ± 0.6	8.1 ± 0.6	8.8 ± 0.5	0.06
SPMSQ (0–10 scale)	3.3 ± 0.4	2.5 ± 0.4	2.3 ± 0.3	0.19
PHQ-9 (0–27 scale)	5.2 ± 1.1	2.8 ± 0.6	3.5 ± 0.5	0.10
PPT (0–24 scale)	19.4 ± 0.7	19.7 ± 0.7	20.3 ± 0.6	0.62
Fall history				
Fall in past year (%)	42.3	37.5	42.9	0.85
>1 fall in past year (%)	19.2	22.5	17.1	0.79

Mean ± standard error;

* $p<0.05$ compared to sufficient group;

† $p<0.05$ compared to insufficient group

ADL: Activities of Daily Living; BMI: Body Mass Index; IADL, Instrumental Activities of Daily Living; PHQ-9, Patient Health Questionnaire; PPT, Physical Performance Test; PTH, parathyroid hormone; SPMSQ, Short Portable Mental Status Questionnaire