Disuse Osteoporosis

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Abstract: Reduction of mechanical stress on bone inhibits osteoblast-mediated bone formation and accelerates osteoclast-mediated bone resorption, and leads to what has been called disuse osteoporosis. Prolonged therapeutic bed rest, immobilization due to motor paralysis from injury of the central nervous system or peripheral nerves, application of cast to treat fractures, a common causes of disuse osteoporosis. Imaging diagnosis shows coarse trabecular pattern and thinning of cortical bones. Bone metabolism markers have been used to evaluate bone metabolism. From the viewpoint of bone metabolism, antiresorptive agents should be administered to inhibit bone resorption. Rehabilitation, including bed positioning, therapeutic exercise and electrical stimulation, should be prescribed to subject the atrophied bone to an appropriate level of mechanical stress. In spite of these aggressive and continuous treatments, most cases of disuse osteoporosis require a long time for bone to recover its bone mineral density and strength. Hence, we have to keep in mind that there are no treatments better than prophylaxis of disuse osteoporosis.

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INTRODUCTION

Disuse osteoporosis is defined as localized or generalized bone loss resulting from reduction of mechanical stress on bones. Low or loss of mechanical stress on bones induces acceleration of osteoclast-mediated bone resorption and inhibition of osteoblast-mediated bone formation leading to bone loss. Therapeutic bed rest, prolonged voluntary bed rest (1), localized immobilization due to paraplegia or paraparesis due to spinal cord injury (2), hemiplegia or hemiparesis due to stroke (3) or application of a cast to treat fractures (4) cause disuse osteoporosis.

The morphological characteristics of disuse osteoporosis are a decrease in bone mineral density (BMD) and thinning of cortical bone at the diaphysis, which result in a reduction of bone strength and an increase risk of fractures. It takes a long time to recover from disuse osteoporosis in spite of continuous and aggressive treatment involving medication and rehabilitation. Hence, we have to keep in mind that there are no treatments better than prophylaxis of disuse osteoporosis. This review refers to the mechanism, the diagnosis using imaging techniques and bone metabolism markers, and treatment and prophylaxis of disuse osteoporosis.

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Mechanism of disuse osteoporosis

Mechanical stress on bone is one of the determinants of bone morphology, BMD and bone strength. Therefore, disuse accelerates bone resorption, especially of cancellous bone, and consequently bone becomes atrophic and fragile. Osteocytes embedded in the bone matrix respond to mechanical load and changes of bone metabolism (5-7). The gap junction of the long processes of osteocytes plays an important role in transmitting mechanical load (8) through intracellular signal transmitters (cAMP, cGMP) (9)

and extracellular signal transmitters (PGE_2, IGF-I, IGF-II, TGF-β) (10) to induce bone formation by osteoblasts, inhibition of bone resorption by osteoclasts, or a combination of the two (Fig. 1).

Bones with a high proportion of cancellous bone are at the highest risk of disuse osteoporosis. The pattern of bone loss in different regions varies, and the difference may be ascribable to a site-specific cortical to trabecular bone ratio. Einhorn (11) showed that the relative content of trabecular bone varied among the different parts of the skeleton, and that the content of trabecular bone was 66-90% in the vertebrae, 50% in the hip (intertrochanteric region), 25% in the hip (femoral neck), 25% in the distal radius, 1% in the mid-radius, and 5% in the femoral shaft. As for bone metabolism, the trabecular bone is approximately eight times as active as cortical bone, because the surface of trabecular bone is larger than that of cortical bone, and its response to metabolic changes is faster (12). Recumbency for one week induced a 1% decrease of bone mineral content of the vertebral body (13). Based on this fact, changes resulting from low mechanical stress on bone are logically more prominent in trabecular bone than in cortical bone.

As for differences of bone metabolism during bed rest or under a microgravity environment, Shigematsu *et al*. (14) showed that under microgravity environment, there was a significant difference in disuse bone atrophy between weight-bearing bones and non-weight-bearing bones, and that under microgravity environment in the space, the BMD of the lumbar spine decreased , in contrast, the BMD of the skull increased. Moreover, 17 weeks of continuous bed rest induced a decrease of BMD of weight-bearing bones and an increase of BMD of non-weight-bearing bones, such as skull (15). The mechanisms by which bone mineral metabolism varies during bed rest and in a microgravity environment have not been clarified.

Assessment of disuse osteoporosis

Characteristic physical findings of disuse osteoporosis

Most cases of disuse osteoporosis of upper and lower extremities are associated with muscle atrophy and weakness of the muscles attached to the atrophied bone. If the mass of the skeletal muscle and muscle strength are diminished, mechanical stress on bone will be reduced, bone resorption and bone formation will be inhibited, resulting in bone atrophy, disuse osteoporosis. Therefore, assessment of muscle atrophy and muscle weakness allows us to predict the occurrence of disuse osteoporosis.

Circumference of upper arm (COUA), circumference of forearm (COFA), circumference of thigh (COT) and circumference of lower leg (COLL) are measured to assess muscle atrophy. More than 1 cm difference between the right side and left side in COUA, COFA, COT and COLL would indicate mus-

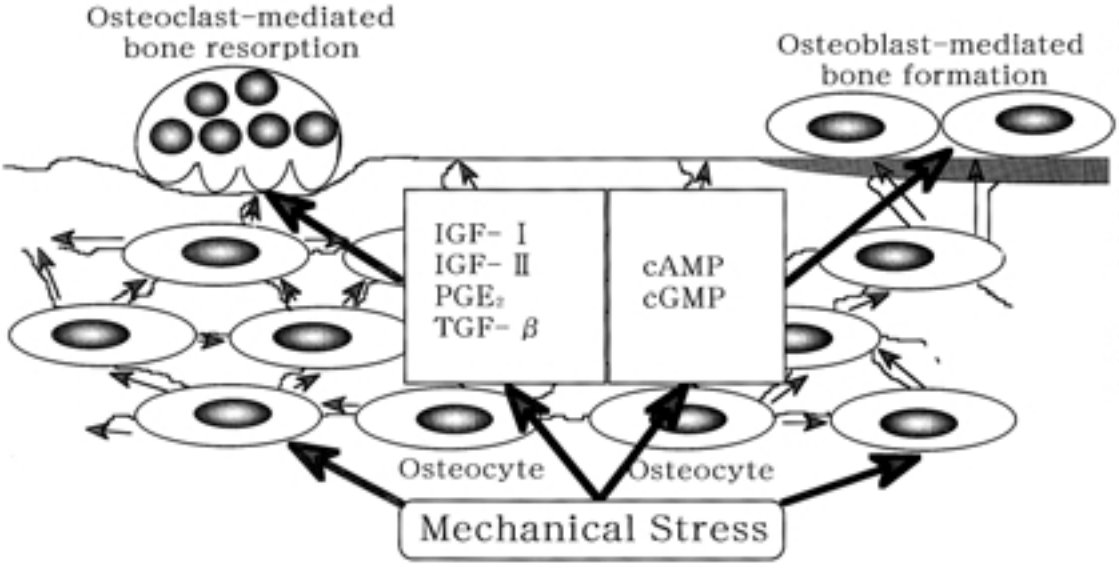

Fig. 1 Mechanism of transduction of mechanical stress to bone. The gap junction of the long processes of osteocytes plays an important role in transmission of mechanical stress through intracellular signal transmitters (cAMP, cGMP) and extracellular signal transmitters (PGE_2, IGF-I, IGF-II, TGF-β), inducing thereby bone formation by osteoblasts and bone resorption by osteoclasts, or both.

cle atrophy of those with a smaller circumference. Table 1 shows manual muscle testing. If muscle strength is significant different between the right side and left side, disuse osteoporosis of the side with lower muscle strength should be suspected.

Plain X-ray film

1. Tubular bone

A plain X-ray film reveals important features of disuse osteoporosis affecting tubular bones, thinning of cortices, increased radiolucency and rarefication of bone trabeculae. There are 4 patterns of bone resorption, subperiosteal, endosteal, intracortical and trabecular bone resorption (16) (Fig. 2). Subperiosteal bone resorption results from hyperparathyroidism.

Table 1. Grading system of manual muscle test using Lovett Method and Rehabilitation Treatment

Grade	Lovett Method	Rehabilitation Treatment
5/5	Normal (N)	Resistive exercise
4/5	Good (G)	Resistive exercise
3/5	Fair (F)	Active exercise
2/5	Poor (P)	Active assistive exercise
1/5	Trace (T)	Passive exercise Electrical stimulation EMG biofeedback
0/5	Zero (Z)	Passive exercise Electrical stimulation

Endosteal bone resorption is characteristic of senile osteoporosis. Our previous study showed that immobilization by sciatic neurectomy resulted in a decrease of the periosteal circumference of bone, whereas endosteal circumference did not change (17). This fact suggested that immobilization induce periosteal bone resorption by activating osteoclasts in the periosteum.

The Singh Index (18) was introduced to classify bone atrophy of the proximal end of the femur from Grade I to VI according to the degree of bone resorption.

This score is useful to predict femoral neck fracture in the patient with osteoporosis.

2. Spine

The radiographic manifestation of disuse osteoporosis of the vertebral body include increased radiolucency, framed appearance (picture framing), and stand out vertical striation of the vertebral body. The criteria of radiographic oseopenia was proposed by the Research Group on Osteoporosis from the Japanese Ministry of Health and Welfare ; this ranges from Grade I to III according to the resorption of the longitudinal trabeculae (Table 2) (19).

Dual energy X-ray absorptiometry

Dual energy X-ray absorptiometry (DXA) has been used to measure total body and regional BMD, and

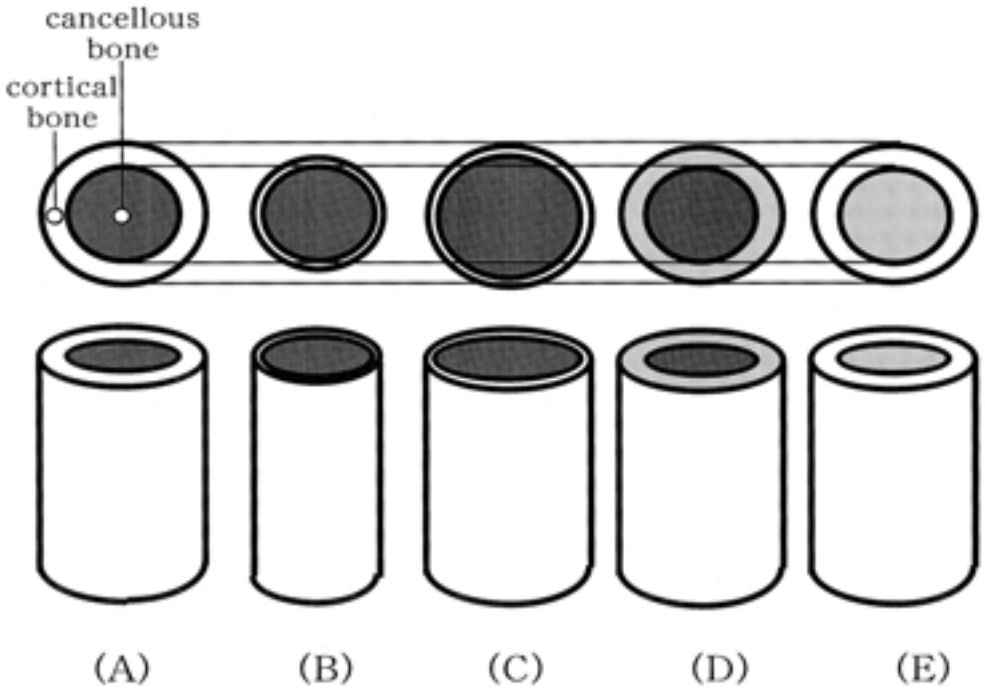

Fig. 2 Patterns of resorption of tubular bones.
(A) Normal, (B) Periosteal bone resorption, (C) Endosteal bone resorption, (D) Intracortical bone resorption, (E) Trabecular bone resorption.

Table 2. The criterion of radiographic osteopenia[19]

Grade	Radiographic appearance of the vertebral body
1	The longitudinal trabeculae are prominent
2	The longitudinal trabeculae are coarse
3	The longitudinal trabeculae are unclear

soft tissue composition. DXA has proved to be of diagnostic value in metabolic bone disease and has become a useful tool to measure total body BMD and soft tissue mass composition (20, 21). In previous studies dual photon absorptiometry (DPA) with ^{153}Gd was applied to measure total body BMD and regional BMD (17). However, the coefficient of variation (CV) for DXA for total body BMD and soft tissue mass was 0.5% -1.0% (21), whereas the CV for DPA for total body BMD was 1.0% -2.0% (22).

1. Brachial plexus injury

We measured BMD and soft tissue composition in a patient with left sided brachial plexus injury using DXA. The function of the left arm was severely impaired. The results showed that bone mineral content, BMD and lean mass of the injured arm were lower than those of the intact arm, whereas fat mass, % fat of the injured arm are higher than those of the intact arm (Table 3).

2. Atraumatic vertebral fracture

We studied the characteristics of regional BMD and soft tissue composition in patients with atraumatic vertebral fractures using DXA. Regional BMD and soft tissue mass were measured by DXA. Total body BMD, BMDs of the lumbar spine, thoracic spine, pelvis of the fracture group were significantly lower than those of the non-fracture group ($P<0.001$). Fat mass and lean mass of total body and respective regions did not differ significantly between the two groups. The results showed that the BMD of weight bearing bones, except for bones of legs of the fracture group, was significantly lower than that of the non-fracture group (23). The results suggest that immobilization resulting from atraumatic vertebral fracture accelerates bone resorption of weight bearing bones.

3. Osteoarthritis

Osteoarthritis (OA) is the most common disease of joints. Clinical manifestations of OA are pain, swelling and decreased range of motion. The most frequently affected joint is the knee joint. As OA worsens, the gait of the patient is disturbed and this may cause loss of mechanical stress on the bones of the legs with involved knee joint, which will in turn lead to disuse osteoporosis.

We compared the BMD and soft tissue composition of legs between patients with OA of the knee and controls matched for gender, age, body mass index, and mean BMD of the 2nd to 4th lumbar vertebrae. The results showed that BMD, bone mineral content and lean mass of leg with OA of the knee were lower than those of the leg of controls. These findings suggest that immobilization resulting from pain in the knee leads to low mechanical stress on the bones of the leg with OA of knee, resulting in disuse osteoporosis of that leg (unpublished data).

Computed tomography and biophysic evaluation

Yonezu *et al*. (17) studied the effects of immobilization induced by sciatic neurectomy on the femur of rats using peripheral quantitative computed tomography (pQCT) and Fourier transform infrared spectroscopy (FTIR). Cortical bone mineral content, bone area , and the periosteal circumference of the femoral shaft measured by pQCT, were significantly smaller than those of the control, whereas the cortical BMD did not differ significantly. Cancellous bone mineral

Table 3. Bone mineral content, bone mineral density, lean mass, fat mass, fat mass+bone mineral content, total weight, and %fat of the arm in the injured side and the intact side, of a patient with brachial plexus injury, as determined by dual energy X-ray absorptiometry.

	Injured side	Intact side	injured/Intact
Bone mineral content (g)	78.6	133.0	0.59
Mone mineral density (cm^2)	0.555	0.719	0.77
Lean mass (g)	1,431.5	2,472.5	0.58
Fat mass (g)	632.3	417.1	1.52
Lean mass+bone mineral content (g)	1,510.1	2,605.5	0.58
Total weight (g)	2,142.5	3,022.6	0.71
%Fat (%)	29.5	13.8	2.14

content and BMD at the metaphysis of the femur on the neurectomized side decreased significantly compared with the control. These facts suggest that immobilization induced by neurectomy inhibits periosteal bone formation or accelerates bone resorption.

Quantitative assessment of macro-and microstructural features may contribute to a more accurate estimation of bone strength. The methods available for quantitatively assessing the macrostructure include (besides conventional radiographs) quantitative computed tomography and volumetric quantitative computed tomography.

To determine bone strength, quantitative analysis of the trabecular microstructure by micro-computed tomography (muCT) and high-field proton nuclear magnetic resonance (NMR) is more important than that of trabecular macrostructure of bone by conventional radiography.

High-field proton NMR is applied to analyze trabecular microstructure quantitatively, which obtain high contrast between the marrow proton signal and the bone as three-dimensional volumetric proton NMR microimaging (24, 25). muCT is also a useful tool to analyze the microstructure of bones. muCT is principally applicable *in vitro* (26).

Markers of bone metabolism

1. Bed rest and microgravity environment

Bed rest induces disability of the central nervous system, digestive system, respiratory system and circulation system as well as of bones, leading to disuse syndrome. Therefore, disuse osteoporosis is one of the symptoms of disuse syndrome. Bed rest for 12 weeks decreased BMD of the femoral neck. Among bone metabolism markers, serum parathyroid hormone (PTH) and 1,25-dihydroxyvitamin D decreased within respective normal levels, whereas serum osteocalcin (OC) and serum bone specific alkaline phosphatase (BAP) did not change during bed rest. As for markers of bone resorption, urinary hydroxyproline (HP), urinary deoxypyridinoline (D-Pyr) and urinary type I collagen cross-linked N-telopeptides (NTx) increased with significant difference, however, after ambulation, these markers tended to decrease with time (27).

In order to clarify the effects of microgravity on bone mineral metabolism, the markers of bone formation and bone resorption were assessed during 6 degrees head-down tilt bed rest for 7 days. Serum OC shows the earliest response of bone to head-down tilt bed rest. Serum OC increased and remained elevated during bed rest, however, within 5 days of reambulation, serum OC returned to pre-bed rest values. Urinary Pyr, D-Pyr and HP increased promptly after bed rest, which were paralleled by tartrate-resistant acid phosphotase (TRAP) with significant increases. Urinary HP, urinary Pyr and serum TRAP remained high for 2 weeks after reambulation (28). Base on these facts, osteoclast-mediated bone resorption during head-down tilt bed rest was assumed to remain higher than that during no head-down tilt bed rest. Furthermore, urinary Pyr and D-Pyr increased 40-50% of their respective pre-bed rest levels ; in contrast, in a microgravity environment in the space, these values increased twofold their respective values before space flight (29). There is a marked difference in the activity of osteoclasts between microgravity and the 1G gravity environment on the earth.

2. Ischemic Cerebral Vascular Disease (Stroke)

The BMD of the upper and lower extremities on the affected side decreases in patients with hemiplegia (30, 31), and results in disuse osteoporosis. In the acute phase of stroke, serum Pyr, serum procollagen type I C-terminal telopeptide (ICTP) and serum beta2-microglobulin increased (32). This fact suggests that serum beta2-microglobulin may be a good indicator of bone resorption in a patient with stroke. In the chronic phase of stroke, bed rest for 30 to 180 days induced an increase in urinary Pyr, urinary D-Pyr and serum ICTP. In contrast, serum BAP and serum carboxyterminal propeptide of human type I procollagen (PICP) remained at normal levels (33). This result indicates that prolonged bed rest to treat stroke affects bone resorption, not bone formation

A study done to clarify the effects of etidronate on bone metabolism in patients with hemiplegia showed that etidronate increased serum $1,25(OH)_2D$, serum PTH and serum OC, whereas it decreased serum ICTP and serum ionized Ca. These results suggest that etidronate prevents bone loss by increasing serum $1,25(OH)_2D$ and decreasing (31).

3. Spinal cord injury

One of the complications of spinal cord injury is disuse osteoporosis due to increased bone turnover. A six-month longitudinal follow-up of bone metabolism markers showed that urinary Pyr, urinary D-Pyr and urinary NTx increased and reached to their respective maximal levels by 10 to 16 weeks after injury, whereas serum OC and serum BAP increased only a little (34). Qadriplegia and paraplegia accelerates bone resorption compared with bone formation, increasing the risk of fractures. In the chron-

ic phase of spinal cord injury, after mean time period of 19 years from spinal cord injury, serum PICP, serum BAP, serum OC, serum ICTP and urinary HP showed no signs of acceleration of bone formation nor of bone resorption (35). Bone metabolism markers in the chronic phase do not seem to be useful to assess bone metabolism. In the acute phase of spinal cord injury, intravenous injection of pamidronate inhibited the increase of bone resorption markers and the consequent decrease of BMD, suggesting it is effective to treat disuse osteoporosis (36).

4. Autoimmune disease

Rheumatoid arthritis (RA) is a chronic polyarthritis associated with gradual progressive development of joint pain, swelling and destruction. RA is one of the causes of secondary osteoporosis. If steroidal hormones are administered to RA patients to alleviate a pain of the involved joints, bone resorption will be accelerated and the risk of fractures will increase (37, 38). In the early stage of RA, bone atrophy is obscured around the involved joints ; this is called juxta-articular osteoporosis. In progressive RA, bone atrophy tends to extend to other joints leading to become generalized osteoporosis.

Kameyama *et al*. (39) showed that the mean level of urinary Pyr and urinary D-Pyr were significantly higher in RA patients than in healthy controls ; in addition, the Pyr/D-Pyr ratio in the RA patients was higher than that in normal control. Interestingly, urinary Pyr increased as the Lansbury's joint score increased. Urinary Pyr may serve as an indicator of the activitity of RA, because urinary Pyr includes a lot of collagen type II. The decrease in lumbar BMD significantly correlated with bone serum OC and serum ICTP. In addition, the decrease of femoral neck BMD correlated with only serum OC (40). Based on these facts, measurement of serum OC and serum ICTP may predict changes in BMD in the lumbar spine and femoral neck .

Furumitsu *et al*. (41) measured synovial fluid (SF) Pyr and SF D-Pyr to elucidate the major source of pyridinium crosslinks in RA, and showed that the levels of SF D-Pyr were significantly higher in patients with RA than in patients with osteoarthritis, and that the levels of both SF Pyr and SF D-Pyr showed a significantly positive correlation with levels of SF interleukin 1beta or SF interleukin 6 in patients with RA. As stated in this study, the levels of serum Pyr and serum D-Pyr were significantly higher in patients with RA than in healthy controls. The authors suggested that the increase of serum Pyr in RA would derive mostly from involved joints and that an increase of serum D-Pyr in RA may indicate systemic bone resorption.

Ankylosing spondylitis (AS) is also causative of disuse osteoporosis. AS is an inflammatory arthritis of the spines, sacroiliac joints, hip joints and shoulder joints. Involvement of peripheral joints is less common in AS. With progression of ankylosis of joints, the activity of the patients decreases inducing disuse bone atrophy and generalized osteoporosis. Yilmaz *et al*. (42) showed that urinary Pyr and urinary D-Pyr were higher in AS patients than in healthy controls. In AS, osteoclasts are activated to resorb bone, whereas the activity of osteoblasts remains normal .

5. Fracture

During treatment of fractures, disuse osteoporosis is inevitable, because for conservative and operative treatment of fractures, a cast is applied to immobilize the bones and joint and , thereby, stabilize and fix the fracture.

In patients with hip fracture, serum OC at the time of admission was 20% lower in the fractured women than in healthy controls. In contrast, urinary Pyr and urinary D-Pyr were significantly higher in the fractured women than in healthy controls. Within 18 hours after hip fracture, serum OC did not change, however, its value decreased with time until the 3rd postoperative day (43).

Ohnishi *et al*. (44) studied changes of bone metabolism markers during healing of hip fracture in patients with osteoporosis. The authors showed that urinary Pyr, urinary D-Pyr and urinary type I collagen cross-linked C-telopeptide (CTx) started to rise from 1 week after operation, but they returned to the respective initial values by week 24 after operation. In contrast, serum OC increased week 8, and was still high at week 24. These facts suggested that in the early stage of hip fracture, bone resorption is facilitated by acute osteonecrosis and bed rest, and after that, bone formation is accelerated by callus formation or increase in mechanical stress on bone.

Bone metabolism markers have become promising predictors of fractures. Women with both low femoral BMD and high levels of bone resorption markers (urinary CTx and urinary D-Pyr) are at a greater risk of hip fractures. The odds ratio than women with only low BMD or high level of bone resorption markers were 4.8 and 4.1, respectively (45). Moreover, Vergnaud *et al*. (46) showed that high level of circulating undercarboxylated OC were associated with a high risk of fracture, independently

of femoral neck BMD, in elderly women.

Treatment and prophylaxis

Rehabilitation

1. Bed positioning

Prolonged bed rest produces profound changes in muscles and bones, particularly of the lower limbs, leading to disuse osteoporosis and decubiti. The significant physiological changes induced by weightlessness are cephalic fluid shift, which lead to facial edema, nasal congestion, increase of urinary flow, decrease in creatinine excretion, decrease in lower leg volume, and disuse atrophy of bone and skeletal muscles of upper and lower extremities (47). To avoid cephalic fluid shift, the patients should be maintained in a head-up position on the bed, except while sleeping. To prevent decubiti during bed rest, turning the patients with spinal cord injury and stroke every two hours is recommended (48).

2. Therapeutic exercise

The main cause of disuse osteoporosis is loss or reduction of mechanical stress on bones, which produces compressive and vertical loading on weight-bearing bones, spine, pelvis and leg bones. Hence, to produce mechanical stress, early weight bearing ambulation, with or without crutches, is recommended. Further more, disuse osteoporosis is always associated with muscle atrophy and muscle weakness. Therefore, therapeutic exercise is effective to increase not only muscle volume but also BMD. Furthermore, therapeutic exercise increases or maintain the mobility of joints and soft tissues, which results in an increase of the microcirculation in skeletal muscles. An adequate medical evaluation is essential before therapeutical exercise to prevent complications. Therapeutic exercise is prescribed according to muscle strength evaluated by manual muscle test.

In RA treatment, therapeutic exercise should be performed prudently to avoid injury of joint cartilage, because repeated and stressful joint motion will contribute to further deteriorate the inflammation of joints. Motion of inflammatory joints should be kept to a minimum during therapeutic exercise. In order to strengthen bilateral biceps brachialis muscles, isometric exercises are prescribed using a beach ball resistance. If there are no cardiovascular considerations, a 6-second maximum contraction, twice daily, can be prescribed.

3. Electrical therapy

We stress that disuse osteoporosis is always associated with atrophy and weakness of the skeletal muscles attached to the bone . Therefore, if muscle strength and muscle mass can be recovered by electrical therapy, electrical stimulation, disuse osteoporosis must improve. As shown in table, electrical stimulation should be applied to patients with poor (1/5) or zero (0/5) muscle strength. Passive muscle contraction by electrical stimulation allows atrophied bone to recover its BMD or BMC by accelerating osteoblast-mediated bone formation or inhibiting osteoclast-mediated bone resorption.

The most important condition of electrical stimulation is the stimulation frequency. For electrical stimulation, we should select a stimulation frequency at which the patient does not feel discomfort or pain during stimulation. Furthermore, we have to know the difference of energy metabolism of skeletal muscles between high stimulation and low stimulation frequency. A recent study (50) showed that during muscle contraction induced by electrical stimulation, low frequency stimulation at 30 Hz was useful to maintain a low energy level and intracellular pH, whereas the energy level and intracellular pH during high frequency stimulation at 100 Hz recovered rapidly to values before stimulation, after they dropped to a minimum. Further studies are required to clarify the therapeutic effects on muscle mass and muscle strength using electrical stimulation. In the near future, we will select the stimulation frequency by considering and understanding the difference of therapeutic effect on skeletal muscles.

4. Pharmacologic treatments

During prolonged bed rest, the main cause of disuse osteoporosis is loss or reduction of mechanical stress on bones to accelerate bone resorption. From the viewpoint of the mechanism of disuse osteoporosis, pharmacologic intervention using antiresorptive agents (i.e. bisphosphonate (51), calcitonin (52), vitamin K_2 (53)) are recommended.

Bisphosphonates strongly inhibit bone resorption, and have been administered to treat primary osteoporosis and secondary osteoporosis, including disuse osteoporosis, all over the world. Bisphosphonates contain two phosphonate groups attached to a single carbon atom, forming a "P-C-P" structure. The 3rd generation bisphosphonates are 10,000 times more active than the 1st generation bisphosphonate etidronate (54). Kedlaya *et al*. (55) showed that a single dose of pamidronate effectively improved hypercalcemia

induced by immobilization in patients with paraplegia. An experimental study, on the other hand, showed that clodronate increased bone ash weight, maximal torque capacity, maximal angle capacity and rigidity of the bone atrophied by immobilization (56). It is certain that bisphosphonates are useful to treat disuse osteoporosis and hypercalcemia induced by immobilization. Markers of bone resorption are good indices of the effects of the bisphosphonates on disuse osteoporosis.

At present, bisphosphonates are being administered to treat disuse osteoporosis in patients with RA. Cantatore *et al*. (57) studied the effects of oral alendronate on bone metabolism and parameters of osteoclastic activity in early RA, and showed that alendronate decreased interleukin-1, interleukin-6, tumor necrosis factor-alpha, and beta2 microglobulin associated with a decrease of erythrocyte sedimentation rate and C-reactive protein. These results suggest that alendronate may have an antiarthritic effect. Alendronate may become the drug of choice to treat RA and RA-induced generalized osteoporosis as well as disuse osteoporosis.

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