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Bone fractures after stroke

Złamania kości u osób po udarze mózgu

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Summary

Stroke is a major cause of disability and death. Patients after stroke are susceptible to accelerated bone loss, more evident at the paretic side and at lower extremities, as well as to osteoporotic fractures. Main factors that influence decrease in bone mineral density (BMD) are duration of hemiplegia-induced immobilization, time and degree of functional recovery, and severity of functional deficits.

Strategies for prevention of post-stroke fragility fractures should be focused on inhibition of bone mass loss and reduction of incidence of falls. Effective management, including physical exercise regimens, can improve bone health as well as patients' mobility. Hip protectors can be used as effective shock absorbers. Vitamin D deficiency has to be corrected. In patients with low BMD and increased fracture risk antiresorptive treatment with bisphosphonates, such as risedronate, alendronate, ibandronate or zoledronic acid, as well as vitamin B_{12} and folate supplementation need to be used.

Streszczenie

Udar mózgu jest jedną z głównych przyczyn niesprawności i śmierci. Pacjenci po udarze mózgu są podatni na przyspieszony ubytek masy kostnej, silniej zaznaczony po stronie niedowładu i w kończynach dolnych, oraz na złamania osteoporotyczne. Głównymi czynnikami, które wpływają na obniżanie się gęstości mineralnej kości (BMD), są: czas trwania unieruchomienia w następstwie niedowładu połowiczego, szybkość i stopień odzyskiwania sprawności ruchowej oraz zaawansowanie deficytów funkcjonalnych.

Strategia postępowania mająca na celu zapobieganie złamaniom u osób po udarze powinna być ukierunkowana na zahamowanie ubytku masy kostnej i zmniejszenie częstości upadków. Odpowiednio prowadzona rehabilitacja ruchowa może poprawić stan układu kostnego oraz mobilność osób po udarze. Ochraniacze bioder mogą być stosowane jako skuteczne amortyzatory ograniczające siłę urazu. Niedobór witaminy D musi zostać wyrównany. U pacjentów z niską wartością BMD i wysokim ryzykiem wystąpienia złamań należy wdrożyć leczenie z wykorzystaniem bisfosfonianów, takich jak: ryzedronian, alendronian, ibandronian lub kwas zoledronowy, a także suplementację witaminy B_{12} i kwasu foliowego.

Conflict of interest
Konflikt interesów
None
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"I was looking forward to my 61st birthday in two days time. I enjoyed life-walks with the wind in my hair, driving to see loved ones, working in my garden for hours. Then my life stopped and I had to learn everything again. How to walk, how to dress and feed myself – everything I took for granted. But having to ask for help was hard – I'd been so independent all my life.

The stroke had wiped out all my left side. I walked with a frame with someone beside me and moving the log of wood that was my leg was exhausting. One doctor said it would be five years before my hand would move. I thought 'never' and worked on it hour after hour until I got one finger to move a fraction. The rest of my fingers came back in three months. I set myself targets and when I walked with a stick three months before the target month I was well chuffed. But last August, a freak fall broke my left hip. This has hit me harder than the stroke did...".

(Letter to Stroke News, Volume 19.2, February 2001)

INTRODUCTION

Stroke is a cause of long-term disability and leaves 90% of post-stroke patients with functional limitations such as muscle weakness, pain, spasticity, cognitive dysfunction, poor balance and frequent falls (1, 2).

The incidence of strokes increases with age. The association of age-related bone loss and sarcopenia together with functional deficits make the patients with stroke vulnerable to falls and osteoporotic fractures.

FALLING

Bone fracture risk in stroke patients depends considerably on their tendency to falls (3). It was found that approximately 40% of patients experience at least one fall within the first year following stroke (4). Whether a fracture occurs when a person falls depends largely on the type and severity of falls (5, 6). As a result of impaired locomotor function, persons with stroke tend to fall towards the paretic side and demonstrate reduced ability to stretch the arm on the weak side in order to absorb the shock impact (3, 7).

Many factors are considered to be predictors of falls among stroke patients, such as: older age, male sex, right hemispheric stroke, post-stroke seizures, previous strokes, widespread white matter lesions, significant motor and mental dysfunctions, intercurrent infections and treatment with numerous drugs, especially analgesics, sedatives and antihypertensives (8). More than 7-fold increase in risk of falling has been described in stroke patients unaided while dressing (9).

BONE LOSS

Bone loss following stroke was found to contribute significantly to increased fracture risk. It starts within a few days following vascular brain injury and progresses until the 3rd-4th month after stroke. In the first year following stroke bone loss in the paretic arm can be the equivalent of more than 20 years of physiological bone loss in healthy individuals of comparable age (10).

Prospective studies determining biochemical markers of bone turnover revealed that bone resorption in hemiplegic patients increased as early as 7 days after stroke. It was accompanied by a decrease in bone formation suggesting significant remodeling imbalance at the bone multicellular unit level (11).

Increased bone resorption results in a rapid mobilization of bone calcium and immobilization-induced hypercalcemia, which is usually mild and can be detected by measurement of serum ionized calcium concentration. Significant positive correlation has been found between the degree of immobilization and serum ionized calcium concentration within the first and next years following stroke (10).

Several studies have reported a marked reduction in bone mineral density (BMD) of the paretic side after hemiplegic stroke (8). Measurements with dual-energy X-ray absorptiometry (DXA) scanning revealed that both upper and lower limbs appeared to be vulnerable to localized bone loss but a decrease in BMD of upper extremities was more evident than that of lower ones (8). It was found that within 1 year following stroke BMD in the paretic lower limb decreased by more than 10%, while BMD in the upper limb without paresis could actually increase, probably due to increased habitual use of the nonparetic hand (12) (fig. 1).

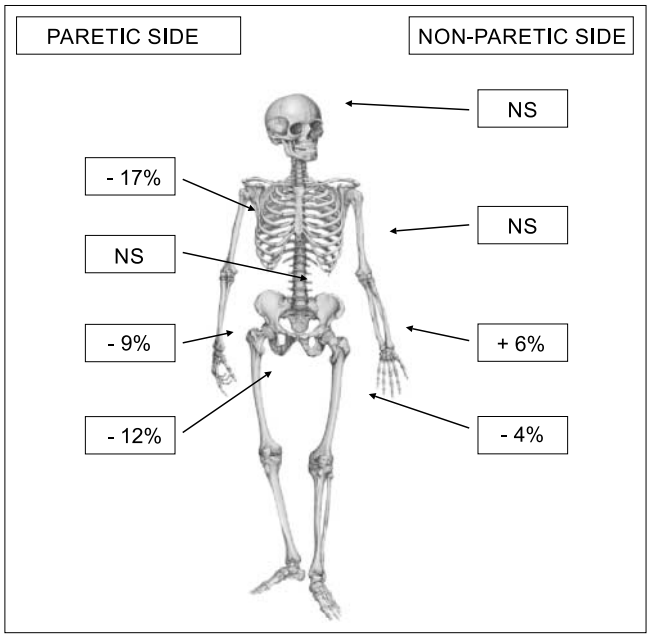

Fig. 1. Regional changes in bone density between 1 and 12 months after stroke in 18 individuals with pronounced paresis from unilateral stroke. Percentages are based on data from Ramnemark et al. (3) NS – non statistically significant

Immobility seems to be a major factor responsible for generalized bone loss. It was found that decrease in BMD correlated with the duration of hemiplegia-induced immobilization, time and degree of functional recovery, and severity of functional deficits (8, 13). Everyday capacity, muscle mass and strength as well as physical fitness of the paretic leg were found to influence BMD of the proximal femur (8, 10, 12).

Apart from reduced physical activity and immobilization the key mechanisms of bone loss in patients following stroke include: endocrine, nutritional, and pharmacological factors.

An important role in the development of osteoporosis seem to play disturbances in the vitamin D – parathyroid hormone (PTH) axis. In elderly individuals higher risk of stroke is often combined with vitamin D deficit, dramatically widespread in this population (14). It was shown that up to 83% of inpatients were vitamin D deficient and significant part of them had extremely low serum 25-hydroxyvitamin D concentrations, below 10 ng/mL (10, 15).

In most elderly patients with hemiplegic stroke even severe vitamin D deficiency is not accompanied by secondary hyperparathyroidism. It was suggested that elevated calcium serum levels, being the result of immobilization, reduced PTH secretion, and inhibited renal synthesis of 1,25-dihydroxyvitamin D. Consequently,

stroke patients may show low serum concentrations of both 25OH vitamin D and 1,25$(OH)_2$ vitamin D together with normal or low levels of PTH (10, 16-18).

Another factor that can be implied in post-stroke osteoporosis is vitamin K deficiency. It was found that vitamin K_2 is essential for γ-carboxylation of bone Gla-protein, which is indispensable to set up bone matrix. In hemiplegic persons vitamin K deficiency was associated with low BMD and increased incidence of hip fractures on the paretic side (10).

Older age, mobility impairment, dysphagia, cognitive deficits and social isolation are important factors for poor nutrition frequently found in stroke patients. Apart from reduced vitamins D and K supply malnutrition may result in vitamin B_{12} and folate deficiency, and secondary hyperhomocysteinemia. It was shown that elevated serum homocysteine concentration influenced enzymatic collagen crosslinking in the post-translational modification of collagen molecules, decreased bone tissue quality, and played important role in bone fragility associated with aging (10, 19, 20).

Treatment with oral anticoagulants is essential part of regimen in significant part of elderly stroke patients. It was found that warfarin, probably by inducing vitamin K deficiency, accelerated decrease of BMD in hemiplegic stroke patients compared with hemiplegic patients not given anticoagulants (10, 21).

Long-term therapy with heparin, often used as venous thromboembolism prophylaxis, leads to reduction in BMD and increased risk of bone fractures that may occur within 6 months of starting therapy. Heparin-induced bone loss is dose dependent and reversible upon discontinuation. It was suggested that low molecular weight heparins were associated with fewer fragility fractures while newer heparins, including fondaparinux, were predicted to be bone neutral for bone metabolism (10, 22).

Administration of antiepileptic drugs (AEDs) which attenuate liver 25-hydroxylation of vitamin D is another possible cause of accelerated bone loss in post-stroke patients (10). AEDs were suggested to exacerbate bone disease by increasing activity of cytochrome P-450 system and vitamin D catabolism. It was found that treatment with drugs being liver enzymes inductors, such as phenytoin, phenobarbital, carbamazepine and primidone resulted in greater bone loss compared to noninductors such as clonazepam, topiramate, valproic acid, ethosuximide and gabapentin (23).

FRACTURE RISK

Increased fracture risk is well recognized complication of stroke, particularly in hemiplegic patients. Fracture incidence was reported to be from 7 up to 19.8 per 1000 person-years (7, 24-26). The risk of fracture especially within first year following stroke is significantly increased, from 1.5- to 4-fold, compared with age-matched controls (3, 7, 10). After analysis of more than 16 million hospitalizations over 10 years in Sweden Kanis et al. found a marked increase in risk of any fracture and hip fracture in patients after stroke, at all ages and in both sexes. The risk of hip fracture was highest (> 4-fold) within first year after stroke, declined thereafter, and remained higher than that seen in the general population, except in those aged ≥ 80 years (25).

The results of prospective study that included 1139 stroke Swedish patients showed that fractures of upper limbs were considerably less common than hip fractures (3.7 vs. 6.1%) whereas epidemiological study performed in Scotland found that incidence of both types of fractures was similar, about 1% (7, 24). Vertebral fractures were also frequently observed (27).

Hip fractures are most serious and disabling consequences of falls in stroke patient in terms of morbidity and mortality. Up to 30% of patients with fracture of femoral neck die within a year of acute event. Most hip fractures occur within 6 months after stroke, more than 80% on the paretic side (8). Higher incidence of hip fractures have been observed in patients with milder strokes, as they are subjects for early mobilization and exposed for increased risk of falling (10, 28-30). Andersson et al. found that patients who experienced hip fractures tended to be older, had lower stroke severity, impaired vision, cognitive impairment and/or previous fracture(s) prior to stroke event. All persons sustained their hip fracture indoors, after the initial hospital stay, while performing everyday activities (26). Stroke patients are likely to have pre-existing osteoporosis related to their age but younger age and female sex were found to increase the risk of hip/femur fracture (7, 8, 31).

PREVENTION OF BONE FRACTURES IN STROKE PATIENTS

Bone mass loss and tendency to falls are considered two major factors associated with increased bone fracture rate following stroke. Strategies for prevention of post-stroke fragility fractures have to be focused on inhibition of bone mass loss and reduction of incidence of falls.

The role of hip protectors in prevention of fall-related hip fractures

As the risk of hip fracture is increased as much as 30-fold in case of direct impact to the hip, hip protectors can act as effective shock absorbers. Pooled data of 15 trials (11 of them performed at institutional settings), included in Cochrane Systematic Review updated in 2005, showed reduction in hip fracture incidence by 23% in persons with hip protectors (32). Three randomized trials, however, conducted in community-dwelling participants (n = 5135) showed no benefit of hip protectors in preventing hip fractures. Significant problem with regard to use of hip protectors remains compliance. Clinical trials carried out in institutional settings suggested that proper attitude, education and motivation of staff, the contact person as well as size of the nursing homes all influence users' compliance (8, 33-35).

Improving muscle strength and cardiorespiratory fitness

Effective management, including physical exercise regimens, can improve bone health as well as mobility, movement speed, body balance, postural control, weight-bearing ability, and gait in chronic stroke patients. A randomized controlled trial of community-based fitness and mobility exercise program for patients aged ≥ 50 years following stroke for at least 1 year showed that intervention group (n = 32) experienced significant gains in cardiorespiratory fitness, mobility and muscle strength in the paretic leg compared to controls (n = 31), as well as maintained femoral neck BMD in the paretic leg (36, 39). Cheng et al. verified the efficacy of exercise program in a group of 54 post-stroke patients. Approximately 2-4 months following stroke the patients were subjects of intensive physical training consisting of 30 minutes of symmetrical standing and 20 minutes of repetitive sit-to-stand exercises, performed five times weekly for three weeks. During a six-month follow-up, only 16.7% of the patients experienced a fall, while 41.7% individuals on conventional therapy recorded fall incidents (37). It was also shown (using peripheral QCT) that a 19-week exercise intervention exerted beneficial effects on tibial bone architecture (36).

Calcium and vitamin D supplementation

Hypovitaminosis D had been identified in patients after acute stroke as a significant factor influencing musculoskeletal health during stroke recovery. The authors of randomized controlled trial that included 96 elderly women with post-stroke hemiplegia and vitamin D deficiency reported that daily supplementation of 1000 IU of vitamin D_2, given over 2 years, was associated with an increase in the relative number and size of type II muscle fibres, and improved muscle strength, compared with placebo. Therapy with low doses of vitamin D accounted also for 59% reduction in incidence of falls. Hip fractures occurred in 4 out of 48 patients in the placebo group and in not any woman in the treatment group ($p = 0.049$). Taking into account available research, ensuring that stroke patients are vitamin-D-repleted during stroke rehabilitation seems to be significant constituent of therapy (8).

Antiresorptive drugs

It was found that only a small proportion of poststroke patients (15%) received antiosteoporotic medications prior to their hip fractures. Treatment with bisphosphonates was used in 2.1-2.7% of patients, and did not differ between poststroke and nonstroke groups.

Many hip fractures are preventable, and the effectiveness of antiresorptive agents together with vitamin D and calcium supplementation gives the opportunity for significant fracture risk reduction in stroke survivors (37).

Among oral bisphosphonates risedronate is the drug with proven efficacy in reduction of fracture risk in patients after stroke. In a 12-month, randomized, double-blind placebo-controlled trial of 187 elderly women treated with daily risedronate of 2.5 mg and 187 women who received placebo, only one patient in the treatment group sustained hip fracture, compared to seven fractures in controls (OR = 7.0, $p = 0.036$). During 12 months of the study BMD measured at the second metacarpal bones in both hands of each patient increased by 1.5% in the treatment group and decreased by 4.9% in the placebo group. Similar results were reported in men aged 65 years and over who experienced mild strokes. Oral bisphosphonates are contraindicated in stroke patients with residual dysphagia, but may play an important role in individuals with normal swallowing who are able to retain upright position (8, 38, 39).

An alternative approach in the acute phase of stroke makes treatment with potent intravenous bisphosphonates such as zoledronic acid or pamidronate. This strategy should be targeted to the acute stroke units to protect in-patients from the most rapid phase of bone loss, even in the case of dysphagia. The results of a randomized, controlled trial comparing a single yearly dose of 4 mg intravenous zoledronic acid with placebo have confirmed that the drug completely prevented bone loss in the hemiplegic proximal femur in treated patients, compared to a substantial decrease in BMD in patients given placebo. It is important to remember that vitamin D deficiency and dehydration have to be corrected prior to the treatment with bisphosphonates (8, 40).

Mecobalamin (vitamin B_{12}) and folates

An inverse association between serum homocysteine concentration and hip fracture risk has been reported. In a double-blind, randomized controlled study of over 600 Japanese older adults aged ≥ 65 years with a 2-year follow-up patients were assigned either to treatment with mecobalamin and folate or double placebos. At study completion statistically significant difference in hip fracture rates 10 vs. 43 per 1000 patient-years was found in treatment and placebo groups, respectively) ($p < 0.002$) and calculated number needed to treat (NNT) was 14 (8, 20).

CONCLUSIONS

Opposite to postmenopausal osteoporosis, poststroke osteoporosis is still not properly recognized and treated. Careful and comprehensive fracture risk assessment should be performed, and prevention of bone loss should start as early as possible. The known risk factors for osteoporosis need to be evaluated, and residual walking deficit should be considered a significant potential cause of proximal femur fracture. Measurements of BMD, with DXA scanning at the paretic hip, and serum vitamin D concentration need to be made to assess their baseline values.

After having considered risk factors for falls and fractures effective and multidirectional management should be started. It includes physical exercise regimens, vitamin D supplementation with

adequate calcium intake, antiresorptive treatment with bisphosphonates, as well as vitamin B_{12} and folate supplementation which seems to be safe and effective in preventing hip fractures in chronic stroke survivors. At present risedronate is the only drug that has been shown to prevent bone loss and to reduce hip fracture incidence in stroke patients. In patients with chronic stroke, however, or those who had been previously treated with antiresorptive drugs the other bisphosphonates such as alendronate, risedronate, ibandronate or zoledronic acid can be used.

Intravenous zoledronate has recently been shown to be effective in preventing loss of hip BMD after acute stroke, while overcoming compliance, adherence and swallowing difficulties

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