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Original article

Changes in bone mineral density in unconscious immobile stroke patients from the acute to chronic phases of brain diseases

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ABSTRACT

Objectives: Decreased bone mineral density (BMD) is observed in immobile stroke patients. But it is not clarified yet how rapidly BMD reduction occurs or what the most influencing factor to BMD loss is.
Methods: BMDs in the lumbar vertebrae and the proximal femur of the paralyzed side were measured in 100 immobile stroke patients at 1 week (0 month), 1 month, and 2 months after admission. The levels of serum calcium, phosphorous, 25-hydroxyvitamin D, and urine cross-linked N-telopeptide of type I collagen (NTx) were also measured.
Results: The average age of patients was 75.0 ± 11.4 years (31–94 years). No BMD reduction was identified in the lumbar vertebrae in 2 months; however, BMD in the femur significantly decreased in 2 months in female patients ($P < 0.05$). Serum calcium and phosphorous levels remained within the normal range during hospitalization, and 25-hydroxyvitamin D value rose in 2 months. Urine NTx significantly increased in both males and females in 2 months (male: $P < 0.05$, female: $P < 0.01$).
Conclusions: While there was no significant change in lumbar spine BMD in the 2 month period of immobilization after stroke, BMD in the proximal femur showed a significant reduction, particularly in women. The differential loss of BMD in the 2 regions of interest could possibly be due to the physical forces acting on different body parts during mobilization and nutritional factors. More studies are needed with larger study samples and prolonged follow-up to check the accuracy of these observations.

1. Introduction

With the aging society, the number of older adults who became bedridden due to cerebral stroke is increasing. Bone mineral loss was reported to start within a few days after the onset of cerebral stroke causing severe hemiparesis and to progress within a few months [1,2]. This skeletal fragility increases the risk of fractures in the patients leading to increased morbidity and mortality [3,4]. Immobile status is one of major factors to cause bone mineral density (BMD) reduction, and some articles mentioned that nutrition plays an important role in bone health, and calcium and vitamin D deficiencies are the main risk factors for osteoporosis in severe stroke patients [5,6]. But few reports clearly mentioned what the most influencing factor to cause rapid BMD loss is and how to delay the loss. Dietary supplementation and sunlight exposure of the face and hands are necessary for these patients as treatments for loss of bone minerals [7]. However, most stroke centers prioritize treatments to cerebral infarction for severe stroke patients, and seldom provide sunlight exposure on an acute phase, although bedside rehabilitation of passive exercise is initiated in a few days of admission. This study tries to clarify how rapidly osteoporosis progresses and how to protect the immobile patients from rapid BMD loss, following them from the acute to chronic phase of stroke.

The Teikyo University Ethics Committee approved the study and its protocols (*Teirin 16-020*), and the Teikyo University Conflicts of Interest Management Committee concluded that the study had no conflicts of interest (*TUIC-COI 16–0410*). The study details were explained to the family of each patient, and informed consent was obtained in written form with a signature.

2. Methods

2.1. Patients

The inclusion criteria were: 1) patients with no motor dysfunction before onset of stroke; 2) patients who fell to

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prolonged disturbance of consciousness; 3) patients who became immobile because of strong motor weakness; and 4) patients who had experienced the indicated conditions for at least 2 months. The exclusion criteria were: 1) patients who were hemiparetic before admission because of previous cerebral diseases; 2) patients who had been receiving steroids or anti-osteoporosis agents; and 3) patients who regained their consciousness and motor functions within 2 months. Bedside rehabilitation was started on day 2 after admission.

2.2. Nutrition

For the first 2 days after admission, 30 mL/kg of supplemental fluids with 15 kcal/kg was given to the patients. From day 3 after admission, 25 kcal/kg parenteral nutrition with 30 mL/kg water intake was initiated. From day 7, enteral nutrition was started with tapering of parenteral nutrition while maintaining 25 kcal/kg. During tube feeding, the patient was maintained in a sitting position at 60° and transferred to a wheelchair if possible. After tube feeding was completed, the sitting position was maintained for >1 h hour.

2.3. Measurement of BMD

BMD measurements were performed by dual-energy X-ray absorptiometry with a QDR Series System (HOLOGIC Japan, Tokyo, Japan) as described in other papers [8–11]. Two points were targeted for BMD measurements, the lumbar vertebrae (L2–L4) [12–14] and the proximal femur on the paralyzed side. These points were selected by reference to a report mentioning that bone loss typically takes place on the paretic side after stroke and such patients have a > 7-fold increase in fracture risk mainly at the hip [3,15]. The BMD measurements were performed 3 times during hospitalization; at the acute phase (within 7 days defined as 0 month), at 1, and at 2 months after disease onset. Young adult mean (YAM) of BMD was used for evaluation of osteoporosis. In the Japanese guideline for osteoporosis, YAM < 80% is defined as osteoporosis, and nearly equivalent to −1.5 standard deviation (SD) in an internationally used T-score for YAM of BMD [16]. The World Health Organization definition of osteoporosis in post-menopausal women states that a T-score of YAM −2.5 SD or below is necessary [17], which is identical to 70% or less of YAM in Japan [16].

2.4. Measurements of calcium, phosphorous, 25-hydroxy-vitamin D (25-OH vitamin D), and cross-linked N-telopeptide of type I collagen (NTx) levels

On the day of BMD measurement, serum calcium, phosphorous, 25-OH vitamin D, and serum and urine NTx levels were investigated. NTx is one of elements released during bone resorption, which shows a significant correlation with BMD, and NTx is considered the most clinically useful marker of bone resorption currently available [18,19]. NTx measurements in serum and urine were requested to Bio Medical Laboratories (BML) Incorporation (Tokyo, Japan). Enzyme immunoassay (EIA) was used for serum NTx measurement, and chemiluminescence enzyme immunoassay (CLEIA) was applied for urine NTx analysis. Urine NTx has been used for biomarker of bone resorption. Recent studies mentioned that serum NTx is less variable than urine NTx; however, it has not been concluded that serum NTx measurement is superior to urinary NTx measurement [20]. Therefore, NTx values in both urine and serum were measured in this study. The urine NTx level was corrected by the urine creatinine level.

2.5. Statistical analysis

Excel 2010 software (Microsoft, Redmond, WA, USA) was used to calculate the mean and standard deviation (SD). Student's *t*test was applied for comparisons of mean values between 2 groups and repeated measures ANOVA was applied for comparisons of mean values in 3 different points of time. Values of $P < 0.05$ were considered to indicate statistical significance. Correlation between 2 groups was evaluated by Pearson's correlation coefficient (r). $|r| < 0.02$: no correlation, $0.2 \leq |r| < 0.4$ weak correlation, $0.4 \leq |r| < 0.7$: moderate correlation, $0.7 \leq |r|$: strong correlation.

3. Results

3.1. Epidemiology

This analysis included 100 patients, comprising 59 males and 41 females. The mean age of all patients was 75.0 ± 11.4 years, with males 73.1 ± 13.5 (range: 31–92) years and females 77.8 ± 8.3 (range: 57–94) years. All female patients were post-menopausal women. There was no significant difference in age between males and females. The causes of immobility were brain ischemia in 60 patients, intracerebral hemorrhage in 31, and subarachnoid hemorrhage in 9.

3.2. Alterations in lumbar and femoral BMD (Fig. 1A and B)

On admission, BMD in males was 0.87 ± 0.15 g/cm^2 in lumbar and 0.71 ± 0.09 g/cm^2 in femur (both values: YAM > 80%), and those in females was 0.70 ± 0.09 g/cm^2 in lumbar and 0.56 ± 0.06 g/cm^2 in femur (both values: 70% < YAM < 80%). BMD values in females met the Japanese criteria for osteoporosis in both the lumbar and femur. BMD in L2-L4 slightly increased from 0 to 2 months in both males and females, and BMD in lumbar increased to 0.90 ± 0.17 g/cm^2 (YAM > 80%) in males and 0.74 ± 0.12 g/cm^2 (70% < YAM<80%) in females after 2 months, respectively, but there were no significant differences compared with those at 0 months. Conversely, BMD in femoral bone decreased gradually as the bed-lying period became longer in both males and females. BMD in femur decreased to 0.66 ± 0.08 g/cm^2 (70% < YAM < 80%) in males, but this value was not significantly different from that on admission. In female, BMD in femur decreased to 0.49 ± 0.05 g/cm^2 (YAM < 70%) showing significant reduction (0 months vs 2 months: $P < 0.05$) and the value met the international criteria of osteoporosis.

3.3. Changes in serum calcium and phosphorus (Fig. 2A and B)

Serum calcium mildly increased during the hospitalization within the normal range (8.6–10.2 mg/dL), but there was no significant difference of the value between on admission and in 2 months. Serum phosphorous increased gradually as the days of admission progressed and was significantly higher at 2 months compared with that on admission (0 months vs 2 months, $P < 0.05$) without exceeding the normal range (2.5–4.6 mg/dL). There were no gender differences in serum calcium and phosphorous levels.

3.4. Changes in serum 25-OH vitamin D (Fig. 3)

For healthy bone, serum 25-OH vitamin D of ≥30 ng/mL is internationally endorsed, although ≥ 20 ng/mL may be sufficient to prevent nutritional rickets or osteomalacia [21]. In our system, the lower limit of 25-OH vitamin D was 20 ng/mL, and thus 25-OH vitamin D deficiency was defined as < 20 ng/mL. Most of the patients showed 25-OH vitamin D of < 20 ng/mL on admission. Although the patients stayed in the ward for 2 months, serum 25-OH vitamin D increased over time in both males and females. In

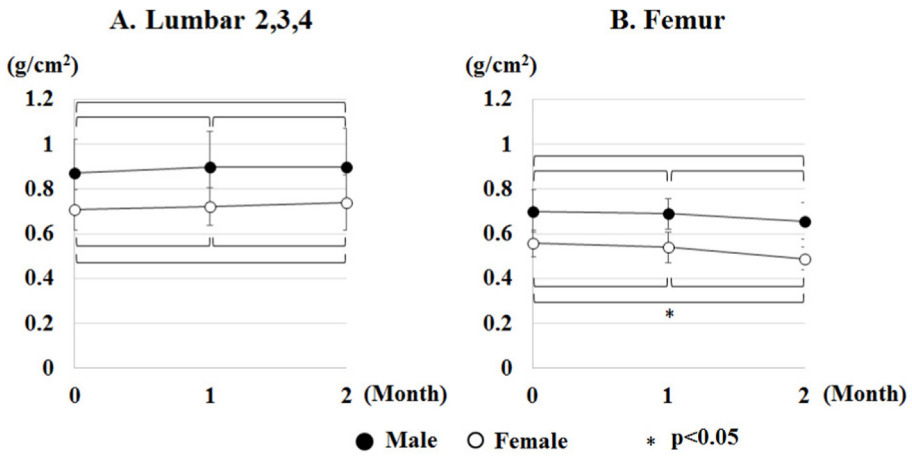

Fig. 1. Changes in BMD of the lumbar vertebrae and femoral bone. On admission, BMD was significantly lower in females than males in both the lumbar vertebrae and femoral bone ($P < 0.05$). (A) Lumbar BMD gradually increased in both males and females, but there were no significant differences among 0, 1, and 2 months (0 month vs 1 month, $P > 0.05$; 1 month vs 2 months, $P > 0.05$; 0 month vs 2 months, $P > 0.05$). (B) On the contrary, femoral BMD gradually decreased in both males and females. In males, there were no significant differences among 0, 1, and 2 months (0 month vs 1 month, $P > 0.05$; 1 month vs 2 months, $P > 0.05$; 0 month vs 2 months, $P < 0.05$). However, in females, BMD at 2 months was significantly lower than that on admission (0 month vs 1 month, $P > 0.05$; 1 month vs 2 months, $P > 0.05$; 0 month vs 2 months, $*P < 0.05$).

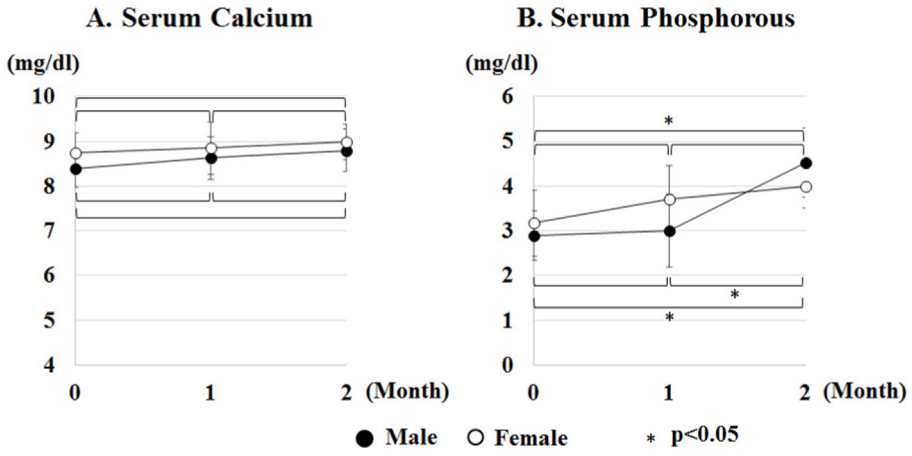

Fig. 2. Changes in serum calcium and phosphorus. The normal range of serum calcium is 8.6–10.2 mg/dl and that of serum phosphorus is 2 limit compared with that on admission. 5–4.6 mg/mL. (A) Serum calcium was constant at the lower normal limit compared with that on admission (0 month vs 1 month, $P > 0.05$; 1 month vs. 2 months, $P > 0.05$; 0 month vs. 2 months, $P > 0.05$). (B) Serum phosphorous increased gradually, and was significantly higher at 2 months than that on admission in both males (0 month vs 1 month, $P > 0.05$; 1 month vs 2 months, $*P < 0.05$; 0 month vs 2 months, $*P < 0.05$) and females (0 month vs. 1 month, $P > 0.05$; 1 month vs 2 months, $P > 0.05$; 0 month vs 2 months, $*P < 0.05$) without exceeding the normal range.

males, mean serum 25-OH vitamin D reached 20 ng/mL after 2 months, but there were no significant differences among 0, 1, and 2 months. In females, serum 25-OH vitamin D increased gradually and a significant increase was recognized at 2 months compared with that on admission (0 months vs 2 months, $P < 0.05$), although the level at 2 months did not reach 20 ng/mL. Serum 25-OH vitamin D was constantly higher in males than in females, and the level was significantly lower in females ($P < 0.05$) on admission. However, the difference became insignificant at 1 and 2 months.

3.5. Changes in NTx (A and B)

The changes in serum and urine NTx are shown in Fig. 4A and B, respectively. The normal ranges of serum NTx are 9.5–17.7 nM BCE/L in males and 10.7–24.0 nM BCE/L in post-menopausal females, while those urine NTx are between 13.0 and 66.2 nM BCE/mM•Cr in males and 14.3–89.0 nM BCE/mM•Cr in post-menopausal females.

In our results, serum NTx was constantly higher than the upper normal limit from admission to 2 months in both males and females. In males, the level fluctuated at 0, 1, and 2 months without significant differences. In females, serum NTx increased as the days of admission progressed, but the increase at 2 months was not significant.

Urine NTx on admission was slightly higher than the upper normal limit in males and within the normal range in females. The level increased remarkably and reached more than twice the upper normal limit at 2 months in both males and females (Fig. 4B). In males, the level at 2 months was significantly higher than that on admission (0 month vs 2 months, $P < 0.05$). In females, the level increased more rapidly and was significantly higher at 1 month and at 2 months than that on admission (0 months vs 1 month, $P < 0.05$; 0 months vs 2 months, $P < 0.01$).

3.6. Correlation between BMD reduction and urine NTx increase (Figs. 5A and 4B)

The difference of BMD values in femoral bone between 0 and 2 months was compared with difference of urine NTx values between 0 and 2 months to identify whether there is correlation between BMD loss and urine NTx increase. In both males and females, urine

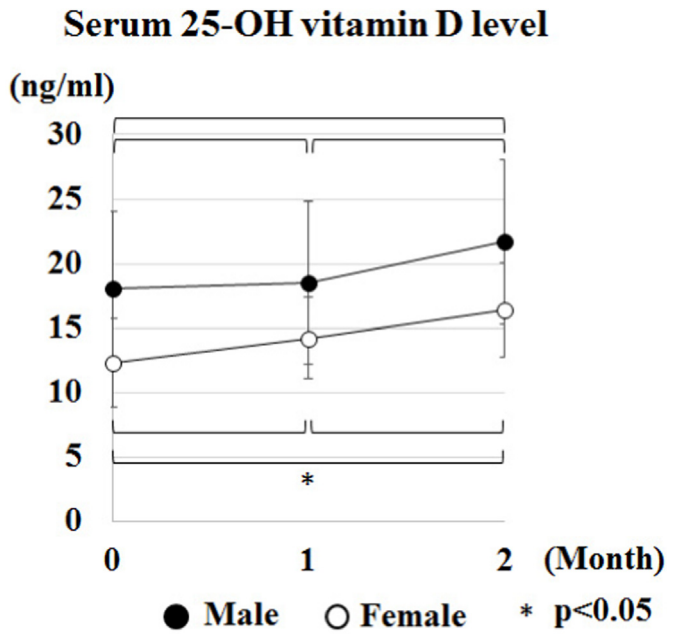

Fig. 3. Changes in serum 25-OH vitamin D. The lower normal limit of serum 25-OH vitamin D is 20 ng/mL, although maintenance of ≥ 30 ng/mL is encouraged for healthy bone. In both males and females, 25-OH vitamin D was lower than the lower normal limit. And particularly in female, the value is significantly lower than in male on admission ($P < 0.05$). However, the concentration gradually increased during admission. In males, there were no significant differences among 0, 1, and 2 months (0 month vs 1 month, $P > 0.05$; 1 month vs 2 months, $P > 0.05$; 0 month vs 2 months, $P > 0.05$), but the level reached 20 ng/mL at 2 months. In females, serum 25-OH vitamin D was significantly higher at 2 months than that on admission (0 month vs 1 month, $P > 0.05$; 1 month vs 2 months, $P > 0.05$; 0 month vs 2 months, $^*P < 0.05$), although the concentration did not reach the lower normal limit.

NTx level rose as the BMD reduced with moderate negative correlation. (male: $r = -0.613$, female: $r = -0.652$).

4. Discussion

BMD loss inevitably occurs in stroke patients with hemiparesis [1–3,15,22–28]. Poor nutritional condition, reduced sunlight exposure, and immobilization are the main factors causing BMD loss [5–7]. Nutrition plays an important role in bone metabolism, and calcium and vitamin D are essential for bone health [5,6]. Older adults who live alone or elder couples tend to be in a state of poor nutrition due to a lack of enough food intake and an unbalanced diet [29–32]. In our series, on admission, serum calcium was close to the lower normal limit (Fig. 2A) and serum 25-OH vitamin D was lower than the lower normal limit in most patients (Fig. 3). The latter finding suggests that vitamin D deficiency is common in elders with a risk of preclinical osteoporosis or osteomalacia. Serum vitamin D steadily increased with enteral nutrition in both males and females in our cases (Fig. 3). This result suggests that enteral nutrition can provide sufficient and well-balanced nutrition and appropriate water intake to unconscious patients. Some papers have described that vitamin D is reduced after stroke because of reduced sunlight exposure [33–36]. In this study, it is not clear that additional sunlight exposure is necessary or not to maintain the normal vitamin D level in immobile patients, because serum 25-OH vitamin D value increased steadily in our patients who stayed in the ward during hospitalization.

Our results strongly imply that immobilization affects the progression of BMD loss in bedridden patients, and that weight loading and physical stimulation to the bone must be an essential factor. In both males and females, the lumbar BMD was increased at 2 months after patients became immobile (Fig. 1A), while the femoral BMD was decreased at 2 months (Fig. 1B). In post-menopausal women in particular, the risk for immobilization-related osteoporosis in the femur was high (Fig. 1B). Sitting position on a bed or in a wheelchair during enteral nutrition may protect against bone mineral loss in the lumbar vertebrae, because a sitting position causes much greater load on the lumbar region than a standing position [37–41]. According to Nachemson et al [37], a sitting position without back support causes 1.4-fold more stress on the lumbar region than a standing position. Furthermore, rotation of the waist to the left and right in changing patient's position, cleaning the body, or changing clothes can also cause physical stimulation to the lumbar spine. On the contrary, loading to the femoral neck is minimal in either a lying or sitting position. Only a standing position can produce loading stress on the femur, and exercises that stimulate the femoral bone, such as raising the lower

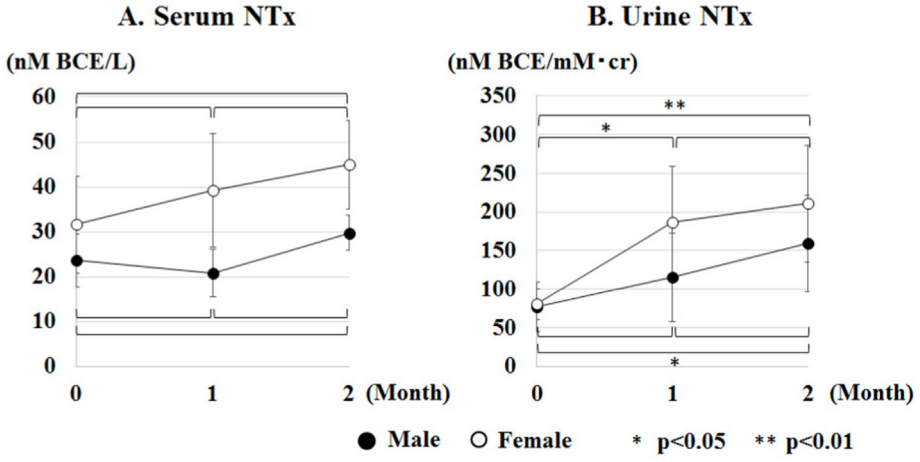

Fig. 4. Changes in serum NTx and urine NTx. The normal range of serum NTx is 9.5–17.7 nM BCE/L in males and 10.7–24.0 nM BCE/L in post-menopausal females, while that of urine NTx is 13.0–66.2 nM BCE/mM•Cr in males and 14.3–89.0 nM BCE/mM•Cr in post-menopausal females. (A) Serum NTx was higher than the upper normal limit in both males and females from 0 to 2 months, and constantly higher in females than in males. The level clearly increased at 2 months, but there were no significant differences among 0, 1, and 2 months in both males and females (0 month vs 1 month, $P > 0.05$; 1 month vs 2 months, $P > 0.05$; 0 month vs 2 months, $P > 0.05$). (B) Urine NTx was markedly increased in both males and females, and reached more than twice the upper normal limit at 2 months. In males, the level at 2 months was significantly higher than that on admission (0 month vs 1 month, $P > 0.05$; 1 month vs 2 months, $P > 0.05$; 0 month vs 2 months, $^*P < 0.05$). In females, the level increased rapidly and was significantly higher at 1 month than that on admission (0 month vs 1 month, $^*P < 0.05$; 1 month vs 2 months, $P > 0.05$; 0 month vs 2 months, $^{**}P < 0.01$).

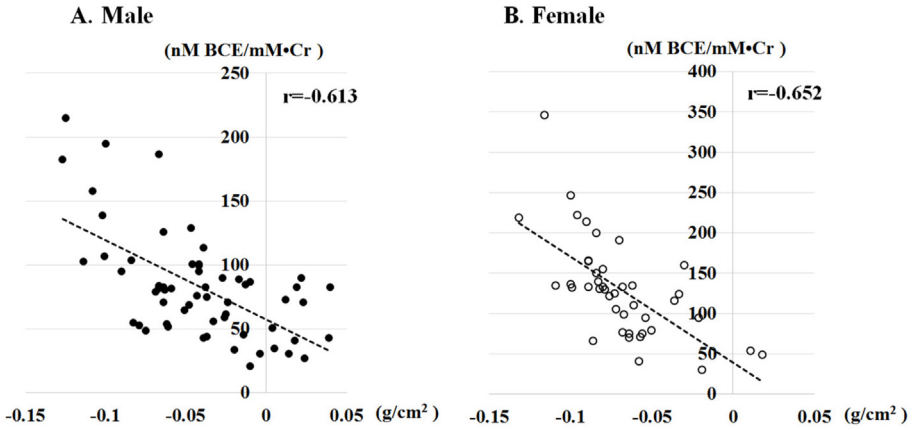

Fig. 5. Correlation between decrease of BMD and increase of urine NTx. In both male and female, negative correlation was identified between decrease of BMD and increase of urine NTx. Pearson's correlation coefficient (r) was −0.613 in male (A) and −0.652 in female (B) demonstrating moderately strong correlation.

limb and flexing or extending the hip joint, are rarely performed except for rehabilitation. Therefore, when a patient is transferred from a bed to a wheelchair or vice versa, it is preferable to help them stand on both legs with assistance and maintain the standing position for a few minutes. This daily physical training may slow the BMD decrease in the femoral bone, as recognized in the lumbar vertebrae.

Serum calcium and phosphorous were reported to increase during the first month in hemiplegic patients [3], so-called immobilization-induced hypercalcemia [15]. This hypercalcemia suggests activation of bone resorption. However, no abnormal increase or decrease was identified in either serum calcium or phosphorous within 2 months in our series. As another evaluation of bone resorption, measurement of NTx in urine is effective [42–44]. NTx is mobilized from bone by osteoclasts and subsequently excreted in the urine, and thus elevated NTx indicates increased bone resorption. In our study, urine NTx was remarkably increased at 2 months after patients became immobilized. The mean urine NTx at 2 months was >150 and >200 nM BCE/mM•Cr in males and females, respectively (Fig. 4B). These results indicate that further decline of BMD continues even after 2 months in the immobile condition with a higher risk for rapid onset of osteoporosis. In conclusion, feeding by enteral nutrition, staying in a bright ward, and achieving sitting and standing positions with assistance may protect immobile patients against osteoporosis for 2 months, although bone resorption progresses steadily under the surface. It was reported that duration of the immobilized condition and severity of palsy are key factors for bone mineral loss [1,23]. It may be better to start prophylactic treatments for BMD loss as soon as possible; however, based on our data, it is not necessary to start the treatments in acute to subacute phase of stroke.

No remarkable reduction of serum calcium, phosphate, and vitamin D values were detected in this study; however, it should be taken into account that type 2 statistical errors could occur in the sample size of this study, and larger number of cases are necessary to prove the accuracy of those results. Other limitations of this study are the change of BMD was followed only for 2 months. It seems to be appropriate to give prophylactic medications for osteoporosis to immobile patients with disturbed consciousness. However, the number of immobile elderly patients with disturbed consciousness is increasing in Japan, and the medical expenses for such patients are becoming enormous. They have few chances to fall to the floor from a bed because of their immobility, but they may experience fractures when staff members transfer them to a wheelchair or give them a bath. When a fracture occurs, medical staffs should take their responsibility for the accident to protect immobile unconscious patients from pathological fractures, letting them stand and sit with careful help is important, and it is recommended that this stand and sit position should be started within 2 months after the onset of the diseases.

5. Conclusions

The most influencing factor of BMD loss in immobile severe stroke patients is lack of load on the bone. Sitting position can cause strong weight loading to the lumber vertebrae but not to the femoral bone. Letting the patients stand with support for a few minutes to delay the BMD loss in femur. It is desirable to start the treatment within 2 months after onset.

CRediT author statement

Shoko Merrit Yamada: Conceptualization, Methodology, Investigation, Data Curation, Writing – Original Draft, and Writing –Review & Editing.

Conflicts of interest

The author declares no competing interests.

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