Fig. 3. Lateral hind paw radiographs of a rat of the CIA group (**A**) and another of the CIA + NTx group (**B**) at 6 weeks after the initial sensitization. Proliferation of radioresistant tissue and bone destruction in the ankle and subtalar joints (arrows) is less prominent in the CIA+ NTx group than the CIA group. CIA, collagen sensitization; NTx, sciatic neurectomy.

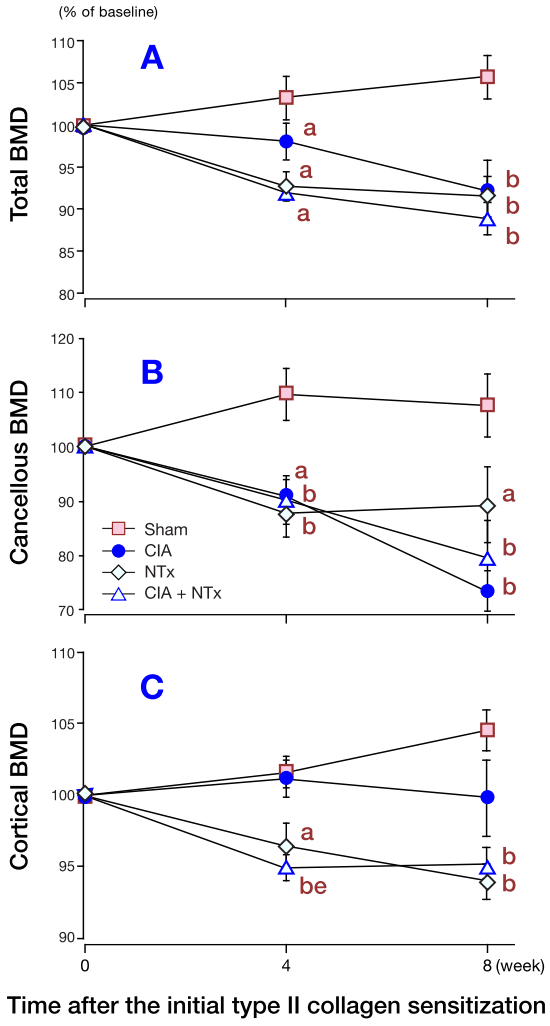

Fig. 4. Changes in total BMD (**A**), cancellous BMD (**B**) and cortical BMD (**C**) of tibial metaphysis. $^{a}P < 0.05$ and $^{b}P < 0.01$ compared with sham rats (Dunnett's test). $^{e}P < 0.05$ compared with CIA rats (Dunn's test). Values expressed as mean ± SE. BMD, bone mineral density; CIA, collagen sensitization; NTx, sciatic neurectomy.

BMD was significantly lower in the CIA, NTx and CIA + NTx groups than in the sham group at 4 and 8 weeks after the initial sensitization, but there was no significant difference among the NTx, CIA + NTx and CIA groups (Fig. 4B). The cortical BMD gradually increased in the sham group but gradually decreased in the NTx and CIA + NTx groups. It was significantly lower in the NTx and CIA + NTx groups than in the sham group at 4 and 8 weeks, and in the CIA+NTx group than in the CIA group at 4 weeks after the initial sensitization (Fig. 4C).

Discussion

Several studies have been reported on arthritis and periarticular bone loss in animal models of RA (Hanyu et al., 1999; Enokida et al., 2001; Hoshino et al., 2001; Yamasaki et al., 2001), but few on arthritis and paralysis. It has been shown that sciatic neurectomy causes bone loss in the lower limbs of the animal models (Okumura et al., 1987; Murakami et al., 1994; Iwamoto et al.,

2003). Okumura et al. (1987) have reported a reduction in the BMD of ovariectomized rats, which deteriorated after sciatic neurectomy. We assumed in the present study that periarticular bone loss deteriorated in CIA + NTx rats as well. To evaluate this hypothesis, we examined the effects of sciatic neurectomy on arthritis and the BMD in CIA and CIA+NTx rats.

Kozina et al. (1977) have reported the effects of peripheral nerve and spinal lesions on arthritis in adjuvant arthritis rats. They found that peripheral nerve and spinal lesions suppressed hind paw swelling and suggested that the effect was due to hind paw paralysis. In our study, sciatic neurectomy reduced hind paw swelling and ankle and subtalar joint destruction in CIA rats. Many reports have described that paralysis suppressed RA, osteoarthritis and arthritis and radiological joint destruction caused by gout in humans (Coste et al., 1935; Bland et al., 1968; Pattrick et al., 1984). Bland et al. (1968) and Pattrick et al. (1984) stated that the restriction of movement due to paralysis may reduce mechanical stress, resulting in the suppression of arthritis. In many cases of osteoarthritis and RA, arthritis is severer in the dominant hands than in the non-dominant hands, suggesting that exercise stress has a significant effect on the severity of arthritis.

The occurrence of periarticular bone loss in arthritis is suggested to be related to synovitis associated with arthritis (Suzuki et al., 1995) and bone marrow lesions in the peripheral bones (Fujimoto et al., 1992; Enokida et al., 2001). In immobilized tibia after sciatic neurectomy in mice, a temporary increase in bone resorption and a continuing decrease in bone formation caused rapid cancellous bone loss (Sakai A et al., 1996). We assumed that immobilization due to sciatic neurectomy might deteriorate cancellous bone loss in the CIA+NTx group; however, there was no significant difference in the degree of cancellous bone loss between the CIA and the CIA+NTx groups. The reason for this may be that arthritis was suppressed by sciatic neurectomy in the CIA+NTx group, which reduced the degree of synovitis due to arthritis.

Enokida et al. (2001) have reported that the decreased proximal tibial cortical BMD in adult CIA rats might be related to changes of the periosteal bone surface and the intracortical bone. Hayashida et al. (1993) have histologically examined the cortical bone adjacent to the affected joint in adjuvant arthritis rats, and reported that both the bone resorption and inflammatory cell infiltration were increased around the intracortical blood vessels, which was similar to histological findings of juxtaarticular osteoporosis in patients with RA. The immobilization-related decrease in the cortical BMD is considered to be associated with a disorder of periosteal modeling-dependent bone gain and an enhancement of endocortical and intracortical bone remodeling-dependent bone loss (Li et al., 1991; Jee et al., 1992; Maeda et al., 1993). Yonezu et al. (2004) have reported that sciatic neurectomy decreased mechanical stress on the bone around paralyzed muscles and reduced periosteal bone formation, thus causing the decrease in the cortical BMD. Since the cortical bone loss mechanism in CIA rats may be different from that linked to immobilization, it is speculated that the cortical bone loss in the CIA+NTx group was greater than in the CIA group.

In summary, the present study revealed that sciatic neurectomy reduced the severity of arthritis, but did not affect the cancellous bone loss in adult CIA rats. It is speculated that limitations of movement due to paralysis reduces exercise stress, which thus ultimately suppresses arthritis.

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References

1 Alenfeld FE, Diessel E, Brezger M, Sieper J, Felsenberg D, Braun J. Detailed analyses of periarticular osteoporosis in rheumatoid arthritis. Osteoporosis Int 2000;11:400–407.

2 Bland JH, Eddy WM. Hemiplegia and rheumatoid hemiarthritis. Arthritis Rheum 1968;11:72–80.

3 Coste F, Forestier J. Hemipligie et nodosites d' Heberden controlaterales. Bull Soc Med Hop Paris 1935;51:772–776.

4 Engelhardt G, Homma D, Schnitzler C. Meloxicam. A potent inhibitor of adjuvant arthritis in the Lewis rat. Inflamm Res 1995;44:548–555.

5 Enokida M, Yamasaki D, Okano T, Hagino H, Morio Y, Teshima R. Bone mass changes of tibial and vertebral bones in young and adult rats with collagen-induced arthritis. Bone 2001;28:87–93.

6 Fujimoto M, Hayashida K, Ochi T. Fluctuation of interleukin-1 and -6 activity in bone marrow serum in collagen-induced arthritis in rats. Biomed Res 1992;13:234–251.

7 Glick EN. Asymmetrical rheumatoid arthritis after poliomyelitis. Br Med J 1967;3:26–29.

8 Hanyu T, Chotanaphuti T, Arai K, Tanaka T, Takahashi HE. Histomorphometric assessment of bone changes in rats with type II collagen-induced arthritis. Bone 1999;24:485–490.

9 Hayashida K, Ochi T. Bone marrow changes osteoporosis in adjuvant-induced arthritis. Clin Calcium 1993;3:1059–1065.

10 Hooyman JR, Melton LJ 3rd, Nelson AM, O'Fallon WM, Riggs BL. Fractures after rheumatoid arthritis. A population-based study. Arthritis Rheum 1984;27:1353–1361.

11 Hoshino K, Hanyu T, Arai K, Takahashi HE. Mineral density and histomorphometric assessment of bone changes in the proximal tibia early after induction of type II collagen-induced arthritis in growing and mature rats. J Bone Miner Metab 2001;19:76–83.

12 Iwamoto J, Takeda T, Ichimura S, Sato Y, Yeh JK. Comparative effects of orchidectomy and sciatic neurectomy on cortical and cancellous bone in young growing rats. J Bone Miner Metab 2003;21:211–216.

13 Jee WS, Akamine T, Ke HZ, Li XJ, Tang LY, Zeng QQ. Prostaglandin E2 prevents disuse-induced cortical bone loss. Bone 1992;13:153–159.

14 Kozina W, Muller W. The influence of nervous system lesions on the course of adjuvant arthritis. Z Rheumatol 1977;36:390–403.

15 Li XJ, Jee WS. Adaptation of diaphyseal structure to aging and decreased mechanical loading in the adult rat: a densitometric and histomorphometric study. Anat Rec 1991;229:291–297.

16 Maeda H, Kimmel DB, Raab DM, Lane NE. Musculoskeletal recovery following hindlimb immobilization in adult female rats. Bone 1993;14:153–159.

17 McEwen C. Heberden's nodes: heredity in hypertrophic arthritis of the finger joints. JAMA 1940;115:2024.

18 Murakami H, Nakamura T, Tsurukami H, Abe M, Barbier A, Suzuki K. Effects of tiludronate on bone mass, structure, and turnover at the epiphyseal, primary, and secondary spongiosa in the proximal tibia of growing rats after sciatic neurectomy. J Bone Min Res 1994;9:1355–1364.

19 Okumura H, Yamamuro T, Kasai R, Hayashi T, Tada K, Nishii Y. Effect of 1 alpha-hydroxyvitamin D_3 on osteoporosis induced by immobilization combined with ovariectomy in rats. Bone 1987;8:351–355.

20 Pattrick M, Doherty M, Dieppe P. Unilateral exacerbation of rheumatoid arthritis by hemiparesis. Br J Rheumatol 1984;23:107–109.

21 Sakai A, Nakamura T, Tsurukami H, Okazaki R, Nishida S, Tanaka Y, et al. Bone marrow capacity for bone cells and trabecular bone turnover in immobilized tibia after sciatic neurectomy in mice. Bone 1996;18:479–486.

22 Suzuki Y, Tanihira M, Ichikawa Y, Osanai A, Nakagawa M, Ide M, et al. Periarticular osteopenia in adjuvant induced arthritis: role of interleukin-1 in decreased osteogenic and increased resorptive potential of bone marrow cells. Ann Rheum Dis 1995;54:484–490.

23 Takamoto S, Masuyama T, Nakajima M, Seikiya K, Kosaka H, Morimoto S, et al. Alterations of bone mineral density of the femurs in hemiplegia. Calcif Tissue Int 1995;56:259–262.

24 Trentham DE, Townes AS, Kang AH. Autoimmunity to type II collagen an experimental model of arthritis. J Exp Med 1977;146:857–868.

25 Weinreb M, Rodan GA, Thompson DD. Osteopenia in the immobilized rat hind limb is associated with increased bone resorption and decreased bone formation. Bone 1989;10:187–194.

26 Yamasaki D, Enokida M, Okano T, Hagino H, Teshima R. Effects of ovariectomy and estrogen replacement therapy on arthritis and bone mineral density in rats with collagen-induced arthritis. Bone 2001;28:634–640.

27 Yonezu H, Takata S, Shibata A. Effects of unilateral sciatic neurectomy on growing rat femur as assessd by peripheral quantitative computed tomography, Fourier transform infrared spectroscopy and bending test. J Med Invest 2004;51:96–102.

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