Scand J Rehab Med 21: 165–170, 1989

BONE METABOLISM IN HEMIPLEGIC PATIENTS

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ABSTRACT. Bone metabolism has been assessed in 36 hemiplegic patients (18–77 years), 26 with CVA and 10 with head injuries. The results show an increase of serum calcium and phosphorous levels in the first month as well as hydroxyprolinuria. The radiological examination showed signs of demineralisation, as well as single photon absorptiometry of both arms. Bone scan by ^{99}Te demonstrated a hypercaptation in both paralysed limbs. From the 36 patients, 17 had a ^{47}Ca kinetic study which showed an average of normal values as far as bone accretion (Vo+) is concerned. However, the two youngest patients (18 and 32 years) had a high value of this parameter. The urinary calcium excretion (Vu) and the fecal calcium excretion (Vf) was also increased in the 17 patients. The bone resorption measured by Vo− was also high at the beginning of the study and significantly decreased 12 months later. Our observations show that neurologic osteoporosis of the hemiplegic patient is related to an unbalance between the synthesis and the degradation of a bone whose metabolism is active. Related to the determination of the intramedullary pressure and intraosseous phlebography, it seems that this resorption is due to a venous stasis. This circulatory modification regime can influence cell differentiation and probably be responsible in a way for this osteoporosis.

Key words: hemiplegia, osteoporosis, bone metabolism, ^{47}Ca kinetic study.

Osteoporosis in the region affected by a lesion of the central nervous system has been recognized for more than a century as "musculoskeletal atrophy" (8). This condition can impede rehabilitation since the risk of fracture in a paralysed limb is not insignificant (20). The functional outcome may thus be compromised. The problem is becoming more important as the concerned patient population becomes younger. This phenomenon is due to new risks, such as use of contraceptives in young women, drug abuse and toxicomany problems as well as the high incidence of head injuries in young people (1, 13).

Although numerous studies of osteoporosis in patients with spinal cord injury (3, 24) or poliomyelitis (12) have been performed, the literature is deficient in relation to hemiplegia where the functional prognosis is generally better (22). The parameters analysed in these studies mainly concern bone modification (3, 4, 22), mineralisation of peripheral skeletal bone (19, 24) and radiological evaluation of cortical thickness (4, 18). It therefore appeared useful to study other parameters so that we could better characterize the bone metabolism in hemiplegia and the aetiopathogenesis of the related osteoporosis.

Many authors have stressed the effect on the motor nervous system dysfunctions leading to "immobilisation" and reduction in mechanical use (14, 18, 21), whereas the effect of neurovascular involvement has never been evoked in discussing the related osteoporosis. The present study enabled a comparison of the influence of each of these effects on the development of lesion-related osteoporosis in the hemiplegic.

PATIENTS AND METHODS

Thirty-six patients (23 men, 13 women) of an age range 18 to 77 years were studied. A cerebro-vascular accident had been diagnosed in 26 cases and traumatic brain damage in 10 cases (Table I). All of these patients who had a proportional sensory motor hemiplegia were followed for one year from the initial event. None of the patients presented osteoarticular, endocrine, gastrointestinal or renal disease which could have influenced the results.

Three patients were excluded from the study: no. 11 because of myocardial infarction at 6 months, no. 14 died at 8 months and no. 17 was lost to follow-up.

A rehabilitation programme had been introduced from the first week of the neurological event and was continued for 1 year. It consisted of passive, then active-assisted mobilisation of the paralysed limbs with active mobilisation of the normal limbs, followed by standing and walking as this became possible.

Blood and urinary electrolytes were determined in all patients at 1, 3, 6 and 12 months. A kinetic radiolabelled calcium (^{47}Ca) study was performed in 17 patients (nos. 1 to 17) as described by Reeve et al. (23). By this method the bone *accretion* (Vo+) as well as the pool of exchangeable calcium (P) are measured while knowing the ingested calcium, the labelled calcium and the calcium excretion in

Table I. *Hemiplegic patients*

No.	Patients	Sex	Age	Side of hemiplegia	C.V.A.	H.I.
1	B.J.	M	61	R	+	
2	V.J.	M	77	L	+	
3	H.B.	F	55	L	+	
4	F.M.	F	62	L	+	
5	E.F.	M	62	L	+	
6	B.R.	F	49	L	+	
7	R.I.	F	64	R	+	
8	W.E.	F	73	L	+	
9	D.G.V.	M	77	L	+	
10	B.J.	F	69	L	+	
11	H.R.	M	70	L	+	
12	M.A.	M	32	R	+	
13	P.M.	F	18	L	+	
14	M.A.	M	52	L	+	
15	B.J.A.	M	57	L	+	
16	J.G.	M	63	L	+	
17	R.Y.	F	58	R	+	
18	D.O.	M	38	L	+	
19	D.J.L.	M	18	L		+
20	G.W.	F	22	L		+
21	M.R.	M	49	R		+
22	M.J.L.	M	18	R		+
23	V.J.	M	54	R		+
24	W.G.	M	23	L		+
25	W.H.	F	21	L		+
26	K.E.	M	18	L		+
27	B.J.C.	M	44	R	+	
28	C.D.	F	25	R	+	
29	M.J.P.	M	56	L	+	
30	M.A.	M	37	R	+	
31	N.R.	M	55	R	+	
32	B.E.	F	56	L	+	
33	G.J.	M	61	L	+	
34	H.J.	F	69	R	+	
35	M.R.	M	56	R	+	
36	J.R.	M	27	R	+	

urine and faeces. These parameters together with the non-radioactive calcium balance enable the calculation of the bone resorption (Vo−).

Seventeen patients (nos. 1 to 17) were transferred to our metabolic unit between the 2nd and the 4th weeks from the onset of their hemiplegia. They received a diet of known constant level of calories, calcium and protein, as well as sodium and phosphates. Only those drinks prepared with distilled water or known low calcium content (Volvic) were permitted.

On the fourth day of the diet, 30 microcuries of 47Ca in the form of a solution of calcium chloride were administered by intravenous injections. Several blood samples were taken on the first day and a single morning blood sample was taken from the 2nd to the 10th day. 24-hour urine collections with added hydrochloric acid, and the faeces were kept for analysis. Graphs of the radioactive calcium excretions over seven days were plotted from these figures. In collaboration with the Centre de Calcul et d'Informatique of the Geneva University Hospital, values for bone assimilation (Vo+), bone loss (Vo−), exchangeable calcium pool and other parameters such as calcium elimination in the urine (Vu), faeces (Vf) and calcium turnover were calculated.

Urinary hydroxyproline excretion was determined on 2 hours morning urine in all patients at 1, 6 and 12 months. During the study, qualitative as well as quantitative measures of the cortical index, X-rays of the limbs, a bone scan and mineralometry (^{125}I) of both forearms were performed, at the same frequency 1, 6 and 12 months. The details of those latter explorations as well as the results are reported elsewhere (26). We will only give here the final results.

RESULTS

Clinically, 8 patients recovered the function of the paralysed limb by 3 months, a further 7 by 6 months; in 18 there was no recuperation of upper limb function after a year. In 27 patients, lower limb function recuperated between 1 and 3 months, 3 by 6 months, and in 2 patients by 9 months. Only one patient did not regain function of the lower limb after 1 year.

Biochemically the only notable observation was the elevation of serum calcium and phosphate, as well as urinary calcium in the 1st month which decreased significantly by 12 months (Table II). The individual analysis showed however an increased value of the Alkaline phosphatase in the younger patients (nos. 13, 19, 20, 22, 24, 25, 26, 28, 36) with a mean value of 121±6 during the first month following the hemiplegia while the average of the whole group is 80±5.96 u/l. As illustrated in Table III, the kinetic calcium 47 study showed the calcium pool (P) remained stable during the 12 months. By contrast, the urinary calcium excretion (Vu) and the faecal calcium excretion (Vf) were elevated at the first month, then decreased significantly after the 6th month, reaching normal values by 12 months. The bone accretion (Vo+) remained normal in the first month, then increased at 6 months, but the difference between the 1st and 12th months remained insignificant. However, again individual analysis showed increased Vo+ values in the first month in young patients (nos. 12 and 13) as showed on Table IV. The index of bone resorption (Vo−) was elevated from 1 to 6 months then significantly decreased by the 12th month. The values for the total calcium exchange (Vt) which represent the sum of the bone accretion and urinary and faecal calcium excretion were increased at the 1st month, then normalised by the 12th month. Again, the 2 youngest patients of the series who sustained the exploration (nos. 12 and 13) had significantly ele-

Table II

Month	Calcium	Phosphates	Creatinine	Alcaline phosph.
Blood				
1st	2.59±0.03*	1.34±0.05*	87.83±6.9	80.00±5.94
3rd	2.46±0.02	1.24±0.06	–	78.94±5.14
6th	2.47±0.02	1.23±0.05	94.00±5.5	82.80±5.58
12th	2.39±0.04*	1.15±0.08*	94.69±6.8	80.55±4.02
*$p<0.05$.	*$p<0.025$.			
Urine				
1st	5.10±0.74*	25.8±5.2	8.22±0.78	
6th	3.86±0.5	20.0±3.7	7.39±0.48	
12th	3.42±0.43*	23.75±4.4	6.37±1.12	
*$p<0.05$.				

vated values ($p<0.005$) during the first month compared with the older age group (Table IV). The non-radioactive calcium balance showed negative values at the beginning which normalised and became positive at 6 and 12 months (Table II).

The urinary hydroxyproline excretion was elevated at the 1st month representing the increased collagen metabolism of bone matrix turnover. By the 12th month, the values returned to the high normal range. The differences between the 1st and 12th months are higly significant (Table V).

Quantitative X-rays of the second metacarpal showed no significant modification of the cortical index of the paralysed side compared to healthy side. On the contrary, qualitative X-rays of both paralysed limbs showed after 2 months signs of osteoporosis. Absorptiometry and bone scan, on the other hand, demonstrated a significant decrease in percentage of the upper limb of the hemiplegic side from the first month (1.84 for 2.58) which increased during the evolution (−0.75 for 2.75 after 12 months). Bone scan showed an increased uptake of the hemiplegic limb which did not change over the year of study.

Table III

	Time from injury		
	1st month	6th month	12th month
^{47}Ca kinetic study (mmol/day)			
Ca pool (mmol)	120.3±16.3	111.5±6.9	125.7±19.3
Vo+	7.04±1.28	8.57±1.40	7.48±1.66
Vo−	8.80±1.49*	8.14±1.25	4.81±1.64*
Vu+Vf	5.77±0.81*	4.34±0.29	3.96±0.49*
Vt	12.80±1.20	12.20±1.40	11.30±1.70
Ca balance (mmol/day)			
Mean values	−1.76*	−0.43	2.67*

*$p<0.05$.

DISCUSSION

As observed in the paraplegic population, signs of osteoporosis of the paralysed limbs in hemiplegia develop rapidly. In the paraplegic, biochemical changes occur in the first few days and are confirmed after the 1st month by bone scan, absorptiometry and kinetic calcium studies (3, 4, 18). Analy-

Table IV. *^{47}Ca kinetic study in young patients (mmol/day)*

Time from onset	Ca pool	Vo+	Vo−	Vt
1 month	88.2 ±14.5	10.83 ±3.5	12.56 ±0.84	18.48 ±0.14

Table V. *Evolution of hydroxyprolinuria*

	Normal values	Time from injury		
		1st month	6th month	12 month
Hydroxy-prolinuria (μmol/day)	76–305	604.2 ±46.7*	491.6 ±55.0	348.4 ±45.1*

*$p<0.01$ ($n=36$).

sis of the results of the present study shows similar modification and indicates active remodeling on the paralysed side of the hemiplegic which is less marked than that observed in the paraplegic.

The urinary hydroxyproline excretion in the studied cases of hemiplegia was increased to twice normal, approaching the value obtained in recent onset paraplegia (at least 3 times normal).

The kinetic calcium 47 study in hemiplegics showed normal bone accretion (Vo+) at the first month following the onset, but much higher values were noted in the younger patients (nos. 12 and 13). The same was noted for the calcium turnover (Vt). In a study we made on paraplegic, Vo+ and Vt were markedly increased from the 1st month, but it could be emphasized that the mean age of the patients in our series was 29 years (4). In contrast the mean age of the hemiplegic patients was 50 years; those 2 patients of comparable age to the paraplegics (18 and 32 years) had similar results. Furthermore 8 patients (nos. 13, 19, 20, 22, 25, 26, 28, 36) aged from 18 to 27 showed an increase of the Alkaline phosphatase level (m: 121 u/l) while the mean value of this parameter for the whole group is 80 u/l. From the 6th month to the end of the study (12th month), the values of all parameters went back to the normal limits whatever the age of the patients. Age therefore appears to be an important factor in the alterations of bone metabolism. However, from the age of 45 years we note a heterogeneity of bone metabolism response, such as was described by Whyte et al. (30). This kinetic study suggests furthermore that the younger the patient, the more active is the metabolism of bone. The coincidence of a high resorption and an increased accretion is not a singularity. Lacroix & Ponlot (16) as well as Dhem (9) have described interesting observations on post-traumatic osteoporosis. More recently, we have shown similar observations in paraplegic patients (4, 6).

Independent of the type of neurological syndrome (paraplegia or hemiplegia) the patients received a program of rehabilitation involving mobilisation several times per day from the onset of their paralysis. Immobilisation does not seem therefore to be the only factor responsible for the osteoporosis of the paralysed limbs.

While not denying the importance of the mechanical factor in maintaining bone mineralisation and structure, we believe its role is limited when there is involvement of the nerve supply to the bone. Certainly the rapidity with which the bone scan, mineralometric and radiological signs appear in patients with a central nervous system lesion is not found in experiments with immobilised healthy subjects (7, 10). In these studies, the first signs of demineralisation of the calcaneum occurred only after 3 months, without modification of urinary hydroxyproline excretion during 9 months of immobilisation. The studies of Lockwood et al. (19) and Vogel & Whittle (29) show non evidence of demineralisation before the passage of several months. Recently a histomorphologic study of bone biopsies of healthy volunteers before and after 4 months in bed showed no modification of the different parameters and in particular the bone trabecular volume (28).

Wolff's law, postulating that activity against gravity must be performed daily to maintain skeletal homeostasis and normal bone remodelling, appears to be applicable in hemiplegia. Although the motor lesion leads to reduced mechanical use, there are compensatory rehabilitation exercises, and spasticity which appears after several days or weeks. Despite this, and the report of Lanyon et al. (15) claiming that a minimum of exercises enables maintenance of a stable bone mass, an early and major bone loss on the paralysed side was observed in this study.

Involvement of the sensory nervous system, as seen in the hemiplegic may also contribute to the appearance of osteoporosis. Singh et al. (25) have shown that sensory denervation leads to a significant decrease in osteoblastic activity and bone matrix formation.

As we have already demonstrated in prior studies (4), involvement of the autonomic nervous system by a central nervous system lesion plays a major role in the development of neurological osteoporosis. In that work we demonstrated in 6 hemiplegic patients that the femoral intramedullary pressure of the paralysed side was increased, while on the unaffected side the mean was within normal limits (7). Considerable venous stasis on the paralyzed side was indicated by intraosseous phlebography (7). The determination of femoral blood gases showed an increased mean percentage oxygen saturation and a reduced mean percentage CO_2 saturation on the affected side, while the pH was not significantly different between the 2 sides. Claude Bernard (2) was the first to observe in 1859 that the venous blood of animals with spinal cord sections was

more oxygenated than is normal. Galibert et al. (11) as well as Rossier et al. (24) showed that opening of arteriovenous shunts could explain this in paraplegics.

These various signs confirm a modification of intraosseous circulation. This could influence cellular differentiation as indicated by Trueta (27) and Dhem (9).

During paralysing neurologial diseases the involved bone attempts to compensate the resorptive loss by increasing bone formation as we have shown in paraplegics as well as in this study. Despite active formation, the equilibrium of resorption-formation is disturbed leading to the development of osteoporosis. A study of PTH and calcitonin levels in paraplegia (5) has shown that these hormones do not influence bone metabolism during the first months of the neurological syndrome.

We therefore conclude that PTH and calcitonin are not involved at the onset, but may later participate in the bone remodelling, depending on the alterations of the autonomic nervous system and the resulting circulatory disorders.

In conclusion, our observations of this hemiplegic population indicate, as seen in the paraplegics in a previous study (4, 6), an unbalance between resorption and formation of metabolically active bone mostly in the young patients. In this neurological osteoporosis, furthermore, autonomic nervous system lesion seems to play a role in the very high level of resorption as indicated by the determination of the intramedullary pressure and intraosseous phlebography. These explorations show a venous stasis which probably is responsible in some way for this osteoporosis. Further studies are required to allow us to clarify possible humoral and cellular mechanisms and so to formulate therapeutic approaches for this type of osteoporosis.

ACKNOWLEDGEMENTS

The authors are indebted to Dr Jonathan Reeve for his valuable assistance in providing with a computer program, and for his review of the manuscript.

They are also grateful to Professor J.-R. Scherrer for his precious help in elaborating the statistics program.

This study benefited from a grant from the Swiss Fonds National de la Recherche Scientifique (FNRS, no. 3.904.0.81).

REFERENCES

1. Beaumont, V. & Beaumont, J. L.: Thromboses vasculaires secondaires à la prise d'œstro-progestatifs de synthèse. Un mécanisme immunologique. Nouv Press Méd *10:* 503–507, 1981.
2. Bernard, C.: Leçons sur les propriétés physiologiques et les altérations pathologiques des liquides de l'organisation. Baillière et Fils, Paris, 1859.
3. Chantraine, A.: Clinical investigation of bone metabolism in spinal cord lesions. Paraplegia *8:* 253, 1971.
4. Chantraine, A.: L'ostéoporose et les para-ostéo-arthropathies au cours de la paraplégie. Editions Arscia SA, Bruxelles, 1979.
5. Chantraine, A., Heynen, G. & Franchimont, P.: Bone metabolism, parathyroid hormone, and calcitonin in paraplegia. Calcif Tiss Intl *27:* 199, 1979.
6. Chantraine, A., Nusgens, B. & Lapiere, C. M.: Bone remodelling during the development of osteoporosis in paraplegia. Calcif Tiss Intl *38:* 323, 1986.
7. Chantraine, A., Van Ouwenaller, C., Hachen, H. J. & Schinas, P.: Intramedullary pressure and intra-osseous phlebography in paraplegia. Paraplegia *17:* 391, 1979.
8. Charcot, J. M.: Sur quelques arthropathies qui paraissent dépendre d'une lésion du cerveau ou de la moelle épinière. Arch Phys Normale et Pathol *I:* 379, 1868.
9. Dhem, A.: Les mécanismes de destruction du tissu osseux. Acta Orthop Bel *39:* 423, 1973.
10. Donaldson, C. L., Hulley, S. B., Vogel, J. M., Hattner, R. S., Bayers, J. H. & McMillan, D. E.: Effect of prolonged bed rest on bone mineral. Metab *19:* 1071, 1970.
11. Galibert, P., Fossati, P., Lopez, C., Cécille, J. P., Bonte, G., Decoulx, P. & Laine, E.: Etude angiographique de la circulation des membres inférieurs aux différents stades évolutifs d'une paraplégie. Neurochirurgie *7:* 181, 1961.
12. Heaney, R. P.: Radiocalcium metabolism in disuse osteoporosis in man. Am J Physiol *2:* 188, 1962.
13. Kraus, J. F., Black, M. A., Hessol, N., Ley, P., Rokaw, W., Sullivan, C., Bowers, S., Knowlton, S. & Marshall, L.: The incidence of acute brain injury. Am J Epidemiol *119:* 186–201, 1984.
14. Lanyon, L. E., Rubin, C. T., O'Connor, J. A. & Goodship, A. E.: Osteoporosis and mechanically adaptative bone remodelling. *In* Osteoporosis (ed. J. Menczel, G. C. Robin, M. Makin & R. Steingerg), pp. 135–147. Wiley & Sons, Chichester, 1982.
15. Lanyon, L. E.: Osteoporosis and mechanically related bone remodelling. *In:* Osteoporosis (ed. J. Menczel, G. C. Robin, M. Makin & R. Steingerg), pp. 148–156. Wiley & Sons, Chichester, 1982.
16. Lacroix, P. & Ponlot, R.: Remarques sur l'histopathologie de l'ostéoporose post-traumatique. Acta Chir Belg, Suppl. 1: 149, 1956.
17. Lockwood, D. R., Vogel, J. M., Schneider, V. S. & Hulley, S. B.: Effect of the diphosphonate EHDP on bone mineral metabolism during prolonged bed rest. J Clin Endocrinol Metab *41:* 533, 1975.
18. Minaire, P.: L'ostéoporose d'immobilisation: données biologiques et histologiques quantitatives. Thèse de médecine, Lyon, 1973.
19. Minaire, P., Meunier, P., Edouard, C., Bernard, J., Courpron, P. & Bourret, J.: Quantitative histological

data on disuse osteoporosis. Calcif Tiss Res *17:* 57, 1974.
20. Mulley, G. & Espley, A. J.: Hip fracture after hemiplegia. Postgraduate Med J *55:* 264, 1979.
21. Naftchi, N. E., Viau, A. T., Marshall, C. H., Davis, S. & Loman, E. W.: Bone mineralisation in the distal forearm of hemiplegic patients. Arch Phys Med Rehabil *56:* 487, 1975.
22. Panin, N., Gorday, W. J. & Paul, B. J.: Osteoporosis in hemiplegia. Stroke *2:* 41, 1971.
23. Reeve, J., Wootton, R. & Hesp, R.: A new method for calculating the accretion rate of bone calcium and some observation on the suitability of strontium-85 as a tracer for bone calcium. Calcif Tiss Res *20:* 121–135, 1976.
24. Rossier, A. B., Bussat, Ph., Infante, F., Zender, R., Courvoisier, B., Muchim, G., Donath, A., Vasey, H., Taillard, W., Lagier, R., Gabbiani, G., Baud, C. A., Pouezat, J. A., Very, J. M. & Hachen, H. J.: Current facts on para-osteo-arthropathy (POA). Paraplegia *11:* 36, 1973.
25. Singh, I. J., Herskovits, M. S., Chiego, D. J. & Klein, R. M.: Modulation of osteoblastic activity by sensory and autonomic innervation of bone. *In* Factors and Mechanisms Influencing Bone Growth (ed. A. D. Dixon & B. G. Sarnat), pp. 535–551. A. R. Liss, New York, 1982.
26. Speich, J., Donath, A., Van Ouwenaller, C., Uebelhard, D. & Chantraine, A.: under preparation.
27. Trueta, J.: The dynamics of bone circulation. *In* Bone Biodynamics (ed. H. M. Frost), pp. 245–258. Little Brown & Co., Boston, 1964.
28. Vico, L., Chappard, D., Alexandre, L., Palle, S., Minaire, P., Riffat, G., Moruckov, B. & Rakhmanov, S.: Effects of a 120 day period of bed-rest on bone mass and bone cell activities in man: attempts at countermeasure. Bone Mineral *2:* 383–394, 1987.
29. Vogel, J. M. & Whittle, M. W.: Bone mineral changes: the second manned Skylab mission. Aviat Space Environ Med *47:* 396–400, 1976.
30. Whyte, M. P., Bergfeld, M. A., Murphy, W. A., Avioli, L. V. & Teitelbaum, S. L.: Postmenopausal osteoporosis: a heterogenous disorder as assessed by histomorphometric analysis of iliac crest bone from untreated patients. Am J Med *72:* 193–202, 1982.

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