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Original Article

Effect of Supplementation with Vitamin D_3 and Calcium on Quantitative Ultrasound of Bone in Elderly Institutionalized Women: A Longitudinal Study

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Abstract. Supplementation of elderly institutionalized women with vitamin D and calcium decreased hip fractures and increased hip bone mineral density. Quantitative ultrasound (QUS) measurements can be performed in nursing homes, and easily repeated for follow-up. However, the effect of the correction of vitamin D deficiency on QUS parameters is not known. Therefore, 248 institutionalized women aged 62–98 years were included in a 2-year open controlled study. They were randomized into a treated group ($n = 124$), receiving 440 IU of vitamin D_3 combined with 500 mg calcium (1250 mg calcium carbonate, Novartis) twice daily, and a control group ($n = 124$). One hundred and three women (42%), aged 84.5 ± 7.5 years, completed the study: 50 in the treated group, 53 in the controls. QUS of the calcaneus, which measures BUA (broadband ultrasound attenuation) and SOS (speed of sound), and biochemical analysis were performed before and after 1 and 2 years of treatment. Only the results of the women with a complete follow-up were taken into account. Both groups had low initial mean serum 25-hydroxyvitamin D levels (11.9 ± 1.2 and 11.7 ± 1.2 μg/l; normal range 6.4–40.2 μg/l) and normal mean serum parathyroid hormone (PTH) levels (43.1 ± 3.2 and 44.6 ± 3.5 ng/l; normal range 10–70 ng/l, normal mean 31.8 ± 2.3 ng/l). The treatment led to a correction of the metabolic disturbances, with an increase in 25-hydroxyvitamin D by 123% ($p < 0.01$) and a decrease in PTH by 18% ($p < 0.05$) and of alkaline phosphatase by 15% ($p < 0.01$). In the controls there was a worsening of the hypovitaminosis D, with a decrease of 25-hydroxyvitamin D by 51% ($p < 0.01$) and an increase in PTH by 51% ($p < 0.01$), while the serum calcium level decreased by only 2% ($p < 0.01$). After 2 years of treatment BUA increased significantly by 1.6% in the treated group ($p < 0.05$), and decreased by 2.3% in the controls ($p < 0.01$). Therefore, the difference in BUA between the treated subjects and the controls (3.9%) was significant after 2 years ($p < 0.01$). However, SOS decreased by the same amount in both groups (approximately 0.5%). In conclusion, BUA, but not SOS, reflected the positive effect on bone of supplementation with calcium and vitamin D_3 in a population of elderly institutionalized women.

Keywords: Institutionalized elderly; Secondary hyperparathyroidism; Ultrasound of bone; Vitamin D deficiency

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Introduction

Elderly institutionalized women are at a particularly high risk of hip fracture, and hip fractures occurring in nursing homes have higher mortality than those occurring in private homes [1]. In addition to a high risk of falling, the elderly have a persistent increase in bone turnover [2] that accelerates bone loss, in part due to hypo-vitaminosis D with secondary hyperparathyroidism. This hypovitaminosis D results from a major decrease in the endogenous production of vitamin D, principally due to a lack of sun exposure, which is not

balanced by an adequate vitamin D intake [3,4]. The correction of the vitamin D deficiency and therefore of the secondary hyperparathyroidism by combined treatment of subjects living in nursing homes with calcium and vitamin D leads to a significant reduction in nonvertebral fractures – up to 25% after 18 months [3] – the positive effect still being present after 3 years [5]. Calcium and vitamin D supplementation over 3 years also had a beneficial effect on the rate of nonvertebral fractures in a population of healthy ambulatory American men and women aged more than 65 years [6]. On the other hand, in a population of elderly Dutch subjects, living independently in apartments for the elderly person, or in homes for the elderly, Lips et al. [7] showed no effect of vitamin D supplementation without calcium on the incidence of hip fractures and other peripheral fractures.

Quantitative ultrasound (QUS) of bone is increasingly used in evaluating the osteoporotic fracture risk [8,9]. The ultrasonic parameters measured are BUA (broadband ultrasound attenuation), which is the attenuation through the medium of a band of frequencies, expressed in dB/MHz, and SOS (speed of sound), which is the velocity through the medium, expressed in m/s. QUS is able to discriminate normal subjects from subjects with low bone mineral density (BMD) or with fractures due to osteoporosis [10–15], and longitudinal studies showed significant decreases in QUS parameters over time [14,16–18]. Both BUA [19,20] and SOS [19] can predict future hip fracture risk in older women, with a relative risk of about 2 per standard deviation decrease in QUS parameters. This performance is as good as that observed with dual-energy X-ray absorptiometry (DXA) of the hip [12,19,20]. Only very few longitudinal data are available on the effect of specific treatments on QUS parameters. Previous studies have assessed the effect of either hormone replacement therapy [21], bisphosphonates [22] or calcitonin [23] on QUS. All these studies showed that QUS parameters were positively influenced by the treatment in postmenopausal women, whereas in untreated controls QUS parameters showed a significant decrease. In a Swiss population of elderly institutionalized women, QUS parameters (especially BUA) were correlated with the hyperparathyroidism resulting from hypovitaminosis D [24].

The aim of this study was to assess the effect of supplementation with vitamin D and calcium on QUS parameters and metabolic disturbances in elderly institutionalized women.

Subjects and Method

Two hundred and forty-eight women aged 62–98 years, living in 19 nursing homes in the Lausanne area, were randomized in an open controlled study. The treated group received 500 mg calcium (1250 mg calcium carbonate) and 440 IU vitamin D_3 twice daily (combined by Novartis). The control group received nothing. The drugs were given by the nursing staff, to avoid lack of compliance with the treatment by the subjects. All subjects gave their written consent, and the study was accepted by the ethics committee of the Medical Faculty of the University of Lausanne.

Table 1. Drop-outs from the study

	Treated group (*n*)	Controls (*n*)
Randomized	124	124
Drop-outs		
Administrative reasons[a]	*11*	*10*
Death	*21*	*26*
Missed or refused follow-up	*32*	*30*
New treatment of osteoporosis	*0*	*3*
Psychiatric disturbances + severe illnesses	*3*	*2*
Upper GI side effects	*6*	*0*
Hypercalcemia	*1*	*0*
Total drop-outs	74	71
Total completing the 2 years follow-up	50	53

[a]Closure of one home and refusal of another home to continue the study.

Among the 248 randomized women, 103 (42%) had a complete QUS follow-up of 2 years: 50 in the treated group, 53 in the controls. One hundred and forty-five women could not be followed for 2 years. Concerning these drop-outs, there was no difference in any of the measured parameters between the treated subjects and the controls (Table 1). Only 6 subjects (4%) interrupted the treatment because of moderate upper gastrointestinal side-effects. One subject developed hypercalcemia due to primary hyperparathyroidism. In general, the treatment was well tolerated and, in particular, no death has been related to the medication. The relatively high rate of 'missed or refused follow-ups' is partially explained by the difficulty of influencing these elderly women or their families positively once they has adopted a negative attitude towards the study giving no explanation.

Only the results of the women with a complete 2-year follow-up were analyzed and reported here. Since the drop outs were evenly distributed among treated and untreated subjects, the two groups who completed the 2 years of treatment remained comparable (Table 2). They showed no significant differences in any of the measured parameters, except for body mass index (BMI).

All subjects were assessed by QUS of their calcaneus and, if a subject consented, by a fasting serum analysis (calcium, phosphate, 25-hydroxyvitamin D, parathyroid hormone, alkaline phosphatase and creatinine).

Ultrasound measurements were performed at the calcaneus with an Achilles ultrasound apparatus (Lunar, Madison, WI). BUA and SOS through the heel were measured. The reproducibility of the method has been assessed in a previous study [13], when coefficients of variation were 1.8% for BUA and 0.3% for SOS. Quality control was assessed each day of use with a phantom. There was no significant variation in the parameters over time. QUS measurements were all done

by the same investigator (M.A.K.). Since the results are automatically given by the device, they could not be modified.

All biochemical measurements were performed in a masked fashion. Albumin, calcium, phosphate, creatinine and alkaline phosphatase concentrations were measured by standard laboratory methods. Serum 25-hydroxyvitamin D was measured by protein binding assay (Amersham Life Science, Little Chalfont, Bucks, UK); the normal range for Swiss adults is 6.2–42.0 μg/l (and for Swiss adults older than 65 years is 4.3–40.5 μg/l) [25]. Serum intact parathyroid hormone (PTH) was measured by Allegro (Nichols Institute, San Juan Capristrano, CA), with a normal range for our laboratory of 10–70 ng/l).

For comparisons between independent groups, Mann–Witney *U*-tests were performed. To assess the evolution in each group, Wilcoxon signed-rank tests were performed. The differences were considered statistically significant for p values < 0.05. An intent-to-treat analysis was not included in the protocol; in any case, the relatively high rate of refusal for follow-up also excluded further examination of these subjects.

Results

Table 2 shows the baseline characteristics of the two groups of women who completed the 2-year study. There was a significant difference between the treated group and the controls for BMI, but not for age or the ultrasound parameters. Figure 1 shows the evolution of the ultrasound data. In the treated group, after 2 years, there was a significant increase of 1.6% ± 0.8% (mean ± SEM) for BUA, whereas in the controls there was a significant decrease of 2.3% ± 0.8%. After 2 years there was significant difference of 3.9% for BUA ($p = 0.0016$) between the treated group and the controls. For SOS, after 2 years, there was a significant decrease of 0.5% in each group with no difference between the two groups.

Due to the potential difficulty of taking blood samples in such a population of advanced age, it was specified in the study design that refusal of the blood analysis was not an exclusion criterion. Seventy-two out of 103 subjects (70%) had a complete biochemical follow-up. Table 3 and Fig. 2 show the evolution of the biochemical markers of bone metabolism during the study. As expected, in the treated group the calcium serum level

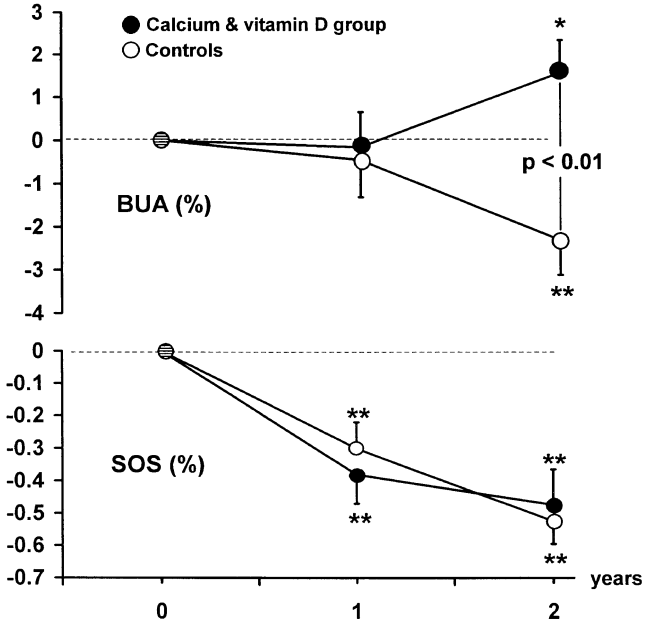

Fig. 1. Effect of daily supplementation with 880 IU vitamin D_3 and 1 g calcium on quantitative ultrasound of the calcaneus in 50 elderly institutionalized women (aged 84 ± 8 years) and 53 controls (aged 85 ± 7 years). The results are expressed as the mean percentage changes compared with the initial values. After 2 years there was a significant difference between the treated group and the controls for BUA ($p < 0.01$); there was no difference for SOS. $*p < 0.05$, $**p < 0.01$ compared with initial values.

Table 2. Characteristics of the subjects who completed the study

	Treated group (n = 50)	Controls (n = 53)	p value
Age (years)	84 ± 8	85 ± 7	NS
Body mass index (kg/m^2)	25.7 ± 4.8	23.8 ± 5.4	0.042
Quantitative ultrasound of the calcaneus			
BUA (dB/MHz)	93.6 ± 8.9	92.4 ± 9.4	NS
SOS (m/s)	1465 ± 25	1466 ± 22	NS

Values are the mean ± SD.

Table 3. Evolution of the biochemical markers of bone metabolism during the 2 years of the study

	Treated group (n = 34)			Controls (n = 38)		
	Initial	1 year	2 years	Initial	1 year	2 years
Calcium (mmol/l)	2.32 ± 0.02	2.33 ± 0.02	2.31 ± 0.02	2.29 ± 0.01	2.24 ± 0.02*‡	2.23 ± 0.01**‡
25-hydroxyvitamin D	11.9 ± 1.2	29.8 ± 0.9**	26.5 ± 1.6**	11.7 ± 1.2	8.3 ± 1.1**‡	5.7 ± 1.0**‡
PTH (ng/l)	43.1 ± 3.2	32.1 ± 2.4**	35.5 ± 2.7*	44.6 ± 3.5	55.4 ± 4.4**‡	67.2 ± 5.7**‡
Alkaline phosphatase (U/l)	88.2 ± 5.4	73.9 ± 4.5**	75.7 ± 5.1**	86.7 ± 4.9	87.6 ± 5.1†	83.6 ± 5.6

Values are the mean ± SEM.
$*p < 0.05$, $**p < 0.01$ compared with initial values.
$†p < 0.05$, $‡p < 0.01$ compared with treated group.

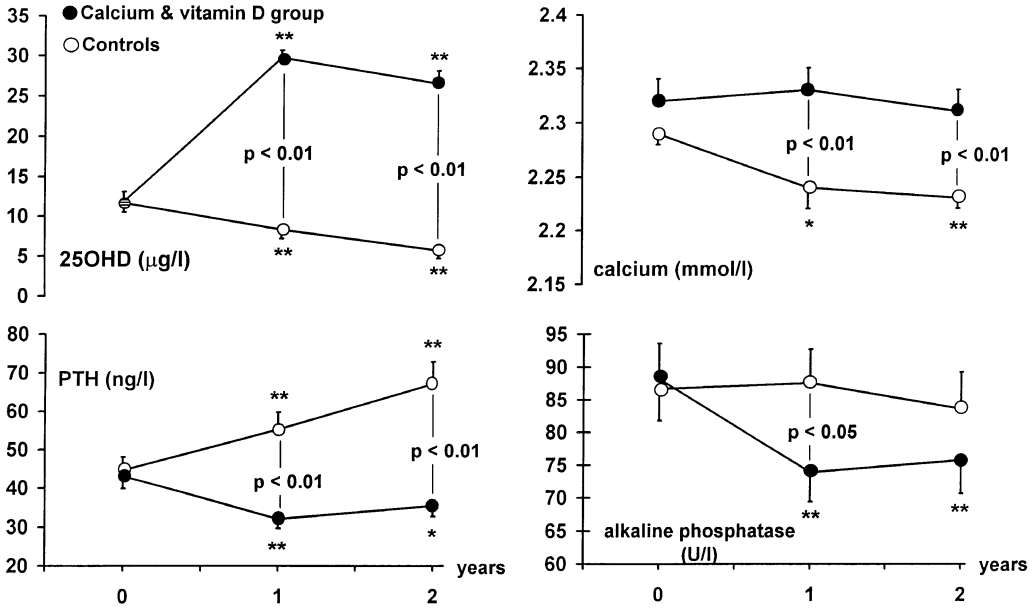

Fig. 2. Effect of a daily supplementation of 880 IU vitamin D_3 and 1 g calcium on the mean values of biochemical parameters in 34 institutionalized elderly women compared with 38 controls. After 1 year there was a correction of the metabolic disturbances in the treated group, whereas there was an important worsening of the hypovitaminosis D and the secondary hyperparathyroidism in the controls, with a trend to hypocalcemia. 25 OHD, 25-hydroxyvitamin D; PTH, parathyroid hormone. $*p<0.05$, $**p<0.01$ compared with initial values.

Table 4. Overview of longitudinal studies with quantitative ultrasound of bone (Achilles, Lunar)

Reference	Age of the subjects (years)	No. of subjects (treated/controls)	Treatment	Follow-up (years)	Difference between QUS parameters in treated subjects and controls after a 2-year follow-up (%)
Giorgino, 1996 [21]	46–57	44/47	Estradiol 50 μg/day + progestin	2	BUA 5.8% SOS 0.7%
Giorgino, 1996 [22]	42–71	32/42	Alendronate 5 mg/day	2	BUA 5.1% SOS 0.3%
Giorgino, 1996 [23]	50–64	78/34	Nasal calcitonin 200 Iu/day (1 month/2)	2	BUA 4.2% SOS 0.8%
This study	64–98	50/53	Vitamin D 800 U/day + calcium 1 g/day	2	BUA 3.9% SOS 0%

remained stable, 25-hydroxyvitamin D increased significantly by 123%, PTH decreased significantly by 18%, and alkaline phosphatase decreased by 15%. In the controls, the calcium serum level decreased slightly but significantly by 2%, 25-hydroxyvitamin D decreased by 51% and PTH increased by 51%. In the treated group, there was no significant difference between the second assessment (after 1 year) and the third assessment (after 2 years) for calcium, 25-hydroxyvitamin, PTH and alkaline phosphatase. The serum phosphate level remained stable in the two groups.

Discussion

This study was performed in a population of very old, institutionalized women, with almost no outdoor life and no vitamin D supplementation. This explains why after 2 years the controls showed a 51% decrease of the serum level of 25-hydroxyvitamin D, the mean value falling below the lower limit of the normal Swiss adult population (<6.4 μg/l). This was associated with a slight but significant decrease in the serum calcium level, and a significant rise in the mean serum PTH level. The latter was already above the normal mean at the beginning of the study [26], and got close to the upper normal limit of 70 pg/l. This means that during the 2 years without supplementation, the metabolic consequences of vitamin D deficiency became worse in these control subjects. As expected, and in agreement with the literature [3], supplementation with vitamin D and calcium corrected this hypovitaminosis D, decreased the relatively elevated serum PTH level, and lowered the serum alkaline phosphatase level. The full metabolic effect of the treatment was already present after the first year and persisted thereafter.

BUA decreased in the control group. Why it decreased in a nonlinear manner remains unexplained. The small

decrease after 1 year was below the precision limit of the technique (1.8%) [13]. The decrease over the 2 years was associated with the continuing drop in serum levels of 25-hydroxyvitamin D, and the worsening of the secondary hyperparathyroidism, mentioned above. Compared with the populations of younger women (mean age 67 years) examined by Schott et al. [16] and van Daele et al. [17], who assessed longitudinal changes in QUS parameters, our much older institutionalized women had a higher loss of BUA. The decreases in SOS were similar to that observed by Schott, but higher than that observed by Van Daele. These differences could be explained by the fact that our population consisted of institutionalized elderly women with a rela-tively important and worsening trend toward secondary hyperparathyroidism. In the treated group BUA increased significantly, reflecting the effect of supplementation with calcium and vitamin D. After 2 years the change in BUA differed by 3.9% between the two groups; the values of SOS were not different.

Giorigino et al. [21,22] and Gonnelli et al. [23] found positive effects on QUS parameters in women treated by hormone replacement therapy, bisphosphonates or calcitonin, when compared with controls. Their results differed from ours principally in that the effects of their treatments were also seen in the values of SOS (Table 4). In their treated populations SOS increased significantly or remained stable, whereas it decreased in the controls. This difference from our study, in which the therapeutic effect was seen only with BUA, might be linked to the fact that their study populations were younger than that examined here and probably did not suffer from hypovitaminosis D and secondary hyperparathyroidism. Finally, their therapeutic interventions had different actions on bone metabolism from that of vitamin D, since they directly inhibit bone resorption. The difference may also be explained by the hypothesis that BUA and SOS measure different characteristics of bone (architecture, elasticity), and that our treatment did not act on all of them.

In conclusion, in a population of elderly institutionalized women, BUA but not SOS reflected the correction of hypovitaminosis D and secondary hyperparathyroidism that was obtained by supplementation with vitamin D and calcium over 2 years. Therefore, QUS could be a promising method for evaluating the effects of treatments on bone in groups of osteoporotic subjects.

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