Age and Ageing 2019; **0:** 1
doi: 10.1093/ageing/afy221

Expression of concern

Effect of immobilization on vitamin D status and bone mass in chronically hospitalized disabled stroke patients

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Age and Ageing (1999) **28**: 265–269, doi: 10.1093/ageing/28.3.265

The Editor has been alerted by readers (14th August 2018) to concerns about the integrity of the above paper. The issues raised include the following;

- There is a lack of information in the paper about key aspects of governance, with no ethics or funding statement, and no information provided on the laboratory conducting the biochemical measures reported in the study.
- The numbers recruited to the study are implausibly high, given the short recruitment window and the limited capacity of the hospital in which the work was conducted.
- Some of the data values reported in the study are duplicated in other publications by Sato *et al.* This includes in retracted papers in European Neurology [1] and Archives of Physical Medicine and Rehabilitation [2] and a paper in Bone [3].
- Readers should also note that there have been other expressions of concern and retractions for other research papers from this group [4].

The Editor has contacted the authors of the Age and Ageing paper and the institution under whose aegis the research was conducted, raising the above issues. No responses have been received from any of these parties.

This Expression of Concern should be taken to indicate that the data presented in the article named above may not be reliable.

References

1. Sato Y, Honda Y, Asoh T *et al.* Hypovitaminosis D and decreased bone mineral density in amyotrophic lateral sclerosis. Eur Neurol 1997; 37: 225–9.
2. Retraction: Sato *et al.* Am J Phys Med Rehabil 2005; [illegible]:692–8. *American Journal of Physical Medicine & Rehabilitation* 2018; [illegible](12):932. doi: 10.1097/phm.0000000000001019
3. Sato Y, Oizumi K, Kuno H *et al.* Effect of immobilization upon renal synthesis of 1,25-dihydroxyvitamin D in disabled elderly stroke patients. Bone 1999; 24: 271–5.
4. Bolland MJ, Avenell A, Gamble GD *et al.* Systematic review and statistical analysis of the integrity of 33 randomized controlled trials. Neurology 2016; 87: 2391–402.

Age and Ageing 1999; **28:** 265–269

Effect of immobilization on vitamin D status and bone mass in chronically hospitalized disabled stroke patients

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Abstract

Objective: to assess the influence of immobilization upon vitamin D status and bone mass in chronically hospitalized, disabled, elderly patients following stroke.
Design: cross-sectional study.
Setting: department of geriatric neurology in a Japanese hospital.
Subjects: 129 chronically hospitalized, disabled, elderly stroke patients and 28 age-matched controls.
Results: we observed a deficiency of both 1,25-dihydroxyvitamin D (1,25-[OH]$_2$D; 24.3 pg/ml) and 25-hydroxyvitamin D concentrations (25-OHD; 11.7 ng/ml) in stroke patients compared with controls. A high serum ionized calcium (mean; 2.648 mEq/l) was an independent determinant of the Barthel index (66) and 1,25-[OH]$_2$D. When the patients were categorized into three groups by 25-OHD level (deficient, insufficient and sufficient), there was no difference in the mean 1,25-[OH]$_2$D levels. Parathyroid hormone levels were normal or low and did not correlate with 25-OHD. Serum bone turnover variables and bone mineral density (BMD) of the second metacarpal in patients were significantly decreased compared to control subjects. Independent determinants of BMD included Barthel index, 25-OHD and 1,25-[OH]$_2$D.
Conclusions: 1,25-[OH]$_2$D deficiency in immobilized stroke patients is not caused by substrate (25-OHD) deficiency but by hypercalcaemia. Immobilization-induced hypercalcaemia may inhibit parathyroid hormone secretion and thus 1,25-[OH]$_2$D production, resulting in decreased BMD. Immobilization itself also may be responsible for decreased BMD. Exogenous 1,25-[OH]$_2$D (calcitriol) rather than dietary vitamin D supplementation may be required in disabled elderly stroke patients who have a deficiency of 1,25-[OH]$_2$D in order to prevent hip fractures, which frequently occur in this population.

Keywords: *hypercalcaemia, immobilization, stroke, vitamin D*

Introduction

There is a high incidence of hip fracture in stroke patients [1–5], especially elderly women (odds ratio, 2.0) [6]. The relationship between immobility and osteoporosis is well established [7]. We have previously reported that, following hemiplegic stroke, bone loss on the paralysed side is proportionate to the degree of paralysis and to vitamin D deficiency [8, 9].

To assess skeletal status in chronically hospitalized, elderly patients with stroke, we measured bone changes and biochemical indices of bone metabolism and turnover.

Methods

Stroke patients from the Futase Geriatrics Hospital (a long-term care unit) in Iizuka, Japan, were screened by history and chart review. Exclusion criteria included: age younger than 65 years, total disability, quadriparesis, less than 2 years of hospitalization, diseases or use of medications that might interfere with vitamin D metabolism, primary disease other than stroke or time spent outside the hospital during the past 6 months. Also, patients with stroke were excluded if they had other known causes of osteoporosis, such as hyperparathyroidism or renal osteodystrophy; impairment of

hepatic, renal (serum creatinine > 2.0 mg/dl), cardiac or thyroid function. Of 321 individuals screened, 129 (70 women and 59 men) were eligible to participate in the study. Informed consent was obtained from all patients in the presence of a witness.

According to the Classification of Cerebrovascular Diseases III of the National Institute of Neurological Disorders and Stroke [10], strokes were classified as brain infarction ($n = 59$), brain haemorrhage ($n = 23$), subarachnoid haemorrhage ($n = 10$) and vascular dementia with features of parkinsonism ($n = 37$). Of these, 89 patients had hemiplegia.

As controls, 28 age-matched residents of the local community (14 women and 14 men) with no vertebral fractures were recruited.

Data collection

We collected data from July 1996 to August 1996 (the summer season in Japan). The Barthel index (BI) [11] and duration of illness were recorded for all patients. Body mass index and hand grip strength on the intact side in hemiplegic patients and on the right side in non-hemiplegic subjects were recorded for patients and controls.

On the day of bone evaluation for patients and controls, a fasting blood sample was obtained in the morning. 25-hydroxyvitamin D (25-OHD), 1,25-dihydroxyvitamin D (1,25-$[OH]_2D$), intact parathyroid hormone (PTH), intact bone Gla protein (BGP; an osteoblastic bone formation marker [12]), pyridinoline cross-linked carboxy-terminal telopeptide of type I collagen (ICTP; an osteoclastic bone resorption marker [13]) and ionized calcium concentrations were measured in patients and control subjects as described previously [9].

Plain radiographs of the right hand in non-hemiplegic patients and the intact side in hemiplegic patients were used to determine bone changes based on an aluminium step scale. Bone mineral density (BMD) was calculated at the centre of the second metacarpal using computed X-ray densitometry as described previously [14, 15].

Vitamin D intake was determined in patients by a 7-day food record. Information on sunlight exposure was obtained from the patients' hospital charts.

Data are presented as means ± SD. Student's *t*-test was used to assess the significance of differences between stroke patients and controls. Spearman's rank correlation coefficients were calculated to determine the relationship between each variable. Multivariate linear regression analysis was used to estimate the independent effects of predictor variables on BMD, BI or 1,25-$[OH]_2D$ in stroke patients. One-way ANOVA and Fisher's protected least significant difference were used to assess differences between the three stroke groups categorized by 25-OHD levels. *P* values of < 5% were considered statistically significant.

Results

Clinical characteristics of study subjects

Results are presented in Table 1. Group composition did not differ between patients and controls with respect to age or gender. Grip strength and body mass index were lower in patients than in controls. Mean duration of hospitalization was 4.6 years. Mean BI score was 66. Thus, all patients had limited mobility that prevented them from venturing outdoors and consequently they were in a sunlight-deprived state. Ten patients (8%) consumed less vitamin D than the Japanese recommended daily allowance (100 IU). All 70 female patients were postmenopausal.

Serum indices of bone metabolism and bone mineral density

The mean serum concentrations of 25-OHD, 1,25-$[OH]_2D$, calcium, intact PTH, intact BGP and ICTP are presented for all cohorts in Table 2. Patients had low 25-OHD (mean 11.7 ng/ml) and 1,25-$[OH]_2D$ (mean 24.3 pg/ml) concentrations, high concentrations of ionized calcium, normal or low PTH concentrations and decreased BGP and ICTP concentrations. BMD in hospitalized patients was significantly decreased compared with control subjects. There was no significant difference in serum creatinine levels between the two groups. No significant differences with respect to gender were seen between the serum concentrations of 25-OHD, 1,25-$[OH]_2D$, calcium, PTH, BGP or ICTP.

Relationships between BMD, BI or vitamin D and each variable

BMD correlated with the BI score ($r = 0.351$, $P < 0.0001$), 25-OHD, 1,25-$[OH]_2D$, BGP and ICTP concentrations, but not with calcium and PTH concentrations or hand grip strength ($P = 0.26$; Table 3). The BI score correlated positively with 25-OHD or 1,25-$[OH]_2D$ and negatively with calcium. In addition, serum ionized calcium correlated negatively with 25-OHD, 1,25-$[OH]_2D$ and ICTP, and 1,25-$[OH]_2D$ correlated negatively with calcium and ICTP. Serum creatinine did not correlate with any indices. There was no correlation between 25-OHD and PTH ($P = 0.0829$).

Table 1. Clinical characteristics of study subjects

Variable	Controls ($n = 28$)	Patients ($n = 129$)	*P* value
Age (years)	70.2 ± 4.1	71.2 ± 4.7	0.57
Gender (M/F)	14/14	59/70	0.68
Duration of illness (years)	–	4.6 ± 2.9	–
Barthel index	–	66 ± 31	–
Grip strength (kg)	23 ± 6	13.8 ± 4.9	< 0.0001
Body mass index (kg/m^2)	22.3 ± 2.0	20.7 ± 3.4	0.0066

Table 2. Biochemical data and bone mineral density in patients and controls

Variable	Mean value ± SD Controls ($n = 28$)	Patients ($n = 129$)	Student's t-test
25-hydroxyvitamin D (ng/ml)	25.2 ± 4.0	11.7 ± 5.3	< 0.0001
1,25-dihyroxyvitamin D (pg/ml)	57.4 ± 14.0	24.3 ± 12.2	< 0.0001
Ionized calcium (mEq/l)	2.529 ± 0.105	2.648 ± 0.232	0.0089
Intact parathyroid hormone (1–84) (pg/ml)	34.5 ± 12.0	29.4 ± 17.5	0.14
Bone Gla protein (ng/ml)	6.415 ± 3.529	4.527 ± 2.371	0.0015
ICTP (ng/ml)	9.416 ± 4.626	7.076 ± 1.171	0.0077
Creatinine (mg/dl)	1.024 ± 0.307	1.143 ± 0.396	0.13
Bone mineral density (mmAl)	2.574 ± 0.354	2.248 ± 0.525	0.00[illegible]

ICP, pyridinoline cross-linked carboxy-terminal telopeptide of type I collagen.

Multiple regression analysis

The results of multiple regression analysis with BMD, BI and 1,25-$[OH]_2D$ as dependent variable are shown in Table 4. BI, 25-OHD and 25-$[OH]_2D$ were significantly related to BMD; 25-$[OH]_2D$, ionized calcium, ICTP and BMD to BI; and BI and calcium to 25-$[OH]_2D$.

Correlation of 1,25-$[OH]_2D$ concentration with serum levels of 25-OHD

Serum 25-OHD concentration was defined as deficient when less than 10 ng/ml, insufficient at 10–20 ng/ml and sufficient when exceeding 20 ng/ml [9]. No significant difference in the mean 1,25-$[OH]_2D$ levels between the three groups was noted (ANOVA, $P = 0.39$). The serum concentrations of 1,25-$[OH]_2D$ were 23.1 ± 12.0 pg/ml in patients with deficient levels of 25-OHD ($n = 55$), 24.9 ± 12.4 pg/ml in patients with insufficient levels ($n = 68$) and 29.7 ± 11.7 in patients with sufficient levels ($n = 6$).

Discussion

Previous studies have evaluated the vitamin D and calcium status of patients in long-term care [16–20]. 25-OHD deficiency with compensatory hyperparathyroidism has been described in this population [17, 19, 20]. These studies showed 25-OHD deficiency caused by sunlight deprivation and low vitamin D intake [17–20] is associated with only a slight decrease in the concentration of 1,25-$[OH]_2D$ (the most active metabolite form of vitamin D) in old people in nursing homes [19, 20]. The populations studied have had a wide variety of medical diagnoses, including stroke. We examined elderly patients who were hospitalized chronically for the sequelae of stroke to assess the bone status of this population.

The mean serum 25-OHD concentration in our population was similar to that previously reported for elderly people in nursing homes [17–20]. Generally, immobilization-induced hypercalcaemia is associated with conditions in which bone turnover is high, as in children or adolescents with acute neurologic diseases (such as poliomyelitis or spinal cord injury [21–25]). The serum ionized calcium level is chronically low in isolated 25-OHD deficiency, resulting in feedback stimulation of the parathyroid glands, which causes secondary hyperparathyroidism.

In the present study, PTH was normal or low and no correlation between 25-OHD and PTH was found. Thus, compensatory hyperparathyroidism may not occur in spite of 25-OHD deficiency because inhibition of the parathyroid gland by hypercalcaemia may have overshadowed compensatory PTH secretion. We

Table 3. Correlation between variables

Variable	BMD	Barthel index	Ionized calcium	1,25-[OH]2D
25-hydroxyvitamin D	0.387	0.452	−0.254[a]	0.127[c]
1,25-dihydroxyvitamin D	0.203[b]	0.245[a]	−0.625	-
Ionized calcium	−0.070[c]	−0.398	-	−0.625
Parathyroid hormone	−0.053[c]	-	−0.030[c]	−0.018[c]
Bone Gla protein	0.182[b]	0.002[c]	0.047[c]	0.017[c]
ICTP	−0.203[b]	0.001[c]	0.219[b]	−0.288[a]
Creatinine	−0.004[c]	0.063[c]	−0.028[c]	−0.064[c]

Values represent Spearman's rank correlation coefficients with the probability values symbolized as follows: $P < 0.0001$, [a]$P < 0.01$, [b]$P < 0.05$, [c]$P > 0.05$.
BMD, bone mineral density; ICTP, pyridinoline cross-linked carboxy-terminal telopeptide of type I collagen.

Table 4. Multiple regression analysis of bone mineral density, Barthel index and 1,25-dihydroxyvitamin D with each index selected as independent variable

	Bone mineral density		Barthel index		1,25-dihydroxyvitamin D	
	SC	*P*	SC	*P*	SC	*P*
Barthel index	0.266	0.0081	–	–	0.151	0.0362
Bone mineral density	–	–	0.221	0.0075	−0.145	0.12
25-hydroxyvitamin D	0.282	0.0018	−0.092	0.24	–	–
1,25-dihydroxyvitamin D	0.152	0.0323	0.213	0.0015	–	–
Ionized calcium	–	–	−0.276	0.0009	−0.190	0.0352
Bone Gla protein	0.027	0.74	–	–	–	–
ICTP	−0.148	0.09	−0.281	0.0005	−0.181	0.057
Multiple *R*	0.251	0.613	0.379			
Adjusted R^2	0.501	0.375	0.144			
F	7.994	14.303	6.027			

SC, standardized coefficient. ICTP, pyridinoline cross-linked carboxy-terminal telopeptide of type I collagen.

found no significant difference in 1,25-[OH]$_2$D levels between the three stroke groups categorized by 25-OHD level. Also, there was no correlation between creatinine and 1,25-[OH]$_2$D levels in these patients. Multiple regression analysis demonstrated that calcium level and BI were independent determinants of 1,25-[OH]$_2$D. These results suggest that 1,25-[OH]$_2$D deficiency is not caused by substrate (25-OHD) deficiency but by hypercalcaemia. Hypercalcaemia may inhibit PTH secretion and thus, 1,25-[OH]$_2$D production in the kidney. Since calcium was an independent determinant of BI, the hypercalcaemia may be caused by immobilization. The observed 25-OHD deficiency due to sunlight deprivation has been previously reported [9].

In addition, we demonstrated that BI, 25-OHD and 1,25-[OH]$_2$D were the independent determinants of decreased BMD in this population. This finding suggests that immobilization may cause hypovitaminosis D. In hemiplegic stroke, dependency in the activities of daily living results in decreased mobility of the contralateral limb, as evidenced by weakness in the fingers of the contralateral side compared with controls. Weakness also occurred in non-hemiplegic patients as reflected in low activities of daily living scores. Osteopenia was not due to weakness in the hand used for BMD measurement or PTH concentration since no correlations were observed between BMD and hand grip strength or PTH concentration.

In the older, long-term care stroke patients assessed in this study, bone remodelling may almost reach equilibrium, resulting in a steady rate of bone loss [26]. Indeed, decreases in the serum BGP and ICTP concentrations were observed and biochemical indices of bone turnover did not differ significantly between genders—probably because older patients were used in this study. ICTP was an independent determinant of BI. This indicates that prolonged immobilization results in increased bone resorption.

Although a longitudinal study would have been desirable to assess continuous changes of bone and biochemical parameters which occur during after stroke, this cross-sectional study has demonstrated the influence of immobilization on BMD, vitamin D status and bone turnover variables in chronically hospitalized, disabled stroke patients. Dietary vitamin D supplementation with cholecalciferol can reduce bone loss or prevent nonvertebral fractures in elderly patients. This treatment increases serum 25-OHD concentrations and consequently, inhibits PTH secretion [27, 28]. However, exogenous 1,25-[OH]$_2$D (calcitriol or its analogue) [15, 29] rather than dietary vitamin D supplementation may be required in dependent elderly stroke patients with deficiencies of 1,25-[OH]$_2$D to prevent the hip fractures on the hemiplegic side [1–5]. In addition, calcitonin treatment may lower immobilization-induced hypercalcaemia, which tends to suppress 1,25-[OH]$_2$D production [30, 31].

Key points

- A deficiency of both 1,25-dihydroxyvitamin D (1,25-[OH]$_2$D; 24.3 pg/ml) and 25-hydroxyvitamin D (25-OHD; 11.7 ng/ml) and a high serum ionized calcium (mean, 2.648 mEq/l) are present in chronically hospitalized, disabled stroke patients.
- Hypercalcaemia may be caused by immobilization.
- 25-[OH]$_2$D deficiency is not caused by substrate (25-OHD) deficiency but by hypercalcaemia. Immobilization-induced hypercalcaemia inhibits PTH secretion and thus, 1,25-[OH]$_2$D production.
- Bone mineral density (BMD) of the second metacarpal in patients was significantly decreased compared to control subjects and independent determinants of BMD were the Barthel index, 25-OHD and 1,25-[OH]$_2$D.

- Exogenous 1,25-$[OH]_2D$ (calcitriol) rather than dietary vitamin D supplementation may be required in disabled elderly stroke patients who have a deficiency of 1,25-$[OH]_2D$ to help prevent hip fractures.

References

1. Peszczynski M. The fractured hip in hemiplegic patients. Geriatrics 1957; 12: 687–90.

2. Mulley G, Espley AJ. Hip fracture after hemiplegia. Postgrad Med J 1979; 55: 264–5.

3. Poplingher AR, Pillar T. Hip fracture in stroke patients. Acta Orthop Scand 1985; 56: 226–7.

4. Hooper G. Internal fixation of fractures of the neck of the femur in hemiplegic patients. Injury 1979; 10: 281–4.

5. Chiu KY, Pun WK, Luk KDK, Chow SP. A prospective study on hip fractures in patients with previous cerebrovascular accidents. Injury 1992; 23: 297–9.

6. Grisso JA, Kelsey JL, Strom BL *et al.* Risk factors for falls as a cause of hip fracture in women. N Engl J Med 1991; 324: 1326–31.

7. Biering-Sørensen F, Bohr HH, Schaadt OP. Longitudinal study of bone mineral content in the lumbar spine, the forearm and the lower extremities after spinal cord injury. Eur J Clin Invest 1990; 20: 330–5.

8. Sato Y, Maruoka H, Honda Y, Asoh T, Fujimatsu Y, Oizumi K. Development of osteopenia in the hemiplegic finger in patients with stroke. Eur Neurol 1996; 36: 278–83.

9. Sato Y, Fujimatsu Y, Kikuyama M, Kaji M, Oizumi K. Influence of immobilisation on bone mass and bone metabolism in hemiplegic elderly patients with a long-standing stroke. J Neurol Sci 1998; 156: 205–10.

10. Special Report From the National Institute of Neurological Disorders and Stroke. Classification of cerebrovascular diseases III. Stroke 1990; 21: 637–76.

11. Mahoney FI, Barthel DW. Functional evaluation: The Barthel index. Md State Med J 1965; 14: 61–5.

12. Garnero P, Grimaux M, Seguin P, Delmas PD. Characterization of immunoreactive forms of human osteocalcin generated in vivo and in vitro. J Bone Miner Res 1994; 9: 255–64.

13. Eriksen EF, Charles P, Melsen F, Mosekilde L, Risteli L, Risteli J. Serum markers of type I collagen formation and degradation in metabolic bone disease: correlation with bone histomorphometry. J Bone Miner Res 1993; 8: 127–32.

14. Matsumoto C, Kushida K, Yamazaki K, Imose K, Inoue T. Metacarpal bone mass in normal and osteoporotic Japanese women using computed X-ray densitometry. Calcif Tissue Int 1994; 55: 324–9.

15. Sato Y, Maruoka H, Oizumi K. Amelioration of hemiplegia-associated osteopenia over 4 years following stroke by 1 a-hydroxyvitamin D3 and calcium supplementation. Stroke 1997; 28: 736–9.

16. Corless D, Beer M, Boucher BJ, Gupta SP, Cohen RD. Vitamin-D status in long-stay geriatric patients. Lancet 1975; 1: 1404–6.

17. Petersen MM, Briggs RS, Ashby MA *et al.* Parathyroid hormone and 25-hydroxyvitamin D concentrations in sick and normal elderly people. Br Med J 1983; 287: 521–3.

18. Webb AR, Pilbeam C, Hanafin N, Holick MF. An evaluation of the relative contributions of exposure to sunlight and of diet to the circulating concentrations of 25-hydroxyvitamin D in an elderly nursing home population in Boston. Am J Clin Nutr 1990; 51: 1075–81.

19. Komar L, Nieves J, Cosman F, Rubin A, Shen V, Lindsay R. Calcium homeostasis of an elderly population upon admission to a nursing home. J Am Geriatr Soc 1993; 41: 1057–64.

20. Gloth FM III, Gundberg CM, Hollis BW, Haddad JG, Tobin JD. Vitamin D deficiency in homebound elderly persons. JAMA 1995; 274: 1683–6.

21. Minaire P. Immobilisation osteoporosis: a review. Clin Rheumatol 1989; 8: 95–103.

22. Henke JA, Thompson NW, Kaufer H. Immobilisation hypercalcemic crisis. Arch Surg 1975; 110: 321–3.

23. Hyman LR, Boner G, Thomas JC, Segar WE. Immobilisation hypercalcaemia. Am Dis Child 1972; 124: 723–7.

24. Lawrence GD, Loeffler RG, Martin LG, Connor TB. Immobilisation hypercalcaemia. J Bone Joint Surg 1973; 55: 87–94.

25. Stewart AF, Adler M, Byers CM, Segre GV, Broadus AE. Calcium homeostasis in immobilisation: An example of resorptive hypercalciuria. N Engl J Med 1982; 306: 1136–40.

26. Riggs BW, Melton LJ III. Involutional osteoporosis. N Engl J Med 1986; 314: 1676–86.

27. Chapuy MC, Arlot ME, Duboeuf F. Vitamin D3 and calcium to prevent hip fractures in elderly women. N Engl J Med 1992; 327: 1637–42.

28. Dawson-Hughes B, Harris SS, Krall EA, Dallal GE. Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. N Engl J Med 1997; 337: 670–6.

29. Tilyard MW, Spears GFS, Thomson J, Dovey S. Treatment of postmenopausal osteoporosis with calcitriol or calcium. N Engl J Med 1992; 326: 357–62.

30. Clouston WM, Lloyd HM. Immobilisation-induced hypercalcaemia and regional osteoporosis. Clin Orthop Rel Res 1987; 216: 247–52.

31. Wimalawansa SJ. Long-and short-term side effects and safety of calcitonin in man: a prospective study. Calcif Tissue Int 1993; 52: 90.

Received 7 January 1998; accepted in revised form 11 June 1998

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