Quality of Life Research (2019) 28:1377–1386
https://doi.org/10.1007/s11136-019-02100-4

Effects of a simple home exercise program and vitamin D supplementation on health-related quality of life after a hip fracture: a randomized controlled trial

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Accepted: 3 January 2019 / Published online: 9 February 2019

Abstract
Purpose To test the effects of vitamin D intervention and a simple home exercise program (HE) on health-related quality of life (HRQL) in the first 12 months after hip fracture.

Methods HRQL was reported in 173 acute hip fracture patients (mean age 84 years, 79% females, 77% community dwelling) who were enrolled in the 12-month 2 × 2 factorial Zurich Hip Fracture Trial. Pre-fracture HRQL was assessed at baseline (4.2 ± 2.2 days post-surgery) and then again at 6 and 12 months after hip fracture surgery by the EuroQol EQ-5D-3L index value (EQ-5D-3L questionnaire). The effects of vitamin D intervention (2000 vs. 800 IU vitamin D_3) and exercise (HE vs. no HE) or of the combined interventions on HRQL were assessed using multivariable-adjusted repeated-measures linear mixed-effects regression models.

Results The EQ-5D-3L index value significantly worsened from 0.71 pre-fracture to 0.57 over 12 months, but the degree of worsening did not differ between individual or combined interventions. However, regarding only the late recovery between 6 and 12 months, the group receiving neither intervention (800 IU/day and no HE) experienced a significant further decline in the EQ-5D-3L index value (adjusted mean change = 0.08 [95% CI 0.009, 0.15], $p = 0.03$) while all other groups remained stable.

Conclusion Hip fractures have a long-lasting negative effect on HRQL up to 12 months after hip fracture. However, HE and/or 2000 IU vitamin D per day may help prevent a further decline in HRQL after the first 6 months following the acute hip fracture event.

Keywords Hip fracture · Quality of life · Exercise · Vitamin D · RCT · Elderly

Introduction

Despite being one of the most prevalent and severe injuries among seniors aged 75 years and older, hip fractures remain a leading cause of morbidity, mortality, and healthcare

K. Renerts and K. Fischer have contributed equally to this work.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s11136-019-02100-4) contains supplementary material, which is available to authorized users.

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expenditure [1–4]. Additionally, hip fractures exert lasting negative changes on health-related quality of life (HRQL) among affected seniors [5, 6]. Thus, well-tolerated interventions that both influence morbidity and HRQL are urgently needed to be broadly implemented among the rising number of seniors with hip fractures. In the original Zurich Hip Fracture Trial, a simple home exercise program (HE) reduced falls by 25% after hip fracture, and vitamin D supplementation of 2000 IU per day reduced hospital readmission after hip fracture by 39% driven by a significant 60% reduction of fall-related injuries [7]. This trial also showed that people engaging in the HE at least once a week had a significantly better knee extensor strength, grip strength, and functional mobility when compared with those who were not randomized in the HE group or those who did not engage in the HE. The reduction in hospital readmissions was mainly driven by fewer fall-related injuries and fewer infections. However, whether these inexpensive and well-tolerated strategies also help maintain HRQL after hip fracture is still unclear.

Any effect of exercise on HRQL is most likely mediated by physical as well as psychological aspects, as exercise can positively influence physical functioning, psychological wellbeing, and self-efficacy [8, 9]. Engaging in exercise in healthy adolescent individuals e.g., was correlated with higher HRQL [10]. However, the available literature of exercise affecting HRQL after a hip fracture is limited and not conclusive. Several randomized controlled intervention trials (RCTs) enrolling between 95 and 176 study participants have shown positive effects of home exercise programs on HRQL after hip fracture [11–15], while others have found no benefit [16, 17].

Maintaining normal levels of vitamin D can positively affect diverse body functions encompassing such fundamental domains as muscle health [18] and maintaining lower blood pressure [19], which could contribute to a better HRQL. Vitamin D might even be involved in immunomodulatory processes, although a recent review of RCTs does not support its role in lowering levels of chronic systemic inflammatory markers [20]. Some studies have attempted to directly explore the association between vitamin D and HRQL. Indeed, serum 25-hydroxyvitamin D (25(OH)D) levels have been associated with better HRQL in two observational studies [21, 22]. Further, vitamin D supplementation (4000 IU/day vs. 600 IU/day) improved wellbeing in an RCT among middle-aged adults [23], and moreover, a combination of vitamin D and resistance improved muscle strength in older adults [24]. However, to our knowledge, no study has explored the effects of combined vitamin D supplementation and exercise on HRQL.

In the present study, taking advantage of the original Zurich Hip Fracture Trial data set, we aimed to test whether a simple HE and vitamin D supplementation (800 U vs. 2000 IU per day) individually or in combination influence HRQL over 12 months of treatment after hip fracture surgery. Additionally, we aimed to assess both the early recovery (baseline to 6 months) and late recovery (6 to 12 months) separately.

Methods

Study design

The present HRQL ancillary study takes advantage of the Zurich Hip Fracture Trial data set [7]. The original trial employed a 2 × 2 factorial design with participants randomly assigned to vitamin D intervention (800 IU/day vs. high-dose 2000 IU/day; 800 IU/day was considered a standard of care) and exercise intervention (HE vs. no HE) over a follow-up of 12 months. The allocation ratio was similar in all intervention groups, and the trial was powered for the main outcome–rate of falls. The trial complies with the World Medical Association Declaration of Helsinki, was approved by the local Cantonal Ethics Committee at the University of Zurich, and is registered at ClinicalTrials.gov (NCT00133640). Written informed consent was obtained from each participant. In the present HRQL ancillary study, we investigated both the individual effects of vitamin D and HE, as well as the combined interventions, on HRQL. Among the four combined interventions, 800 IU vitamin D per day combined with no HE was considered the “control” group.

Participants

A total of 667 patients aged 65 years or older admitted to a single medical center (Triemli City Hospital, Zurich) with an acute hip fracture from January 1, 2005 through December 31, 2007 were screened for the trial [7]. A total of 173 participants were able and willing to participate, and were included in the original trial. The following inclusion and exclusion criteria were applied: newly fractured hip with no previous hip fractures, surgical intervention of the newly acquired hip fracture, no metastatic cancer or chemotherapy in the year prior to fracture, creatinine clearance above 15 mL/min, no kidney stones in the past 5 years, no hypercalcemia, no primary hyperparathyroidism, no sarcoidosis, able to walk at least 3 m prior to fracture, a Mini-Mental State Examination (MMSE) score of at least 15 points (a higher score indicating a better cognitive function), no severe visual or hearing impairment, and able to understand German.

During the 12-month trial, 45 participants dropped out after a mean follow-up of 118 (112) days; of these, 20 died, 10 stopped for personal reasons (i.e., they were overwhelmed or lost interest), 6 withdrew because of illness and overall decline, and 9 withdrew because they wanted to discontinue the study medication therapy. Subjects who discontinued their study medication therapy were encouraged to return for all subsequent follow-up evaluations. Due to drop outs and individual missing information at single follow-up time points, the analytical sample sizes at 6 months and 12 months were $n = 120$ and $n = 119$, respectively. The dropouts showed lower scores in MMSE compared to the rest of participants (25.43 vs. 22.78, $p < 0.0001$) and were more likely to be male (see Supplementary Table 1 for more information).

Interventions

All participants took 400 IU of vitamin D and 500 mg of elemental calcium for breakfast and at bedtime. Additionally, depending on the intervention group, they took a study capsule containing either 1200 IU vitamin D or placebo for breakfast. The study capsules were prepared in a single batch (Streuli AG, Uznach, Switzerland); an assay confirmed that the dose was 1269 IU of vitamin D. Adherence was assessed during the monthly phone calls and was 92.2% for the combined vitamin D/elemental calcium capsule and 93.6% for the vitamin D/placebo capsule. The measured serum 25(OH)D levels significantly correlated with the adherence-adjusted dosage of cholecalciferol at 6-month (0.48, $p < 0.001$, $n = 117$) and 12-month (0.44, $p < 0.001$, $n = 116$) follow-up visits. Randomization for the vitamin D intervention was double-blinded.

During acute care, all participants received physiotherapy of 30 min/day, and participants randomized in the HE group received an additional 30 min of HE instruction each day. In total, participants in the HE group received 292 min of physiotherapy during the acute care versus 176 min in the no HE group. Upon discharge from the hospital, participants from the HE group received a leaflet illustrating the HE program and a recommendation to follow the program for 30 min daily. The HE consisted of balance, strength, and functional mobility components [7]. All study staff except for the treating physiotherapist, who did not participate in data collection, were blinded for the HE allocation. To ensure this, the assessment of adherence to the HE was done only at the 12-month follow-up visit or by a phone call, if the participant could not visit the study center. From the 87 participants randomized to the HE group, 65 could be reached for follow-up and 45 (69%) reported being adherent, i.e., performing the HE at least once a week. From the adherent participants, 17 (38%) reported feeling a lot stronger and a lot more mobile due to the HE, 24 (53%) felt somewhat stronger and somewhat more mobile and 4 (9%) saw no improvements in their strength or mobility.

Assessment of HRQL

HRQL was a pre-specified secondary outcome of the original RCT, and was assessed by the EuroQol EQ-5D instrument at baseline, 6-month and 12-month follow-up. The EQ-5D-3L version of EQ-5D is a standardized generic instrument to assess HRQL and was developed by the EuroQol Group [25]. It comprises five dimensions (5D): mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension can be described by one of the three levels of problems: no problems, some problems, severe problems. A German translation of EQ-5D-3L was used in our RCT, and a German Time-Trade-Off value set was used to calculate the EQ-5D-3L index value [26] ranging from 1.000 (best possible score, indicating optimal HRQL), to −0.594 (worst possible score, indicating worst HRQL). The minimal clinically important difference for the EQ-5D index value has been estimated by Walters et al. to be 0.074 [27].

Baseline assessments of the EQ-5D-3L index value were conducted during acute care 4.2 ± 2.2 days after the hip fracture surgery; here, participants were asked to choose statements best describing their health in the 6 months prior to the fracture. At 6 months and 12 months, participants were asked to choose statements best describing their health status in the past 3 months prior to the assessment.

Assessment of covariates

Age, sex, Charlson Comorbidity Index (CCI), MMSE, and living status (assisted vs. non-assisted) were assessed by questionnaires during acute care, on average 4.2 ± 2.2 days after hip fracture surgery. The CCI (score 0–37) is a tool predicting the 1-year mortality due to comorbid conditions a year after hospital admission and was developed in a cohort of 559 medical patients [28]. More specifically, the CCI is a weighted index taking the number and seriousness of diseases (in total 19 conditions) into account. Each condition is assigned a score of 1, 2, 3, or 6, depending on the risk of dying associated with the condition. Individual scores are summed to provide a total score predictive of mortality. The CCI has been repeatedly validated in various disease groups and widely used in longitudinal studies [29]. The MMSE (score 0–30, with a score ≥ 24 indicating a normal cognition) is a tool to quantify the global cognitive performance covering orientation to time and place, registration, attention and calculation, recall, language, repetition, and complex commands [30]. The MMSE can be administered in ca. 10 min and has a good test–retest reliability [31]. BMI was calculated as weight (in kilograms) divided by height (in meters) squared. Height and weight were measured with participants having light clothing and without shoes. Baseline 25(OH)D concentration was obtained from venous blood samples using a radioimmunoassay (Diasorin, Inc., Stillwater, Minnesota).

Statistical analysis

Differences in population characteristics between intervention groups were analyzed by using a χ^2 test for categorical variables and a Student's t test for continuous variables.

We used multivariable-adjusted repeated-measures mixed-effects linear regression models (i) to compare the EQ-5D-3L index value over time, (ii) to compare the effect of the individual or combined study interventions on the EQ-5D-3L index value at each time point, and (iii) to explore the overall effect of the individual or combined study interventions on the EQ-5D-3L index value over time. All models included random effects for patients to account for correlation over time. The model analyzing individual interventions included indicator variables for the time point, allocation to vitamin D intervention, and allocation to HE intervention, as well as the two-way and three-way interactions between these factors. The model analyzing combined interventions included an indicator variable for allocation to the combined interventions and the two-way interaction between time and intervention. Both models were further adjusted for the predefined confounders age, sex, BMI, CCI, MMSE, baseline serum 25(OH)D concentration, and pre-fracture living situation. To investigate any confounding effects of the occurrence of falls and/or the number of hospital readmissions regarding the impact of the interventions on the EQ-5D-3L index value during the 12-month trial period, we performed a separate sensitivity analysis including these variables as additional covariates in the model.

For our second aim to specifically investigate the early and late recovery after hip fracture separately, we used equivalent, multivariable-adjusted, repeated-measures mixed-effects linear regression models as for the main analysis. These models compared the change in the EQ-5D-3L index value during the early (baseline to 6 months) and late (6 to 12 months) recovery in the control group (standard-of-care 800 IU/day vitamin D and No HE) to that in the other three combined intervention groups (2000 IU/day + HE; 2000 IU/day + No HE; 800 IU/day + HE).

Statistical significance was set at $p \leq 0.05$, and reported p values are two-sided. All statistical analyses were conducted using SAS 9.4 statistical software package (©2002–2012 by SAS Institute Inc., Cary, NC, USA).

Results

Baseline characteristics

Baseline characteristics of the 173 participants enrolled in this study are shown by vitamin D and HE intervention groups (Table 1). The mean age was 84 years, 79% were females, and 77% lived unassisted. Age, sex, BMI, comorbidities, and the baseline EQ-5D-3L index value were evenly distributed across interventions. The participants receiving the HE had significantly higher MMSE scores (25.7 ± 3.1 vs. 23.7 ± 4.0, $p < 0.001$) and serum 25(OH)D concentration (13.9 ± 9.0 vs. 11.3 ± 6.7, $p = 0.03$), and were slightly more

Table 1 Baseline characteristics of the Zurich Hip Fracture Trial participants by intervention strategy

	Vitamin D intervention			HE intervention			
	High-dose (2000 IU/days)	Low-dose (800 IU/days)	*p* value	Yes	No	*p* value	Total
N	86	87		87	86		173
Women (%)	68 (79)	69 (79)	0.97	68 (78)	69 (80)	0.74	137 (79.2)
Age (y), mean (SD)	84.1 (7.0)	84.4 (6.8)	0.78	83.4 (7.2)	85.1 (6.5)	0.1	84.2 (6.9)
BMI (kg/m^2), mean (SD)	24.2 (4.3)	24.3 (4.3)	0.83	24.6 (4.5)	24.0 (4.2)	0.4	24.2 (4.3)
Charlson Comorbidity Index (score 0–37), mean (SD)	2.8 (2.1)	2.5 (1.7)	0.26	2.4 (1.8)	2.8 (2.0)	0.17	2.7 (1.9)
MMSE (score 0–30), mean (SD)	24.8 (36.8)	24.6 (3.6)	0.68	25.7 (3.1)	23.8 (4.0)	< 0.001	24.7 (3.7)
25(OH)D, ng/mL (SD)	13.1 (8.2)	12.1 (7.7)	0.41	13.9 (8.9)	11.3 (6.7)	0.03	12.6 (8.0)
Living situation Home (%)	69 (80.2)	65 (74.8)	0.39	72 (82.8)	62 (72.1)	0.09	134 (77.5)
Living situation Assisted (%)	17 (19.8)	22 (25.3)		15 (17.2)	24 (27.9)		39 (22.5)
EQ-5D-3L index value (− 0.594 to 1.000), mean (SD)	0.77 (0.22)	0.73 (0.24)	0.23	0.74 (0.26)	0.77 (0.20)	0.32	0.75 (0.2)

Data ($n = 173$) are crude means (SD) or n (%). Differences between intervention groups were assessed using Student's t test for continuous variables and a χ^2 test for categorical variables. p values are two-sided and uncorrected. Statistical significance is set at $p \leq 0.05$

BMI body mass index, *EQ-5D-3L* EuroQol 5 dimensions 3 levels measure of health-related quality of life, *HE* home exercise program, *MMSE* Folstein's Mini-Mental State Examination, *25(OH)D* 25-hydoxyvitamin D likely to live unassisted (82.9% vs. 71.1%, $p=0.09$) than the participants who did not receive HE intervention. The final multivariable analyses were adjusted for these baseline differences.

Change in HRQL in the total population

Over time, in the total population, the EQ-5D-3L index value significantly declined and did not recover to pre-fracture levels, resulting in an overall decrease in the EQ-5D-3L index value of 0.14 (95% CI: 0.19, 0.08, $p<0.0001$) from baseline to 12 months (Fig. 1; Table 2). However, during late recovery, between 6 and 12 months, the decline was no longer significant ($p=0.2$; Fig. 1; Table 2).

HRQL of individual and combined intervention groups over time

At both the 6-month and 12-month follow-up, there were no significant differences in the EQ-5D-3L index value between the individual (Fig. 2) and combined (Fig. 3) intervention groups. Further, across all time points, we did not find a significant interaction between the two individual interventions ($p=0.5$), between vitamin D intervention and time ($p=0.9$), or between HE intervention and time ($p=0.3$). In addition, across all time points, there was no significant effect for the combined interventions ($p=0.3$) or the interaction between the combined interventions and time on the EQ-5D-3L index value ($p=0.5$). HRQL significantly decreased in all combined intervention groups except for the group receiving 800 IU vitamin D with HE.

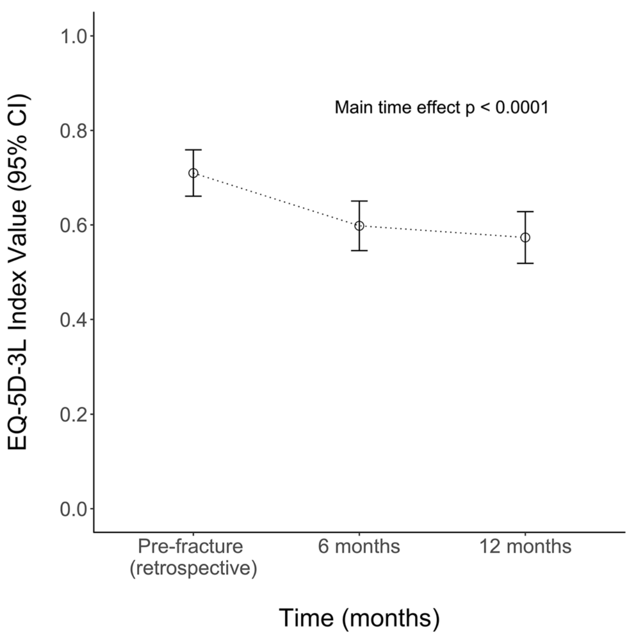

Fig. 1 EQ-5D-3L index values (range −0.594, 1.000) at three study assessments ($n=173$ at baseline, $n=120$ at 6 months, and $n=119$ at 12 months). Pre-fracture scores were assessed retrospectively, during the acute care in the hospital. Open circles at each time point represent adjusted mean change in EQ-5D-3L index value from a multivariable-adjusted repeated-measures mixed-effects linear regression model. Whiskers denote 95% confidence intervals. The model was adjusted for baseline age, sex, Charlson Comorbidity Index, MMSE, living status, BMI and serum 25-hydoxyvitamin-D concentration, EQ-5D-3L EuroQol 5 Dimensions 3 Levels measure of health-related quality of life

HRQL of individual and combined intervention groups during early and late recovery

We found no significant difference in EQ-5D-3L index value between the four treatment groups during the early recovery period between baseline and 6 months (Fig. 2). However, in the late recovery period between 6 and 12 months after hip fracture surgery, participants receiving only 800 IU vitamin D per day and no HE experienced a significant further decrease in the EQ-5D-3L index value (adjusted mean change = 0.08 [95% CI, 0.009, 0.15], $p=0.03$) (Fig. 3; Table 2), whereas participants allocated to either HE and/or 2000 IU/day vitamin D intervention did not show a significant further decline (Fig. 3; Table 2).

In the pairwise comparison, participants receiving 800 IU vitamin D per day and no HE had significantly larger 6 to 12 months declines in the EQ-5D-3L index value compared to participants receiving 800 IU vitamin D per day and HE (adjusted mean change = −0.11 [95% CI −0.22, −0.002], $p=0.046$). This decline difference was less pronounced if compared with 2000 IU vitamin D per day and no HE (adjusted mean change = −0.08 [95% CI −0.19, 0.03], $p=0.15$) or 2000 IU vitamin D per day and HE (adjusted mean change = −0.06 [95% CI −0.17, 0.05], $p=0.29$).

Impact of covariates on HRQL

Independent of the two interventions, for the overall main effects of specific covariates our multivariable-adjusted repeated-measures regression model (Table 3) suggested that better baseline cognitive function (higher MMSE score; $\beta=0.013$; $p=0.004$) and living in the community prior to the hip fracture ($\beta=0.169$, $p<0.0001$) predicted a higher EQ-5D-3L index value over time (including the 6- and 12-month follow-up) after hip fracture, independent of age, BMI, gender, CCI, or baseline serum 25(OH)D concentration ($p>0.1$ for all, Table 3).

In our sensitivity analysis, including the occurrence of falls and/or the number of hospital readmissions during the 12-month trial period as additional covariates in the model, these covariates did not meaningfully change the size and/or direction of the effect of the interventions on the EQ-5D-3L

Table 2 Changes in the EQ-5D-3L index value in the total population and within individual and combined intervention groups over time

Effects	Timeframe	Change in EQ-5D-3L	
		Adjusted mean change (95% CI)	*p* value
Total population			
Time	BL versus 6 months	0.11 (0.16, 0.06)	< 0.0001
	6 months versus 12 months	0.02 (− 0.01, 0.06)	0.2
	BL versus 12 months	0.14 (0.19, 0.08)	< 0.0001
Individual interventions			
2000 IU/day	12 months versus BL	− 0.13 (− 0.21, − 0.06)	0.001
800 IU/day	12 months versus BL	− 0.14 (− 0.21, − 0.07)	0.001
HE	12 months versus BL	− 0.10 (− 0.17, − 0.03)	0.01
No HE	12 months versus BL	− 0.18 (− 0.25, − 0.10)	0.001
2000 IU/day	6 months versus BL	− 0.11 (− 0.19, − 0.04)	0.002
800 IU/day	6 months versus BL	− 0.11 (− 0.18, − 0.04)	0.002
HE	6 months versus BL	− 0.10 (− 0.16, − 0.03)	0.007
No HE	6 months versus BL	− 0.13 (− 0.2, − 0.06)	0.001
2000 IU/day	6 months versus 12 months	0.02 (− 0.03, 0.07)	0.5
800 IU/day	6 months versus 12 months	0.03 (− 0.02, 0.08)	0.2
HE	6 months versus 12 months	0.002 (− 0.05, 0.05)	0.95
No HE	6 months versus 12 months	0.05 (− 0.004, 0.10)	0.1
Combination of interventions			
2000 IU/day + HE	12 months versus BL	− 0.11 (− 0.21, − 0.01)	0.03
2000 IU/day + No HE	12 months versus BL	− 0.15 (− 0.26, − 0.05)	0.004
800 IU/day + HE	12 months versus BL	− 0.08 (− 0.18, 0.02)	0.11
800 IU/day + No HE	12 months versus BL	− 0.20 (− 0.3, − 0.09)	0.001
2000 IU/day + HE	6 months versus BL	− 0.09 (− 0.19, 0.01)	0.07
2000 IU/day + No HE	6 months versus BL	− 0.14 (− 0.24, − 0.04)	0.01
800 IU/day + HE	6 months versus BL	− 0.10 (− 0.2, 0.0)	0.04
800 IU/day + No HE	6 months versus BL	− 0.12 (− 0.21, − 0.02)	0.02
2000 IU/day + HE	6 months versus 12 months	0.02 (− 0.05, 0.09)	0.6
2000 IU/day + No HE	6 months versus 12 months	0.01 (− 0.06, 0.09)	0.7
800 IU/day + HE	6 months versus 12 months	− 0.02 (− 0.09, 0.05)	0.6
800 IU/day + No HE	6 months versus 12 months	0.08 (0.01, 0.15)	0.03

Data ($n = 173$ at baseline, $n = 120$ at 6 months, and $n = 119$ at 12 months) are adjusted mean changes (95% CI) from multivariable-adjusted repeated-measures mixed-effects linear regression models adjusted for baseline age, sex, Charlson Comorbidity Index, Folstein's Mini-Mental State Examination, living status, BMI and serum 25-hydroxyvitamin D concentration. P values are two-sided and uncorrected. Statistical significance is set at $p \leq 0.05$

BL baseline, *EQ-5D-3L* EuroQol 5 dimensions 3 Levels measure of health-related quality of life, *HE* home exercise, *IU/day* international units of vitamin D per day

index value nor were they statistically significant covariates in the model.

Discussion

Our results illustrate the detrimental effect of hip fractures on HRQL as assessed by the EQ-5D-3L index value among senior adults of age 65 years and older. In fact, HRQL in our study did not recover to the pre-hip fracture HRQL state even at 12-month follow-up. Regarding the interventions tested in this trial, HE and vitamin D, we could not demonstrate a benefit of the individual or combined interventions over time, despite the benefit that the interventions demonstrated in the original trial on falls and hospital readmission [7]. Notably, however, assessing early and late recovery separately, participants who received either the higher dose of vitamin D (2000 IU per day) and/or HE did not experience a further decline in the EQ-5D-3L index value from month 6 to month 12 compared with participants who were in the control group receiving only 800 IU vitamin D without HE. Those control patients experienced a further significant decline in the EQ-5D-3L index value between the 6-month and 12-month follow-up.

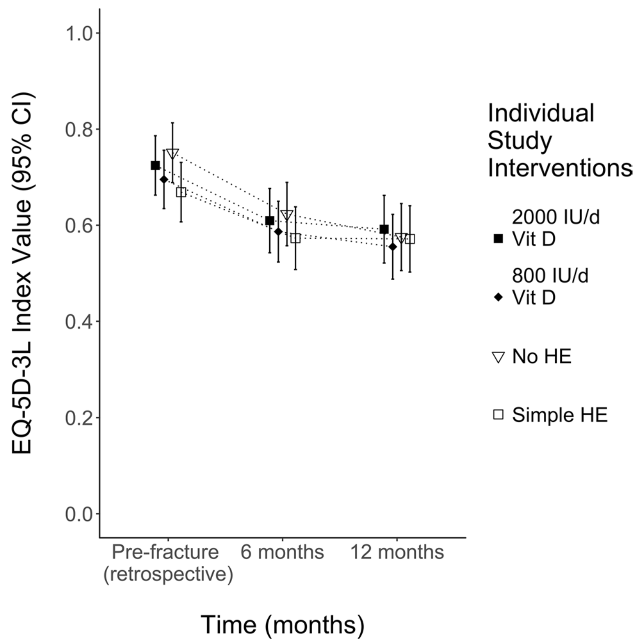

Fig. 2 EQ-5D-3L index values (range −0.594, 1.000) at three study assessments by individual study interventions ($n=173$ at baseline, $n=120$ at 6 months, and $n=119$ at 12 months). Pre-fracture scores were assessed retrospectively, during the acute care in the hospital. Markings at each time point represent adjusted mean change in EQ-5D-3L index value from multivariable-adjusted repeated-measures mixed-effects linear regression model. Whiskers denote 95% confidence intervals. Lines are pattern coded by the combination of study interventions. The model was adjusted for baseline age, sex, Charlson Comorbidity Index, MMSE, living status, BMI and serum 25-hydoxyvitamin-D concentration, EQ-5D-3L EuroQol 5 Dimensions 3 Levels measure of health-related quality of life, HE home exercise, vit D vitamin D

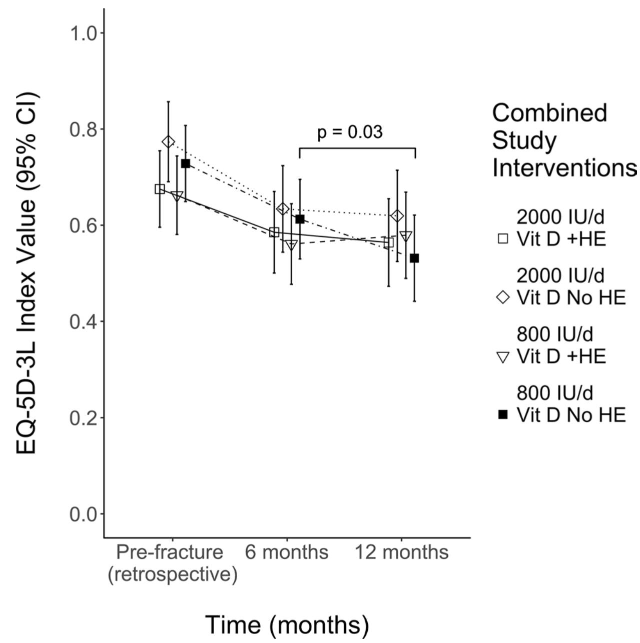

Fig. 3 EQ-5D-3L index values (range −0.594, 1.000) at three study assessments by combinations of study interventions ($n=173$ at baseline, $n=120$ at 6 months, and $n=119$ at 12 months). Pre-fracture scores were assessed retrospectively, during the acute care in the hospital. Markings at each time point represent adjusted mean change in EQ-5D-3L index value from a multivariable-adjusted repeated-measures mixed-effects linear regression model. Whiskers denote 95% confidence intervals. Lines are pattern coded by the combination of study interventions. The model was adjusted for baseline age, sex, Charlson Comorbidity Index, MMSE, living status, BMI, and serum 25-hydoxyvitamin-D concentration, EQ-5D-3L EuroQol 5 Dimensions 3 Levels measure of health-related quality of life, HE home exercise, vit D vitamin D

The detrimental effects of hip fracture and the complicated recovery process have been studied before. A recent systematic literature review by Peeters and colleagues identified 49 prospective studies reporting HRQL or other health status (HS) measures after a hip fracture [6]. Only five of the reviewed studies reported HRQL recovering to pre-fracture levels or reaching population average [12, 32–35]. From the identified 14 studies using the EQ-5D as an HRQL assessment tool, only two demonstrated recovery in HRQL within 12 months [32, 35]. Thus, our results align with those of other studies showing that hip fractures change HRQL permanently without recovery within 12 months after hip fracture. We cannot exclude that recovery of HRQL is reached within a longer follow-up period [33]. However, two studies found incomplete recovery even after 24 months [36, 37]. Due to their severity, hip fractures may also differ from other osteoporotic fractures as suggested in one study among 600 women with osteoporosis, where HRQL reached pre-fracture levels for upper limb fractures, but not for hip and vertebral fractures [38].

In our study, there were no significant differences between the intervention groups across time. However, in the separate assessment of early and late recovery, participants receiving only 800 IU vitamin D without HE declined in their EQ-5D index value more significantly in the late recovery period compared to the other treatment arms (Table 3) who remained stable in their HRQL after their initial decline from baseline to month 6. The progressive decline of the control group (800 IU vitamin D and no HE) in the late recovery period may be considered clinically important, as the HRQL decline is exceeding the minimal clinically important difference for the EQ-5D index value which has been estimated to be 0.074 [27]. A possible explanation may be the fact that in the original trial high-dose vitamin D was associated with a reduction in hospital re-admission, largely explained by a 60% reduction in fall-related injury, and the HE reduced falls by 25% [7].

The role of exercise in maintaining HRQL after fracture is further supported by some prior studies. A multiple component intervention consisting of high-intensity muscle

Table 3 Overall impact of baseline covariates on the EQ-5D-3L index value

Overall main effect[a]	Effect estimate (95% CI)	p value
Age (years)	0.0001 (−0.004, 0.004)	0.95
Female	0.003 (−0.07, 0.08)	0.94
BMI (kg/m^2)	−0.01 (−0.01, 0.0001)	0.05
Charlson Comorbidity Index (score 0–37)	0.003 (−0.01, 0.02)	0.67
MMSE (score 0–30)	0.01 (0.004, 0.02)	0.004
Living at home versus living assisted	0.17 (0.24, 0.09)	0.001
25-hydroxyvitamin (ng/mL)	0.002 (−0.002, 0.01)	0.34

Data ($n=173$ at baseline, $n=120$ at 6 months, and $n=119$ at 12 months) are from multivariable-adjusted repeated-measures mixed-effects linear regression models. P values are two-sided and uncorrected. Statistical significance was set at $p \leq 0.05$. 25(OH)D, 25-hydroxyvitamin D; EQ-5D-3L, EuroQol 5 Dimensions 3 Levels measure of health-related quality of life

BMI body mass index; *MMSE*, Folstein's Mini-Mental State Examination

[a]Status at baseline

training and supportive counseling improved self-reported physical function significantly as captured by the SF-36 among hip fracture patients [11]. Similarly, a supervised strength training combined with a home exercise component improved strength, mobility, and HRQL score as measured by the SF-12 among patients after hip fracture [13]. In addition, occupational training and well-planned home rehabilitation might speed up recovery and improve the scores in HRQL measures [12, 15].

The role of vitamin D intervention in maintaining HRQL is still unclear. A recent systematic review by Hoffmann and colleagues found no consistent improvement in HRQL with vitamin D supplementation [39]. Consistent with our findings in the 800 IU vitamin D group, one study among patients with low-trauma fractures, found that 800 IU vitamin D did not improve HRQL assessed by SF-12 and EQ-5D compared with calcium supplementation alone [40]. On the other hand, one higher dose vitamin D trial, testing 4000 IU vitamin D per day compared with placebo, found a significant improvement in a "wellbeing" score [23].

Our study has several strengths. First, the factorial study design enabled us to investigate individual as well as combined effects of vitamin D and HE on HRQL across time and separately during early and late recovery. Second, we used the EQ-5D-3L tool for the assessment of HRQL, which is a well-validated generic instrument for HRQL assessment. Third, our data come from a well-designed RCT that documented key covariates of HRQL, whereby it was possible to control for the main confounders of HRQL. Our study also has limitations. The study was not primarily designed and powered to investigate changes in HRQL measures after a hip fracture. However, HRQL was a pre-defined secondary outcome. Further, the pre-fracture state was assessed retrospectively and might be either an under- or overestimation of the actual pre-fracture HRQL [6]. Alternatively, as hip fractures are acute events, our retrospective baseline assessment within days of the acute fracture may be the best possible strategy to assess HRQL prior to the hip fracture event. It has to be noted that the adherence to HE after the acute hospital period is based solely on self-reported data. As the adherence to HE was assessed at the 12-month follow-up visit or by a phone call (see Methods), the participants may have retrospectively overestimated or underestimated their compliance with the HE treatment.

In summary, our study supports an extended negative impact of hip fractures on HRQL among seniors of age 65 and older, independent of age, gender, BMI, comorbid conditions, and the treatments tested in the trial. Notably, while we did not find an overall benefit of high-dose vitamin D (2000 IU/day) or a HE, we identified a signal that these interventions may help stabilize HRQL after month 6 of the hip fracture, as their absence contributed to a continued decline of HRQL from month 6 to month 12 after the hip fracture.

In conclusion, hip fractures need to be considered serious also for their detrimental effect of HRQL. According to our findings, implementing HE and/or 2000 IU vitamin D per day in patients with acute hip fractures may help stabilize an otherwise continued decline in HRQL after month 6 of the hip fracture.

Funding This analysis was funded by the Baugarten Centre Grant for the Centre on Aging and Mobility (Dr. Bischoff-Ferrari), and by the University Research Priority Program "Dynamics of Healthy Aging" (Dr. Bischoff-Ferrari), University of Zurich. The original trial was supported by Swiss National Foundations (NFP-53) (Drs Bischoff-Ferrari and Theiler), Vontobel Foundation (Dr Bischoff-Ferrari), Baugarten Foundation (Dr Bischoff-Ferrari), and Swiss National Foundations professorship grant PP00B- 114864 (Dr Bischoff-Ferrari).

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