A study of bone densitometry in patients with complex regional pain syndrome after stroke

V Kumar, J Kalita, R B Gujral, V P Sharma, U K Misra

Abstract

***Introduction*—This study was undertaken to evaluate the bone mineral density (BMD) in patients with complex regional pain syndrome type-I (CRPS-I) after stroke, and to correlate it with various clinical and neurophysiological parameters.**

***Patients and methods*—Twenty patients with CRPS-I after stroke were included and a detailed neurological evaluation was carried out. The severity of CRPS-I was graded on the basis of shoulder hand syndrome score. All the patients underwent bone mineral densitometry of paralysed and non-paralysed forearm by dual energy *x* ray absorptiometry. The BMD of paralysed forearm was also compared with that of age matched healthy controls. Neurophysiological tests included sympathetic skin response in both upper and lower limbs and median somatosensory evoked potentials.**

***Results*—The mean age of patients was 57.2 (45–75) years and eight were females. Eight patients had severe weakness and 12 had moderate weakness of grade 2 on the hemiplegic side. There was significant reduction in BMD in the patients compared with controls ($p<0.01$). The bone density reduction correlated well with duration of illness ($r = -0.673$, $p<0.01$), shoulder hand syndrome score ($r = -0.804$, $p<0.01$), and Canadian neurological scale score ($r = -0.738$ $p<0.01$). Sympathetic skin response was not recordable bilaterally in all patients. Median somatosensory evoked potentials were not recordable in seven out of 20 patients who also had higher grade of CRPS-I.**

***Conclusion*—Our results show significant reduction of BMD in patients with CRPS-I after stroke. The reduction in BMD correlates with the severity of shoulder hand syndrome score, degree of weakness, duration of hemiplegia, and the severity of stroke.**

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Keywords: stroke; complex regional pain syndrome type I; bone mineral density

Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, Uttar Pradesh, India: Department of Neurology
V Kumar
J Kalita
U K Misra

Department of Radiology
R B Gujral

Rehabilitation and Artificaial Limb Centre, K G Medical College, Lucknow, Uttar Pradesh, India
V P Sharma

Correspondence to:
Professor U K Misra, Department of Neurology, Sanjay Gandhi PGIMS, Lucknow 226 014, India
ukmisra@sgpgi.ac.in

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Complex regional pain syndrome type-I (CRPS-I), or reflex sympathetic dystrophy, is an important problem after stroke. It is associated with pain, swelling, joint stiffness, and trophic changes in the paralysed upper limb limiting its mobilisation.[1] Immobilisation of the paralysed limb results in significant bone resorption.[2 3] Hemisensory deficit in stroke patients may result in lack of adequate sensory input that may result in improper positioning and render the limb vulnerable to frequent injuries, which in turn predispose to CRPS-I.

In CRPS-1, autonomic abnormalities result in increased sweating, abnormal resting temperature, and quantitative sudomotor axon reflex test in 98% of patients.[4] The sympathetic dysfunction and disuse of the limb associated with CRPS-I may result in bone demineralisation.[5] We have not come across any study on bone density changes in patients with CRPS-I after stroke. The present study is aimed at evaluating bone mineral density (BMD) in patients with CRPS-I after stroke and its correlation with various clinical and neurophysiological parameters.

Patients and methods

Forty consecutive patients with stroke were evaluated between October 1998 and April 1999. Of these, 20 patients had clinical evidence of CRPS-I. These patients underwent clinical examination, bone mineral densitometry, median somatosensory evoked potentials, and sympathetic skin response. Patients on corticosteroids, antiepileptics, diuretics, or other drugs which could affect BMD were excluded from this study. Patients who were non-ambulant from past stroke, before the qualifying event, were also excluded. Twenty forearms of normal age matched subjects served as controls for interpreting bone mineral densitometry.

The diagnosis of stroke was made according to the definition given by the World Health Organisation and confirmed by cranial computed tomography. The severity of paralysis was assessed by the Canadian neurological scale[6] in which score 0 refers to total paralysis and 1.5 is normal power at proximal and distal joints of upper and lower limbs. The activities of daily living were assessed by the Barthel index score.[7] Biochemical studies included serum calcium, phosphorus, alkaline phosphatase, and renal function tests. Shoulder hand syndrome score was used to grade the severity of CRPS-I, as given in box 1. All patients underwent radiography of the shoulder and hands to assess for bone demineralisation.

All patients underwent BMD measurement of paralysed and normal forearm employing dual energy *x* ray absorptiometry (DEXA) using Hologic QDR 4500 DXA with forearm software. The hologic forearm protocol defines a global region of interest and individual one third distal, mid-distal, and ultradistal regions of forearm. The one third distal region is defined as a region 20 mm wide centred at a

Box 1: Shoulder hand syndrome score

1. SENSORY: PAIN AND HYPERALGESIA
No = 0
Mild = 1
Moderate = 2
Distinct = 3
Severe = 4
Spontaneous = 5
2. AUTONOMIC: DISTAL OEDEMA
No = 0
Mild = 1
Distinct = 2
Severe = 3
3. MOTORIC: PAINLESS PASSIVE RANGE OF MOTION
(A) Humeral abduction
>120° = 0
<120° = 1
<90° = 2
<45° = 3
(B) Humeral external rotation
>30° = 0
<30° = 1
<20° = 2
<10° = 3

distance equal to one third of the forearm length measured from the distal tip of the ulna and contains mostly cortical bone. The ultradistal is a region 15 mm in length positioned proximal to the end plate of the radius and contains mostly trabecular bone. The middistal is the region between the one third distal and ultradistal regions and contain both trabecular and cortical bone. The entire forearm was scanned and a bone map created. BMD was calculated in g/cm^2.

Sympathetic skin response is useful in studying the integrity of peripheral sympathetic-cholinergic (sudomotor) function by evaluating the changes in resistance of skin to electric conduction. Sympathetic skin response was measured on a Neuropack-II electromyograph. Recordings were obtained simultaneously from hands and feet. The low frequency filter was set at 0.1 Hz and high frequency filter at 500 Hz. Sweep speed was 500 ms/division (div) and sensitivity 500 μv/div. The active electrode was placed on the tip of fifth finger for upper limb and great toe for lower limb while the reference was placed on dorsum of hand and feet respectively. An electrical stimulus of 0.1 msec duration, 10–12 mA was applied on the median nerve at the wrist. Three responses were averaged and onset latency was measured. The normal mean (SD) onset latency for hand in our laboratory in 1.5 (0.4) ms and for that of foot 2.1 (0.4) ms. A response was considered absent if it could not be elicited after three stimuli of increasing intensity at an intervals of at least 60 sec.

Median somatosensory evoked potentials were obtained by stimulating the median nerve at the wrist by 0.1 ms square wave pulse at 3 Hz, at an intensity to produce a painless twitch of the thumb. The active surface recording electrode was placed at Erb's point and at the contralateral parietal cortex 3 cm behind and 7 cm lateral to the vertex using a mid-frontal reference. The impedance of electrode was kept below 5 KΩ, frequency band pass was 2–3000 Hz, and analysis time 100 ms. Five hundred and twelve responses were twice averaged at a gain of 1–2 μv/div to ensure reproducibility. Median somatosensory evoked potentials were analysed by the latency of N9, N20, and interpeak latency of N9–N20.

Table 1 Clinical characteristics of patients with CRPS I after stroke (n=20); values are mean (SD)

Characteristic	
Age (years)	57.2 (9.0)*
Sex (M:F)	14:6
Duration of illness (months)	4.15 (2.62)*
Severity of upper limb weakness (Canadian neurological scale)	0.85 (0.56)*
Barthel index score	8.1 (4.36)*
Shoulder hand syndrome score	7.95 (1.63)
Type of stroke	
(A) Haemorrhage	7
Left putaminal	3
Right putaminal	3
Left thalamic	1
(B) Infarction	13
Left MCA	
Total	4
Partial	2
Right MCA	
Total	2
Partial	5

* Significantly related to BMD, p<0.01.
MCA = middle cerebral artery.

Statistical analysis was done using the paired *t* test to compare the BMD of paralysed and non-paralysed forearm and unpaired *t* test was used to compare the BMD of paralysed forearm with that of normal controls. Correlation coefficient (*r* value) was calculated to study the relationship of BMD with severity of weakness, duration of illness, Barthel index score, and shoulder hand score.

Results

Twenty patients with CRPS-I after stroke were included in this study. All the patients were right handed and their mean age was 57.2 (range 45–75) years and 12 were males. Mean duration of stroke was 4.15 (range 2–12) months. Eight patients had stroke for less than three months and remaining had for three or more months. Eight patients had severe weakness with no movement or just a flicker of muscle contraction and 12 patients had moderate weakness on the hemiplegic side (Medical Research Council grade 2/5). The mean (SD) Canadian neurological score for the upper limb was 0.85 (0.56). Seven patients had medium size intracerebral haemorrhages, which were putaminal in six and thalamic in one. Thirteen patients had infarctions, details of which are given in table 1.

All the patients had clinical evidence of CRPS-I in the paralysed upper limb. The symptoms of CRPS-1 appeared after a mean duration of 1.7 (0.5–3) months after stroke. Twelve patients had evidence of severe shoulder and hand disability in the form of hyperalgesia, painful restriction of shoulder and hand movement along with swelling of the hand. The skin was cold and trophic changes were present in six patients. Their shoulder hand syndrome score was ⩾8 (range 8–11). All these patients

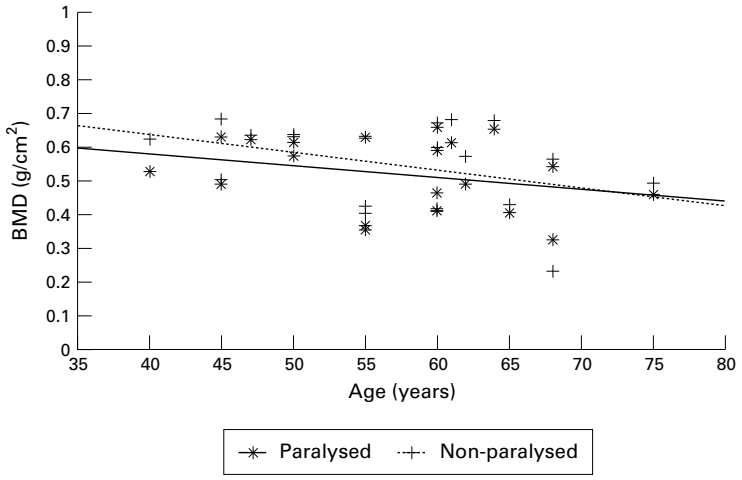

Figure 1 Bone mineral density (BMD) in paralysed and non-paralysed forearm of stroke patients with CRPS-I (n=20).

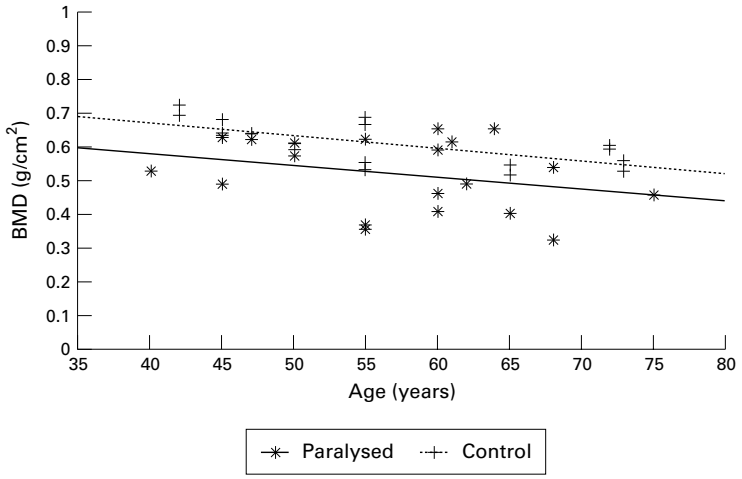

Figure 2 Bone mineral density (BMD) in the forearm of stroke patients on the paralysed side and its comparison with that of normal controls (n=20).

had radiological evidence of osteopenia. The remaining eight patients had milder symptoms and signs of CRPS-I in the form of mild painful restriction of shoulder and swelling of the hand (shoulder hand score <8, range 6–7). Biochemical indices including serum calcium, phosphorus, and alkaline phosphatase were within normal limits thus excluding any underlying metabolic derangement. Renal functions including serum creatinine and blood urea nitrogen concentrations were also normal.

BMD was measured in both forearms of patients and control subjects. The mean (SD) BMD value of the paralysed forearm in g/cm^2 was 0.5075 (0.119) and in the non-paralysed forearm 0.5486 (0.1113) (t = 1.13, not significant, fig 1). The mean BMD value of 20 normal forearms was 0.610 (0.061), which was significantly higher compared with stroke patients (t = 3.43, p<0.01, fig 2). In nine patients the BMD value was reduced on the hemiplegic side and in seven patients it was reduced even on the non-hemiplegic side compared with controls (mean (2 SD)). There was strong correlation of BMD values with the duration of stroke (r = −0.673, p<0.01). Patients who had hemiplegia for more than three months had lower BMD values than those with hemiplegia for three months or less (p<0.01). BMD values also correlated well with the severity of upper limb weakness (r = −0.738, p<0.01) and Barthel index score (r = −0.784, p<0.01). Strong correlation was also found between BMD values and severity of CRPS-I as graded by shoulder hand syndrome score (r = −0.804, p<0.01). There was no significant difference in the BMD values between those with haemorrhagic stroke and with ischaemic stroke and in the paralysed forearm between males and females.

Sympathetic skin responses were unrecordable bilaterally in all the patients. Median somatosensory evoked potentials on the stimulation of the paralysed side were not recordable in seven and the remaining had normal median somatosensory evoked potentials. Five of these patients had total left middle cerebral artery infarct (three on left and two on right), and two had left putaminal haemorrhage. All these patients had greater shoulder disability as evidenced by shoulder hand syndrome score.

Discussion

In the patients with CRPS-I after stroke, a significant reduction in BMD was found. The bone density reduction correlated with duration of immobilisation, severity of pain, and autonomic disturbance in affected limb and severity of upper limb paralysis. Sato *et al* reported earlier bone resorption after a stroke, which was attributed to immobilisation and vitamin D deficiency.[3] Patients in their study, however, had long standing hemiplegia (mean (SD) duration 4.6 (2.1) years). The present study shows evidence of bone resorption as early as two months after a stroke. This may be related to the CRPS-I, which is associated with disuse and autonomic disturbance in the affected limb. The sympathetic dysfunction associated with CRPS-I causes arteriolar spasm and stasis of blood in capillaries and venules which lower the pH and cause early dissolution of bone mineral. Recently complete functional loss of cutaneous sympathetic vasoconstrictor activity in early stage of CRPS-I has been demonstrated. The origin of this autonomic dysfunction has been suggested in the central nervous system.[8] Osteoporosis as an early manifestation of hemiplegia was reported by Goodman in 1971.[9] In his report he documented evidence of osteoporosis within three weeks of onset of stroke and suggested the possible role of shoulder hand syndrome. In this study, however, plain x ray was used to assess bone changes, which cannot give quantitative assessment of BMD. In the present study, DEXA was used to assess BMD. The accuracy of BMD measurements by DEXA has been validated.[10] There was significant difference in BMD values between stroke patients and controls (p<0.01) in our study. Sato *et al* reported more bone resorption in the paralysed forearm than non-paralysed forearm of stroke patients.[2] In our study, the difference was not statistically significant as even the non-paralysed forearm showed bone density reduction that was significant in seven out of 20 patients. This lack of asymmetry may be due to

greater severity of stroke in our study group leading to a prolonged bedridden state. This was further supported by a significant correlation of BMD with duration of illness, severity of stroke, and Barthel index score. In the present study, we have evaluated only the stroke patients with CRPS and compared their BMD with normal controls. A comparison of BMD values for stroke patients with or without CRPS-I would have provided a more definite conclusion about the role of CRPS-I in producing bone demineralisation. There was no correlation between type of stroke (haemorrhage versus infarct) and bone density reduction. However site and size of stroke had an important implication as four patients who had total left middle cerebral artery infarction showed markedly lower BMD values. One patient having a small left capsular infarct also had significantly low BMD values; this could be due to severe hemiplegia and hemisensory deficit.

Sympathetic skin response has been used to study the integrity of peripheral sympathetic cholinergic (sudomotor) functions by evaluating the changes in resistance of skin to electrical stimulus. The sympathetic skin response was unrecordable in all our patients. Clinchot and Lorch reported an augmented response in patients with reflex sympathetic dystrophy and attributed it to heightened sympathetic activity.[11] However, Drory and Korczyn reported a suppressed sympathetic skin response in patients with reflex sympathetic dystrophy and suggested that already increased sympathetic tone cannot be further activated by the external stimulus.[12] The absent sympathetic skin response bilaterally as seen in the present study may be due to involvement of the central autonomic pathway. Corticoreticular fibres, which modulate attention, project bilaterally to the brainstem reticular formation. These fibres may be affected by unilateral infarction of haemorrhage and thus by altering the patient's attention may suppress sympathetic skin response bilaterally. Korpelainen *et al* suggested that the central pathway may have a role in causing bilateral suppression of sympathetic skin responses in stroke patients.[13]

Median somatosensory evoked potentials were not recordable on the affected side in seven out of 20 patients. All these patients also had a higher shoulder hand syndrome score and lower BMD values compared with the remaining 13 patients who had normal median somatosensory evoked potentials. The role of the proprioceptive deficit in reflex sympathetic dystrophy has been reported by Braus *et al* in 1994.[1] Lack of adequate proprioceptive stimulus from the affected limb can predispose to repeated minor trauma, which may predispose to CRPS-I.

It can be concluded from our results that immobility after stroke may be an important factor leading to bone demineralisation in patients with CRPS-I. The possible role of CRPS-I (if any) and its contribution to bone demineralisation needs further evaluation in stroke patients with and without CRPS-I.

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