Reports of Investigation

Bone atrophy in complex regional pain syndrome patients measured by microdensitometry

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Purpose: To determine the usefulness of quantitative measurement of bone atrophy in the diagnosis and the long-term follow-up of patients with complex regional pain syndrome (CRPS). The bone-sparing effect of a 5-hydroxytryptamine (5-HT₂) antagonist was also studied.

Methods: Bone mass was measured by computerized micro-densitometry at the middle position of the second metacarpal. The effect of repeated stellate ganglion blocks (SGBs) three times per week with mepivacaine ($n = 11$), administration of a 5-HT₂ antagonist (sarpogrelate hydrochloride, 300 mg a day po) ($n = 12$), and combined therapy ($n = 10$) were compared by micro-densitometry and conventional visual analogue scale (VAS) for analgesia after three months of treatment.

Results: In CRPS patients, metacarpal index (cortical bone thickness), maximum bone density (cortical bone density), minimum bone density (trabecular bone density), and average bone density were reduced on the affected side (14.1%, 12.1%, 25.0% and 19.3% respectively). The rate of reduction in bone mass correlated with the duration of the disease ($P < 0.05$). Therapy with the 5-HT₂ receptor antagonist (with or without repeated SGBs) decreased pain intensity (from 6.10 to 3.81 with SGB, from 6.30 to 2.91 without SGB, respectively; $P < 0.01$) and bone atrophy evaluated by micro-densitometry ($P < 0.05$). In contrast, repeated SGBs alone reduced pain intensity (from 6.30 to 2.91; $P < 0.01$) but did not ameliorate bone atrophy.

Conclusion: Bone micro-densitometry is useful in the assessment and follow-up of CRPS and for evaluation of treatment. The 5-HT₂ antagonist, sarpogrelate hydrochloride, is a promising treatment for CRPS patients.

Objectif : Déterminer l'utilité de la mesure quantitative de l'atrophie osseuse dans le diagnostic d'algodystrophie sympathique (ADS) et dans le suivi prolongé des patients qui en sont atteints. L'effet d'épargne osseuse de l'antagoniste de la 5-hydroxytryptamine (5-HT₂) a aussi été étudié.

Méthode : La masse osseuse a été mesurée par la microdensitométrie numérisée à la position médiane du second métacarpien. L'effet de blocs répétés du ganglion stellaire (BGS) trois fois par semaine avec la mépivacaïne ($n = 11$), l'administration d'un antagoniste de la 5-HT₂ (le chlorhydrate de sarpogrélate, 300 mg par jour po) ($n = 12$), et la thérapie combinée ($n = 10$) ont été comparés par la microdensitométrie et l'échelle visuelle analogue traditionnelle (EVA) pour l'analésie après trois mois de traitement.

Résultats : Chez les patients atteints d'ADS, l'indice métacarpien (épaisseur de l'os cortical), la densité osseuse maximale (densité osseuse corticale), la densité osseuse minimale (densité osseuse trabéculaire) et la densité osseuse moyenne étaient réduits du côté atteint (14,1 %, 12,1 %, 25,0 % et 19,3 % respectivement). Le taux de réduction de la masse osseuse correspondait à la durée de la maladie ($P < 0,05$). La thérapie avec l'antagoniste du récepteur de la 5-HT₂ (avec ou sans BGS répétés) a fait baisser l'intensité de la douleur (de 6,10 à 3,81 avec le BGS, de 6,30 à 2,91 sans le BGS respectivement; $P < 0,01$) et l'atrophie osseuse évaluée par la microdensitométrie ($P < 0,05$). Par ailleurs, en utilisant seulement les BGS répétés, l'intensité de la douleur a été réduite (de 6,30 à 2,91; $P < 0,01$) mais l'atrophie osseuse ne s'est pas améliorée.

Conclusion : La microdensitométrie osseuse est utile pour l'examen et le suivi de patients atteints d'ADS et pour l'évaluation du traitement. L'antagoniste de la 5-HT₂, le chlorhydrate de sarpogrélate, est un traitement prometteur pour les patients souffrant d'ADS.

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REFLEX sympathetic dystrophy, recently named complex regional pain syndrome (CRPS), is a clinical syndrome characterized by pain, hyperalgesia, skin atrophy, swelling and stiffness of an affected extremity.¹ Usually, the syndrome is provoked by trauma and the sympathetic nervous system is thought to play an essential role in its development.^{2,3} Even though bone atrophy of the affected region is not observed at an acute stage, many patients with the syndrome develop bone atrophy to some extent.^{4,5} Clinical studies, using triple-phase bone scanning, demonstrated that osteal blood flow was altered in CRPS patients.⁶ Until now, there are few reports of the quantitative assessment of bone loss in CRPS patients.^{7,8,9} Microdensitometry is a computerized X-ray measurement of bone density and is widely utilized for the diagnosis of osteoporosis.^{10,11} The method is relatively simple compared with other bone mineral measurements and requires no special equipment. We hypothesized that this quantitative method could detect bone mineral change in CRPS patients, and would be useful in the diagnosis and to follow-up of CRPS.

Several treatments have been utilized for CRPS. Sympathetic ganglion block has been recommended and some reports advocate that sympathetic blockade is started during the early stages of the syndrome to prevent exacerbation.^{2,3} Treatment with vasodilators, such as α -adrenergic blocking agents and calcium channel antagonists, has been reported to ameliorate symptoms.² Steroid and nonsteroidal anti-inflammatory agents have also been proposed. Another possible treatment is bone protection by calcitonin.¹² However, no therapy has been shown to be curative. Recently, several reports have suggested that 5-hydroxy triptamine (5-HT) receptors play an important role in circulatory disorders and pain syndromes.^{13,14} Since hypoperfusion induced by sympathetic hyperactivity is thought to be involved in CRPS pathophysiology, the interruption of a 5-HT signal transduction by an antagonist could be beneficial.

In this study, we measured bone mass in CRPS patients by computerized microdensitometry and compared the values with those of healthy volunteers. Following confirmation that microdensitometry could detect bone loss in CRPS sensitively, the bone-sparing effect of a 5-HT₂ antagonist (sarpogrelate hydrochloride) administration and that of repeated stellate ganglion blocks was examined. Subjective assessment with visual analogue scale (VAS) and objective measurement of bone mass with microdensitometry were utilized to compare the effect of the treatments.

Methods

Following ethics committee approval and after obtaining informed consent, bone masses of 90 healthy vol-

unteers and 33 CRPS patients were measured by computerized microdensitometry. The patients were diagnosed as CRPS affecting an upper extremity by Gibbons'⁴ RSD score (> 5 points). Patients were divided into three groups for treatment; repeated SGBs therapy group (A), 5-HT₂ antagonist (sarpogrelate hydrochloride) therapy group (B), and repeated SGBs and 5-HT₂ antagonist combined therapy group (C), according to choice of each patient after comprehensive explanation of the therapy. No patient had other diseases and patients with severe impairment in arm mobility were excluded from the study. Clinical treatment for each patient was restricted to SGBs, sarpogrelate administration or both. A physical therapy programme was not prepared, but exercises for the affected arms during analgesic periods were recommended. The SGBs were performed three times per week at one or two day intervals (group A and C). And each time, 6 ml mepivacaine 1% were injected at the C₆ level of the affected side. The effect of the block was confirmed by both a positive Horner's sign and an increase in skin temperature ($> \Delta 2^{\circ}\text{C}$ or $>35^{\circ}\text{C}$ ⁵). Sarpogrelate hydrochloride (Mitsubishi Kasei Co. Ltd., Yokohama, Japan) was given to patients as 100 mg tablets (group B and C), three times *po*. Treatment protocols were continued for three months and patient compliance was confirmed by regular interview. Pain intensity of the affected arm was measured by visual analogue scale (VAS; 0 - 10 scale) before and after therapy. At the same time, bone mass was measured by microdensitometry. Patients who needed additional medication, such as opioids, steroids or non-steroidal anti-inflammatory agents, for pain control were excluded from the study.

The microdensitometric method was based on that described by Inoue *et al.*¹⁰ The hands were X-rayed with an aluminium step-wedge as a density standard. The bone optical density was measured at the middle position of the second metacarpal using a computerized microdensitometer (DIP-1000, Hamamatsu Photonics Co. Ltd., Hamamatsu, Japan). The density of the aluminium step-wedge image was used as a reference for further calculation. Metacarpal-index (MCI), maximum bone density (GS_{max}), minimum bone density (GS_{min}) and averaged bone-density (GS/D) were employed for evaluation of bone atrophy (Figure 1).

Values were expressed as means $\pm$ SD. Data obtained by microdensitometry before and after the treatments were analyzed by two-way analysis of variance (ANOVA) for multiple comparison with Scheffe's F test. The VAS values among groups were compared using the Kruskal-Wallis rank test for multiple comparison. *P* values < 0.05 were considered to be statistically significant. The correlation between the

microdensitometric values of the patients and the duration of the disease was analyzed by least square regression analysis.

Results

Microdensitometry parameters in healthy volunteers and CRPS patients.

There were no differences between age and sex of the healthy volunteers (45 male, 45 female, age 60 ± 18 yr) and those in the CRPS group (14 male, 19 female, age 61 ± 12 yr). The absolute values of microdensitometry parameters varied widely in both patients and healthy volunteers. The left and right side differences of each microdensitometry parameter were compared between groups (Figure 2). In CRPS patients, all four microdensitometry parameters were reduced on the affected compared with the unaffected side. Percentage reduction rate of each parameter in the affected arm (values obtained from the unaffected arm were used as denominator) were 14.1% for the metacarpal index (thickness ratio of cortical bone; $P < 0.01$), 12.1% for the maximal bone density (bone density of cortical bone; $P < 0.01$), 25.0% for the minimal bone density (bone density of trabecular bone; $P < 0.01$), and 19.3% for the averaged bone density ($P < 0.01$). In CRPS patients, the difference between each microdensitometer parameter comparing the affected side with the unaffected side increased with the time elapsed after the onset of the first symptom (Figure 3). The degree of asymmetry measured by the metacarpal index, the maximum bone density, the minimum bone density and the averaged bone density correlated with the elapsed time from diagnosis ($P < 0.05$).

Effect of 5-HT₂ antagonism and repeated SGBs

There were no differences among groups for age, sex, RSD score before treatment, and the time from the onset of CRPS symptoms to the start of the respective therapy of each group (Table). Pain intensity (VAS values) decreased after three months of treatment in all groups (Figure 4). But the reduction of VAS (the difference of VAS values before and after each therapy) showed no difference among groups. Asymmetry in bone density indicated by left and right differences of the minimal bone density, the maximal bone density and the averaged bone density decreased after three months of therapy in the 5-HT₂ antagonist administration group and the combined therapy group ($P < 0.05$) (Figure 5B, C). However, no alterations were observed in the repeated SGBs therapy group (Figure 5A). There was no difference between the degree of alteration (the difference of each bone density index before and after the therapy) in the 5-HT₂ antagonist administration

FIGURE 1 Parameters measured by microdensitometry method. The optical density of bone was measured at the middle section of metacarpal II on a radiographic picture using a computerized microdensitometer.

FIGURE 2 Microdensitometric values in patients and volunteers. The left and right side differences of each microdensitometric parameters (MCI; metacarpal index, GSmax; maximum bone density, GSmini; minimum bone density and GS / D; averaged bone density). In the chronic regional pain syndrome (CRPS) patients, all four microdensitometric parameters were reduced on the affected side.

FIGURE 3 Correlation between the chronic regional pain syndrome (CRPS) duration and the microdensitometric values. In the CRPS patients, the difference between each microdensitometric parameter of the affected side and that of the unaffected side increased according to the time after the first symptom. The left and right side differences of MCI (metacarpal index), GSmax (maximum bone density), GSmini (minimum bone density) and GS / D (averaged bone density) correlated with the CRPS duration ($P < 0.05$).

FIGURE 4 Pain intensity measured by visual analogue scale (VAS) after repeated stellate ganglion blocks (SGBs), 5-HT₂ antagonist therapy and combined therapy (SGBs + 5-HT₂ antagonist). Pain intensity (VAS values) of the patients decreased after repeated stellate ganglion blocks, the 5-HT₂ antagonist therapy and the combined therapy ($P < 0.01$).

group and that in the combined therapy group. Asymmetry in the metacarpal index was not improved in all groups.

Discussion

Computerized microdensitometry in CRPS evaluation

The absolute value of bone density has wide variation among subjects because of the difference in long-term

Figure 5A

Figure 5B

Figure 5C

FIGURE 5 Microdensitometric values after repeated stellate ganglion blocks (SGBs) (A), 5-HT₂ antagonist therapy (B) and combined therapy (SGBs + 5-HT₂ antagonist) (C). The left and right side differences of MCI (metacarpal index) did not change after three months therapy. The asymmetry of bone density indicated by minimum bone density (GSmini), maximum bone density (GSmax) and averaged bone density (GS / D) decreased after the three months of treatment with the 5-HT₂ antagonist (group A and C) ($P < 0.05$), but, were not altered after repeated SGB (group B).

nutrition and physical stress. In this study, however, left and right differences of the four microdensitometry parameters were very small in healthy volunteers. The values were similar to those reported by Kimura *et al.*¹¹ In contrast, microdensitometric values in the affected arm of CRPS patients were lower than those in the unaffected arm ($P < 0.01$). Furthermore, the degree of asymmetry increased according to the duration of the disease. The microdensitometric method used in this study was originally described by Inoue *et al.*¹⁰ Recent advances in the computerized image processing technique made it possible to quantify the bone density on radiographic film more efficiently and quickly. When simple radiographic film is used for the diagnosis of bone atrophy, diagnosis is only possible

after a 20 - 30% reduction of bone mass.⁷ The microdensitometric method is 10 - 20 times more sensitive than simple radiographic examination, and bone atrophy can be detected from a very early stage. Hayashi *et al.* reported on the usefulness of computerized microdensitometry for the diagnosis of osteoporosis.¹⁵ Our results suggested that microdensitometry could detect bone loss in CRPS patients from a very early stage. The low cost of this evaluation (approximately \$35 per examination) is another advantage over more expensive imaging devices.

Among the four microdensitometric values measured in this study, the decrease of minimum bone density in the CRPS affected arm was the most prominent. The decreases of metacarpal index and maximum bone density, which represent the loss of cortical bone thickness and cortical bone density respectively, were relatively minor. This means that the bone loss observed in CRPS patients was mainly from loss of bone matrix in the trabecular site. By dual photon X-ray absorptiometry, which mainly indicates trabecular bone density, Arriagada⁷ demonstrated that the bone density of the CRPS affected arm was 28.4 - 45.1% lower than that of the unaffected arm. Bickerstaff *et al.*⁸ measured bone mineral density of the cortical site and the trabecular site separately in CRPS patients by single photon absorptiometry and reported that the loss of trabecular bone mineral was more apparent than that of the cortical site. Although measuring methods were different in these reports, both results implied unique bone loss in CRPS patients and were in agreement with our results. According to the classification by Riggs and Melton,¹⁶ bone atrophy in CRPS patients may be classified as type I (hyperdynamic type), which includes osteoporosis immediately after menopause and bone disorder of hyperthyroidism. Hyperemia during acute stage of CRPS might play a role in this hyperdynamic osteal atrophy.

Riggs and Melton¹⁶ reported that, in patients with acute phase osteoporosis, thickness of cortical bone was considerably reduced with the general decrease of bone mineral density. Mudun *et al.*¹⁷ described patchy absorption of bone mass on X-ray image as a characteristic of Sudeck's atrophy, which is bone atrophy induced by hypoperfusion after a bone fracture. These distinctive features differed from the bone atrophy observed in the CRPS patients mentioned above. Even though the microdensitometric appearance of CRPS bone loss may not be specific for this disease, the detailed assessment of bone loss by microdensitometry might be useful to analyze bone atrophy of patients quantitatively. At present, there is no standard bone mineral examination for CRPS diagnosis. The

TABLE Clinical features of the CRPS patients

Group	Age	Sex	Predisposing	Duration	Gibbons ³	main symptoms (excluding pain and bone atrophy)
case #			factor	(mo)	RSD score	
<i>Repeated SGB therapy group</i>						
1	52	m	idiopathic	48	5	sudomotor disturbance, allodynia
2	42	m	bone fracture	6	6	colour change, * oedema
3	81	m	PHN	3	7.5	colour change, * temperature change, burning pain
4	58	f	chest operation	5	5.5	oedema, * allodynia*
5	60	f	chest operation	8	5	oedema, * burning pain, * skin atrophy
6	62	f	stroke	12	5	allodynia, * oedema
7	63	f	bone fracture	5	6.5	colour and temperature change, * sudomotor disturbance*
8	49	m	neck operation	18	5	colour change, hyperpathia
9	58	m	trauma	15	5	oedema, * colour change, * sudomotor disturbance
10	83	f	trauma	9	6.5	oedema, * hair growth change, * burning pain
11	61	f	stroke	10	7	oedema, * allodynia
mean $\pm$ SD	61 $\pm$ 12	5/6		13 $\pm$ 13	6.0 $\pm$ 1.0	
<i>5-HT₂ antagonist therapy group</i>						
1	68	m	PHN	20	5	colour change, * hair growth change
2	36	m	trauma	8	5.5	colour change, allodynia
3	65	f	trauma	15	5	oedema, * temperature change*
4	67	f	chest operation	14	6.5	oedema, * temperature change, hyperpathia
5	61	f	bone fracture	4	7	allodynia, * oedema, * skin atrophy
6	65	f	PHN	5	6	oedema, * temperature change*
7	87	m	stroke	5	5	allodynia, colour change
8	70	f	trauma	5	5	burning pain, * nail change
9	57	f	trauma	3	6.5	oedema, * temperature change, * nail change
10	81	m	stroke	72	5	allodynia, * sudomotor disturbance
11	48	m	chest operation	9	5.5	oedema, * colour and temperature change*
12	52	f	bone fracture	22	6.5	colour change, * allodynia, * oedema, hair growth change
mean $\pm$ SD	63 $\pm$ 14	5/7		15 $\pm$ 19	5.7 $\pm$ 0.8	
<i>repeated SGBs and 5-HT₂ antagonist therapy group</i>						
1	53	m	idiopathic	54	5.5	hair growth change, * sudomotor disturbance
2	42	m	bone fracture	9	5	colour change, * allodynia, * oedema*
3	68	f	chest operation	18	6.5	oedema, burning pain
4	65	f	trauma	4	5	colour and temperature change, * sudomotor disturbance*
5	52	f	bone fracture	3	6.5	oedema, * hyperpathia, * colour change*
6	62	f	stroke	15	5	oedema, * allodynia, * temperature change
7	70	f	PHN	6	5.5	burning pain, * colour change
8	50	m	chest operation	2	6	oedema, * colour and temperature change*
9	62	m	stroke	15	5	nail change, allodynia
10	48	f	neck operation	18	5.5	sudomotor disturbance, * colour change, * hyperpathia
mean $\pm$ SD	57 $\pm$ 9	4/6		14 $\pm$ 15	5.6 $\pm$ 0.6	

* symptoms improved after the therapy. SGB: stellate ganglion block, PHN: post-herpetic neuralgia.

observations in this study suggest that the microdensitometric method may be useful in the diagnosis of CRPS, as supportive examination, and for the evaluation of therapy.

Effect of 5-HT₂ receptor antagonism in CRPS

In this study, we used a 5-HT₂ receptor antagonist, sarpogrelate hydrochloride, which was developed as an antiplatelet agent.^{18,19} Safety in clinical use has

already been confirmed for this drug which does not have the adrenergic activity observed in ketanserin, another 5-HT₂ antagonist. The analgesic action and bone mineral sparing action of the drug, observed in this study, strongly support the idea that signals mediated by 5-HT₂ receptors may be responsible for exacerbation of CRPS. The 5-HT₂ receptors are widely expressed in vascular smooth muscle and platelets. They are the specific receptor subtypes which mediate

signal-cascade toward vasoconstriction and platelet aggregation.²⁰ Although the underlying molecular mechanism of RSD has not been clarified, a peripheral perfusion disorder is commonly observed in the pathophysiology of the disease.³ Leitha *et al.*⁹ reported that peripheral blood perfusion detected by five-phase bone scintigraphy, was disturbed in RSD patients. Hanna and Peat²¹ implied that excessive vasoconstriction and platelet aggregation are fundamental for the development of the disease. Also, they demonstrated that the 5-HT_{1C} and 5-HT₂ receptor antagonist, ketanserin, improved autonomic nervous system symptoms related to the pain syndrome. On the other hand, Meller *et al.*¹³ and Grubb *et al.*¹⁴ suggested that the 5-HT₂ subtype played an important role in the afferent pain conduction of inflammatory disease. From the results of this study, it is difficult to clarify what pharmacological action of the 5-HT₂ antagonist is essential for the efficacy in CRPS. Probably, both the analgesic and the perfusion improving actions are related to the beneficial effect in CRPS. Although strict physical therapy protocol was not prepared for the subjects in this study, in patient interviewing, we could not find any sign that subjects given 5-HT₂ antagonist mobilized their affected arm more vigorously than did the patients in the other group. Considering that there are no reports describing that the 5-HT antagonist directly improves mobile activity of the musculoskeletal system, the intensity of physical stress to bone may not be primary in the bone-sparing action of 5-HT₂ antagonism.

We demonstrated that a 5-HT₂ antagonist could prevent both pain and bone atrophy associated with CRPS. In contrast, repeated SGBs could only ameliorate pain. The addition of repeated SGBs to the 5-HT₂ antagonist therapy showed no further benefit from that of the 5-HT₂ antagonism alone. One possibility is that bone atrophy in CRPS might not be directly related to sympathetic hyperactivity. Several symptoms of CRPS including bone atrophy are supposed to be independent of sympathetic nerve activity. Recently, the classification by the International Association for Study of Pain renamed regional sympathetic dystrophy (RSD) "complex regional pain syndrome type I" and the involvement of the sympathetic nervous system was not included in the diagnosis criteria.¹ This was because symptoms of RSD could not be fully explained by excessive action of the sympathetic nervous system alone. Another possibility is that the repeated SGBs protocol adopted in this study was not potent enough to prevent bone loss in CRPS. More frequent blocks or continuous nerve block might have some bone conserving action.

Although we could not find any demographic bias among groups, this study was not a randomized double-blind study. Therefore, there should be a limitation in analyzing the results. Randomized studies in large scale are necessary to establish the efficacy of 5-HT₂ antagonism in CRPS. Also, in this study, we limited the prescribed drugs during the study period to simplify the comparison among groups. In future, however, combined therapy with sympatholytics, steroids and 5-HT₂ antagonists might be another possible therapy protocol for CRPS patients. Further studies both in the clinical setting and in the laboratory are indispensable in order to obtain the best treatment regimen for this disease.

In conclusion, assessment of bone atrophy by microdensitometry was useful for the follow-up of CRPS and for the evaluation of therapy. Sarpogrelate hydrochloride, a 5-HT₂ antagonist, was thought to be a promising medicine for CRPS patients.

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