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Annual Injection of Vitamin D and Fractures of Aged Bones

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Summary. In order to investigate the effect of a supplementation of vitamin D in the prophylaxis of fractures of the bones of aged people, an annual intramuscular injection of ergocalciferol (150,000–300,000 IU) was given to two series of aged subjects: first to 199 (45 male) of 479 subjects (110 male) aged more than 85 years who were living in their own home, and second to 142 (29 male) of 320 (58 male) subjects aged 75–84 and living in a home for aged people. This prospective series was divided into treatment groups according to month of birth. These injections were given annually from September to December in the years 1985–1989, two to five times to each participant. The fracture rates, laboratory values, vitamin D levels, possible side effects, and mortality were followed until October 1990. A total of 56 fractures occurred in the 341 vitamin D recipients (16.4%) and 100 in 458 controls (21.8%) ($P = 0.034$). The fracture rate was about the same in both outpatient and municipal home series. Fractures of the upper limb were fewer in the vitamin D recipients, 10/341 = 2.9% ($P = 0.025$), than in the controls, 28/458 = 6.1%, during the follow-up. A similar result was obtained in fractures of ribs, 3/341 = 0.9% and 12/458 = 2.6%, respectively. Fractures of the lower limbs occurred almost as frequently, 31/341 = 9.1%, among the vitamin D recipients as among the controls, 49/458 = 10.7%. The fracture rate was higher in females (22.2%) than in males (9.5%). The fractures were fewer in the vitamin D recipients only in females. No significant differences were found in total mortality, or due to any group of diseases, between the two treatment groups. No deleterious effects of the vitamin D injections were seen. The authors recommend the supplementation of vitamin D in aged people, at least in northernmost latitudes (e.g., as an annual intramuscular injection).

Key words: Intramuscular vitamin D – Aged – Fractures.

A growing problem [1] in geriatric medicine today is that fractures of the bones of aged people are rapidly increasing, and not only in absolute numbers but also proportionally [2, 3]. This might be due in part to the diminished hours spent in outdoor activities, which could weaken the muscles and bones and also reduce the production of vitamin D on the skin [4–6], to many changes in the diet, and to smoking habits [7].

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Among other modes of prophylaxis, a few drugs have been investigated by the present study group with an eye to strengthening the bones, which, due to osteoporosis and osteomalacia, weaken with age. Unfortunately, the medication has often been found deleterious: either it has increased the number of fractures [8] or otherwise damaged the health of aged people, at least for a short period of time [9]. Also hormones, especially the estrogens, have been highly recommended for the treatment of bones, but mainly for postmenopausal osteoporosis, whereas its use in senile osteoporosis is still somewhat controversial [10–15].

The level of vitamin D has been found to be below the average in aged people [16], especially in those who live in an institution or in a hospital [17]. Therefore, we have studied the longer-lasting effect of vitamin D, given each autumn as an annual intramuscular injection, on the organism of aged people and especially its effect on the occurrence of fractures. This has been done both for those who are still capable of living in their own home and those living in a municipal home for the aged.

Materials and Methods

Two groups were investigated for this study. The first group, people aged 85 years or more and living in Tampere in their own home, were invited for a health examination in the geriatric outpatient clinic of Tampere City Hospital. If studied between September 1 and December 31 and if born in an even month, they were given 150,000 IU of vitamin D (ergocalciferol) intramuscularly each autumn beginning in 1985 (half of an ampule of calciferol injection BP BNF 300,000 IU (Evans Medical Ltd, England). (In 1986, however, a whole ampule of 300,000 IU was given). Those of the invited subjects born in an odd month served as controls. There were 199 (45 male) vitamin D recipients, mean age 86.6 years and 280 (65 male) controls, mean age 86.1 years. There were more controls because 36 of the people in the vitamin D group refused to take the injection, and in 32 cases no injection was offered by the doctor because they were taking the vitamin daily in drops, or it was for other reasons considered to be contraindicated. This series consisted of about 30% of people of this age living in their own homes in Tampere.

The second group consisted of all the inhabitants of the municipal old people's home aged 75–84 years at entry in October 1985; those born in an even month were similarly given an injection of vitamin D and those born in an odd month served as controls. All these people were capable of walking independently. There were 142 (28 male) vitamin D recipients, mean age 79.3 years and 178 (30 male) controls, mean age 79.4 years.

Subjects with a serum calcium content of ≥ 2.70 mmol/liter were excluded from the series at entry. Also patients of the outpatient department who, after the investigation, were immediately taken to

Table 1. Time of entering the series

	Outpatients			Municipal home		
Entry	Vit. D	Controls	Total	Vit. D	Controls	Total
Autumn 1985	102	130	232	112	127	239
Autumn 1986	48	68	116	16	29	45
Autumn 1987	24	46	70	6	11	17
Autumn 1988	25	36	61	8	11	19
Total	199	280	479	142	178	320

geriatric wards were excluded from the series because they were not considered suitable subjects for a survival study.

In addition to the autumn of 1985 recipients, new people invited to the health investigation or taken to the municipal home were similarly included in the series in the years 1986–1988, as seen in Table 1. The subjects' first years in this series were calculated as one group irrespective of the year they entered the series.

Of the originally registered 1186 subjects in both series, only those 799 for whom sufficient data were available both from the initial and the first reexamination 12 months later were taken into the series for further analyses. Among the 387 subjects omitted were also 126 deaths, 76 in the outpatient series and 50 in municipal home.

The follow-up of the series ended October 31, 1990 and thus lasted 2–5 years. In the outpatient series, the means of the observation time was 3.49 years for the vitamin D recipients and 3.41 years for the controls and 3.27 year and 3.30 years in the municipal home series, respectively.

All subjects in the outpatient series were examined annually by a doctor. Follow-up of the inhabitants of the municipal home for the aged was done as part of their general care.

The following laboratory tests were done in all subjects each autumn (September–November): serum proteins, creatinine, sodium, potassium, calcium, inorganic phosphate, and alkaline phosphatase. Additionally, in January and March of each year, serum calcium, inorganic phosphate, and alkaline phosphatase were measured in 30 subjects receiving vitamin D and 30 controls, all belonging to the municipal home series.

In eight subjects in the vitamin D group and in eight controls, all living in the municipal home, tests for serum 25 hydroxycholecalciferol (25OHD), 24,25 dihydroxycholecalciferol [24,25$(OH)_2$D] and 1,25 dihydroxycholecalciferol [1,25$(OH)_2$D] were carried out each October before the calciferol injection, each January and each March beginning in October 1985. When some of these died, new subjects similarly treated or not treated with vitamin D in the foregoing October were taken into the series. In 13 subjects in the vitamin D group and in 16 controls in the series who had visited the outpatient department, these vitamin D tests were also made in October 1990. The measurements were also made the second year after the last injection in six vitamin D recipients for the purpose of studying the duration of the effect of the injection. The methods used are those described in references [18–20].

In each case, diagnosis of fractures was based on case history and clinical examination and confirmed by X-ray examination. The vertebral fractures, however, were omitted from the series if considered minor, therapeutically easy, and not needing radiological confirmation. Diagnoses of mortality were obtained from hospital records or the records of the home for the aged. The causes of death [21] were certified from the central mortality register of the district. The study was approved by the local ethical committee of the Tampere Health Center.

Statistical Methods

The directed hypotheses were tested with Fisher's exact test (2 × 2 contingency tables) or with the one-sided *t*-test (means). The undirected hypotheses were tested with Chi-square (contingency tables) or *t*-test (means).

Results

Level of Vitamin D

An earlier study by this group [22] shows that the mean 25 hydroxycholecalciferol level in the vitamin D group among the inhabitants of the home for the aged in the present series remained for a whole year within the normal values (30–130 nmol/liter), whereas in the controls it was below normal ($P < 0.001$).

The mean level of 24,25$(OH)_2$D was also higher in the vitamin D group (1.84 nmol/liter) than in the control group (1.30 nmol/liter) ($P < 0.05$), whereas no difference was seen in 1,25$(OH)_2$D levels (52.0 and 53.8 pmol/liter, respectively).

The 25$(OH)_2$D values decreased slowly during the second year after the injection. In the six patients who had received their last vitamin D injection in October 1989 and whose mean 25OHD in October 1990 was 47.2 nmol/liter showed a mean value of 49.2 nmol/liter in January 1991, 41.3 nmol/liter in March 1991, and, in the surviving five patients, 43.5 nmol/liter in October 1991, only one of them had a mean below 30 nmol/liter.

As can be seen from Table 2, the values of 25OHD in the controls and the 24,25$(OH)_2$D in both vitamin D and control groups were, one year after the last ergocalciferol injection, about twice as high in the outpatient series as in the municipal home series, whereas the 25OHD values in vitamin D recipients and 1,25$(OH)_2$D values in both treatment groups were about the same in both series.

Fractures

Figure 1 shows that the occurrence of fractures was lower in the vitamin D group than in controls both in the outpatient and in the municipal home series (16.4% in the vitamin D group and 21.8% in the controls) ($P = 0.034$).

Table 3 shows that the preponderance of the fractures in the control group did not reach statistical significance in the case of any single fracture location, not even in fractures of ribs, where it came closest ($P = 0.059$), but when all the upper limb fractures are taken as a group, significance is obtained ($P = 0.025$). The difference in upper limb fractures was seen in both the outpatient (3.0%/5.4%) and the municipal home series (2.8%/7.3%).

Of the 156 fractures observed, 133 were first fractures, 21 second, and 2 third fractures in the given subject during the follow-up.

In the outpatient series, 39 fractures occurred in 199 subjects (16.1%) in the vitamin D group and 57/280 (20.4%) in the control group. The corresponding figures in the municipal home series were 24/142 (16.9%) and 43/178 (24.2%) so that fractures were occurring similarly in the two series.

Table 2. The vitamin D derivatives one year after ergocalciferol injection in outpatient and municipal home series

	Outpatients		Municipal home	
	Vit. D (n = 13) Mean (SD)	Control (n = 16) Mean (SD)	Vit. D (n = 16) Mean (SD)	Control (n = 17) Mean (SD)
25OHD (nmol/liter)	49.2 (14.4)	31.1 (14.1)	44.8 (16.0)	13.6[c] (5.2)
$24,25(OH)_2D$ (nmol/liter)	2.86 (1.41)	1.64 (0.85)	1.53[b] (0.68)	0.76[c] (0.46)
$1,25(OH)_2D$ (pmol/liter)	77.6 (36.4)	86.4 (27.1)	64.9 (36.6)	72.3 (24.9)

[b] $P < 0.01$; [c] $P < 0.001$ compared with outpatient series

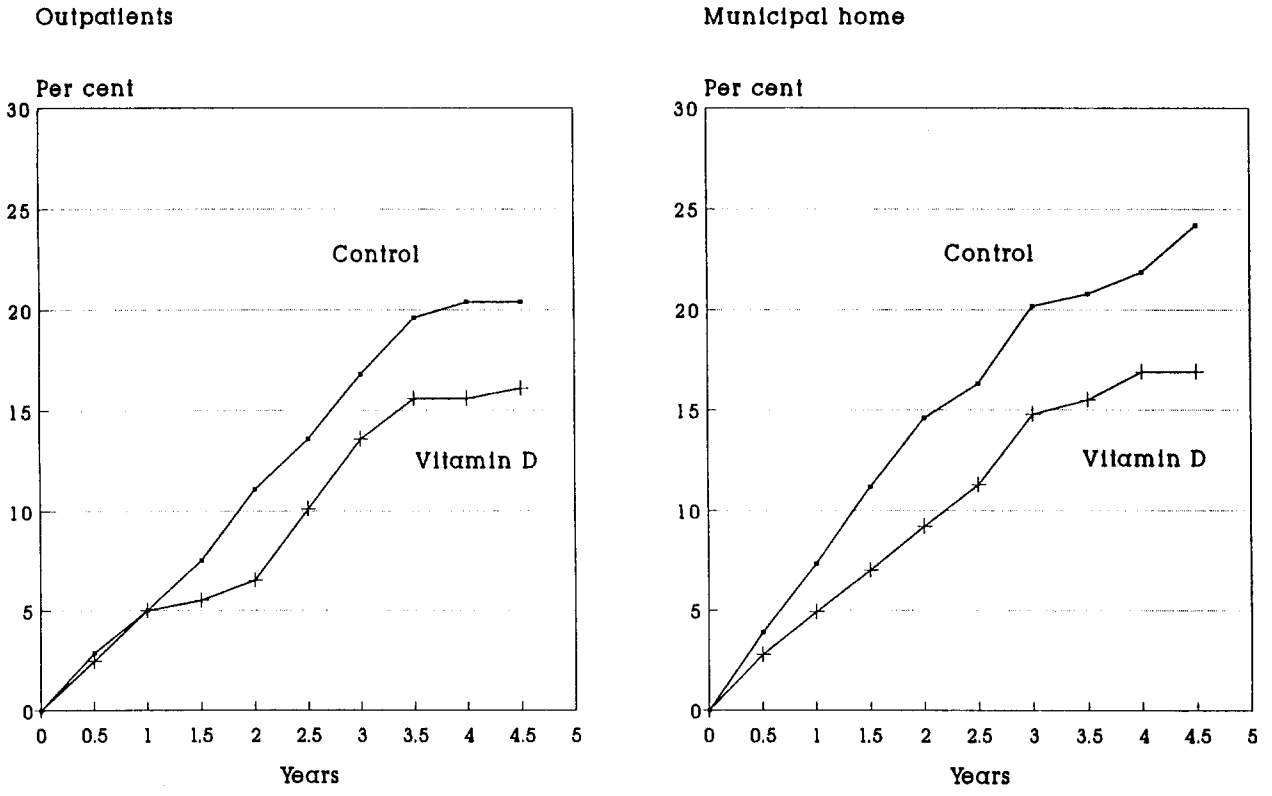

Fig. 1 Cumulative distribution of fractures in outpatient and in municipal home series as percent of the subjects in vitamin D and control groups.

Gender

In 168 males, 16 fractures were seen (9.5% of the male patients); in 631 females, markedly more—140 fractures (22.2%) ($P < 0.001$). The percentages were almost the same in the outpatient series and among the inmates of the municipal home. In males the percentages were 9.1 in the outpatient series and 10.3 in the municipal home; in the females 21.4 in outpatients and 23.3 in the municipal home.

In both treatment groups, eight fractures were seen in males, thus showing no difference between the groups in males. In females, on the other hand, the fractures numbered 48 and 92, giving the percentages 17.9 for the vitamin D-treated subjects and 25.3 for the controls ($P = 0.016$). In the upper limb alone the percentages for females were 3.0 and 7.4 ($P = 0.011$).

Mortality

Of the 76 deaths before the first reexamination in the outpatient series, 34 occurred in the vitamin D group (9.7%) and 42 in controls (9.7%). In the municipal home series, 27 deaths (14.5%) occurred in the vitamin D group and 23 (10.6%) in controls. The death rate in the municipal home was a little higher among the vitamin D recipients than in controls due to pulmonary infections (2.1%/0.5%), coronary diseases (4.8%/3.7%), neoplasms, and central nervous diseases (1.1%/0.0% in both).

Table 3. The location of fractures in different parts of the body

WHO no.	Location	Vitamin D (n = 341)	Controls (n = 458)	Vitamin D (%)	Control (%)	*P*
802	Face bones	2	1			
805	Vertebral column	8	6			
806	Vertebral column					
807	Ribs, sternum	3	12			0.059
808	Pelvis	2	4			
800–809	Skull, neck, and trunk	15	23	4.4	5.0	0.41
810	Clavicle	0	1			
811	Scapula	0	1			
812	Humerus	3	11			0.086
813	Radius and ulna	5	14			0.109
815	Metacarpal bones	2	0			
816	Phalanges of hand	0	1			
810–819	Upper limb	10	28	2.9	6.1	0.025[a]
820	Neck of femur	25	43			0.18
821	Other parts of femur	3	3			
823	Tibia and fibula	1	0			
824	Ankle	2	0			
825	Metatarsal bones	0	3			
820–829	Lower limb	31	49	9.1	10.7	0.27
Total		56	100	16.4	21.8	0.034[a]

[a] $P < 0.05$

Of the 799 subjects taken into the series, 341 died during the observation period, 150 (44.0%) in the vitamin D group and 191 (41.7%) in controls. The mortality was slightly greater in the vitamin D group due to neoplasms (6.7%/4.6%) and pulmonary infections (3.8%/2.0%) but smaller due to coronary diseases (10.6%/12.1%) and other cardiac diseases (1.2%/2.6%).

Laboratory Tests

At entry, serum protein was higher in the outpatients (73.8 ± 4.5 g/liter) than in the municipal home series (72.0 ± 5.0 g/liter). The same was true with creatinine (101.7 ± 24.7/86.9 ± 20.8 nmol/liter) and calcium (2.31 ± 0.10/2.27 ± 0.13 mmol/liter). On the other hand, the potassium and alkaline phosphatase levels were higher in the inhabitants of the municipal home. The values were for potassium (3.98 ± 0.35/4.17 ± 4.00 mmol/liter) and for alkaline phosphatase (118.2 ± 64.4/211.9 ± 96.0 IU/liter). (All differences with $P < 0.001$). Sodium and inorganic phosphate had the same mean values in both series.

No significant differences were found between the vitamin D recipients and the controls in the initial investigation. During the treatment and observation period very few systematic changes occurred in laboratory values (Table 4).

Calcium values in vitamin D recipients, as compared with those of the controls, were higher in January than in October (mean 0.024 mmol/liter), but in March, they were again on the October level.

The changes in inorganic phosphate varied, but were slightly higher in the vitamin D group as compared with controls (mean 0.035 mmol/liter in Octobers, 0.075 in Januaries, and 0.033 in Marches).

The alkaline phosphatase values decreased notably in the vitamin D recipients only after the second injection of vitamin D (300,000 IU). The alkaline phosphatase values taken in January and March showed no uniform change from the October values.

Discussion

We chose the parenteral mode of administration of vitamin D because we wanted to avoid the possible interindividual differences in the absorbtion of vitamin D from the bowel [23] and also to avoid the difficulties in compliance connected with the oral administration of drugs in the aged. That intramuscular injection of vitamin D (ergocalciferol) and sometimes also its administration perorally can raise the level of 25OHD in serum for at least 6 months is well known from the literature [24–28], and we succeeded in showing the same in this series and for the whole year [22].

The effect of this normalization of the 25OHD level and the concomitant slight increase in the level of $24,25(OH)_2D$, while the level of $1,25(OH)_2D$ remained the same, was also tested in this study. As the number of fractures was thereby reduced in our aged subjects, it proves that lower levels of 25OHD than normal (30–130 nmol/liter) really are deleterious for the aged bones and increase their tendency to break. Our results also prove that such a detrimentally low 25OHD level really obtains at least in a Nordic country like Finland (61°30′) both in the aged who live at home and in those who live in an institution.

That the administration of vitamin D is effective in diminishing the occurrence of fractures has not been hitherto proved, and negative results have been experienced especially in connection with $1,25(OH)_2D$ treatment, which, besides, may be dangerous for aged people [29, 30].

To our surprise we found a significant decrease only in the number of fractures to the upper extremities, and this to less than half (10 instead of the expected 21 fractures). This

Table 4. Preponderance in change in some laboratory values

	Outpatients			
	1 year (n = 438)	2 years (n = 247)	3 years (n = 143)	4 years (n = 49)
Calcium	+0.010	+0.004	+0.006	+0.028
Phosphate	+0.004	+0.010	+0.006	+0.042
Alk. phosphatase	+0.273	−10.966	+3.842	+8.500
	Municipal home			
	1 year (n = 317)	2 years (n = 243)	3 years (n = 170)	4 years (n = 103)
Calcium	+0.022	+0.007	−0.034	−0.009
Phosphate	+0.039	+0.051	+0.074	−0.023
Alk. phosphatase	−5.931	−11.670	−8.708	+11.038

+ = the value has risen more or fallen less from the initial value in the vitamin D than in the control group; − = vice versa. Calcium and inorganic phosphate values in mmol/liter, alkaline phosphatase values in IU/liter. Only the values of those patients are presented for whom a value in both initial and control investigation in October was available

effect was also to be seen in somewhat older subjects still living in their own home, and was only slightly less pronounced than in those living in an institution. This would strongly suggest a need for vitamin D treatment also in aged people still capable of living more independently outside the institutions—at least in our Nordic latitudes.

Why the effect of vitamin D injection was most pronounced in the bones of the upper limb—and also in ribs—might be difficult to explain. Nevertheless, one might think that due to the organism's ability to regulate the mineral content of different bones [31], an aged organism with a vitamin D shortage might regulate its supply to different bones according to their needs, keeping the "lazy" bones in a stepchild position and giving the "working" bones the best possible care. Thus, the organism would take less care of the "hanging bones," that is, ribs, and bones of the upper limb, and better care of the "load-bearing bones," that is, those of lower limbs and spine. Again, when there is plenty of vitamin D available, the change would be greatest precisely in the "hanging bones" and only marginal in the "load-bearing bones." Fractures of the upper limbs and ribs occurred in 13/341 (3.8%) in the vitamin D group and in 40/458 (8.7%) in the controls, giving a statistically significant difference ($p = 0.0036$). (In the outpatients, 3.5%/7.5%, $P = 0.049$, in municipal home patients 4.2%/10.7%, $P = 0.034$).

One must further remember that vitamin D is also important for the function of the nerves and the muscles, and may therefore prevent falls in the aged.

Unfortunately, little help in avoiding fractures of the lower extremities could be found in this series. This was also unexpected in view of the many studies showing low levels of 25OHD and sometimes of $1,25(OH)_2D$ also in the serum of hip fractures patients [32–38]. They were only 15% fewer in the vitamin D group than in the controls: 31 fractures instead of the 36.5 expected (n.s.). Though our result does not deny advantages from vitamin D treatment, even in connection with lower limb fractures, the effect, if any, was weak in this series.

The number of fractures registered in other parts of the body in this series was obviously too small to be realistic. Fractures of the vertebrae are so common at this age that many have probably occurred but been left without attention. No conclusions can be drawn from the present study as to the effect of vitamin D treatment on vertebral fractures.

The number of upper limb fractures in this series was smaller than that of lower limb fractures—even among the controls. This is understandable in that the proportion of lower limb fractures, and especially of trochanteric fractures, increases with advancing age [39–46].

That the number of fractures diminished only in female patients was not a serious disappointment because the male bones are much stronger and break more seldom. It must nevertheless be remembered that our male patients were too few to give a conclusive negative result [47].

The different dosages of vitamin D in the present series did not produce significantly different effects on the 25OHD levels nor any other laboratory test except possibly the alkaline phosphatase values. This is in agreement with the findings of MacLennan and Hamilton [48].

The decrease in alkaline phosphatase, much published in the literature in connection with normalization of a subnormal level of vitamin D [49, 50], was seen in the present series only after the injection of 300,000 IU of the vitamin.

It was encouraging that no toxic effect of vitamin D [51] was seen in this series, not even after the injection of 300,000 IU ergocalciferol in autumn of 1986. Coles et al. [52] used 400,000 IU intramuscularly also with no toxic effects.

Other advantages of vitamin D treatment have been registered in the literature, e.g., a decrease in the number of neoplasms in the colon and breast [53, 54]. In this series, nothing of the kind was seen. Our numbers were small and it is possible that an effect on the colon can only be seen when the vitamin is given perorally.

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