CAUSES AND MANAGEMENT OF BONE MASS REDUCTION AFTER STROKES

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Keywords: osteoporosis, strokes Abstract: Introduction: There are multiple causes for the bone loss. In patients with stroke, due to prolonged immobilization and chronic administration of certain drugs (anticoagulants, anticonvulsants, glucocorticoids) the development of osteoporosis is favoured. Osteoporosis is the main bone metabolic disease and is characterized by both quantitative and qualitative damage of the skeleton. Reduced bone mineral density and bone microarchitecture damage bring about decreased bone strength, resulting in increased fracture risk. Prevention and treatment of osteoporosis is an important goal in the management of these patients and thus, it reduces the risk of major osteoporotic fractures. Hip fracture causes an increased rate of mortality through thromboembolic and/or septic complications. The association of medical rehabilitation methods and specific pharmacological treatment for osteoporosis was proved beneficial.

A known problem, but neglected in most cases, is that of osteoporosis in patients after stroke.

Clinical studies have shown increased reduction of bone mass by 1.6% at 1 year after a stroke. Bone loss is rapid in the first 12 months after the stroke (1,2) while the reduction of bone mineral density is directly proportional to the degree of motor deficit.(3) There was found an increase in the incidence of osteoporotic fractures, especially of hip fractures which occur more frequently on the paralyzed side in case of a stroke and which determine the worsening of the prognosis.(4,5,6,7,8) Thus, statistics showed that femoral neck fracture occurs on average at 5.4 to 6.4 years after a stroke, and in 62.5% of fractures, they occur on the paretic side. 31.8% of the patients who could move before the fracture, become homebound.(9)

The evolution of bone mass after the stroke can be assessed by determining bone markers and bone mineral density. In acute and subacute stages after the injury, there occurs an imbalance of bone metabolism highlighted by the progressive increase of bone resorbtion markers that is maximal after 3-6 months, at the same time with the slight increase in bone formation markers. 12 months after the injury, the reduction of bone mineral density is also found out, while 16 months later, there is a tendency for stabilization of bone metabolism. At lumbar spine level, there was noticed an increase in the bone mineral density since wheelchair prolonged sitting may have an osteogenic effect on the vertebrae. Osteoporotic fractures can occur from minor trauma (transfer from chair to bed) and particularly affect the proximal and distal femur, proximal tibia.(10,3,11,12)

The determining factors of osteoporosis in patients after strokes can be grouped as follows:

- Ø carential factors through lack of oxygen intake;
- Ø immobilization;(13)
- Ø old age which is accompanied by a physiological decline of bone mass;
- Ø chronic medication (anticoagulants, anticonvulsants, glucocorticoids) that favours bone demineralization;(14)

- Ø comorbidities that affect bone metabolism (endocrine diseases, gastrointestinal disorders);
- Ø muscle atrophy that is installed after prolonged bed rest;(15)
 - lack of muscle contractions on bone increases bone loss;(16)
 - protective effect of spasticity on bone mineral content is controversial;(17) studies have shown a lower loss of bone mineral density in patients experiencing spasticity compared to the group presenting flaccidity.
- Ø Neurovegetative system damage which is partly responsible for the development of osteoporosis by inducing vascular changes.(18)

The pathophysiological mechanism in the case of post stroke osteoporosis is shown schematically in figure no. 1.

Immobilization is the main trigger of metabolic bone disorders. Lack of muscle activity leads to loss of mechanical stress on the bone according to mechanostat theory. Thus, mechanical stimulation of bone formation is reduced and increases osteoclastic bone resorption evidenced by increased bone resorption markers. Bone calcium is mobilized into the systemic circulation and hypercalcemia/hypercalciuria can be observed that occurs after the first 10 days and is preserved up to 1-6 months. Hypercalcemia occurs after a massive influx of calcium or when the glomerular filtration rate is low. Calcium homeostasis disorder involves endocrine changes, namely in vitamin D and parathyroid hormone.(19,20)

Having a vitamin D deficiency that is installed after the first 3 weeks and that occurs due to reduced sun exposure and decreased food intake leads to a bone metabolic imbalance with increased bone resorption.

Severe reduction of serum vitamin D below 10ng / ml causes a compensatory hyperparathyroidism and increased bone calcium mobilization. In patients with moderate reduction in vitamin D (between 10-20ng / ml), hypercalcemia due to immobilization reduces the secretion of parathyroid

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hormone.(20)

Figure no. 1. The pathophysiological mechanism in post stroke osteoporosis



The mechanisms by which chronic medication can influence the development of bone mass are the following:

- Ø anticonvulsant drugs are inducers of heaptic cytochrome P450 enzyme system (carbamazepine, phenobarbital, phenytoin) and are associated with disorders of bone metabolism; they increased metabolism of vitamin D; they determine the direct effects on bone cells, resistance to parathyroid hormone, calcitonin inhibition and prevent calcium absorption;
- Ø anticoagulants reduce the osteoblastic activity and decrease the adhesion of osteoblasts to protein matrix, resulting in decreased bone formation.

The management of osteoporosis in stroke patients cover both the prophylactic and therapeutic aspects.(21)

Among the pharmacological means that can be used in the prophylaxis and treatment of these patients we can mention: $\mathbf{\tilde{x}}$

- Ø Calcitonin
 - it is a strong inhibitor of bone resorption, with direct effect on osteoclasts and osteoclast precursors;
 - temporarily, it reduces hypercalcemia and hypercalciuria due to immobilization, but it has no real effect on bone loss.(22)
- Ø Bisphosphonates (alendronate, ibandronate, risedronate, etidronate, zoledronic)
 - potent inhibitors of bone resorption, and calcification of soft tissue;
 - reduce hypercalcemia and bone loss;
 - they can be administered preventively or curatively;(23)
 - preventive treatment initiated within 12 months proved to be effective;
 - administration can be done orally or intravenously.(24,25)
- Ø Vitamin D
 - has a major role in calcium homeostasis and bone metabolism;
 - vitamin D deficiency (below 30ng / ml) should be identified and dealt with, which may influence the effectiveness of bisphosphonates;
 - has a significant effect in maintaining bone mineral density after the stroke.(23)
- Ø Denosumab is an anti-RANKL antibody which has bone antiresorptive effect. It is administered as a subcutaneous injection 60 mg / ml for 6 months.(26)
- Ø Parathyroid hormone (PTH) (Teriparatid) increases bone formation.(22) Although higher serum PTH concentrations stimulate bone resorption, when intermittently administered in low doses, PTH can stimulate bone formation. The

recommended dose is 20 mg / day as a subcutaneous injection for at least 24 months.(27)

Ø Sclerotin

- is a protein synthesized by osteocytes playing an important part in the regulation of bone formation by osteoblasts (blocking the osteogenic signal);
- injection of antisclerotin antibodies increases bone formation and bone mineral density
- it is a treatment of perspective.(28)

Non-pharmacological means are essential and must be applied simultaneously with the pharmacological ones. These consist of:

- Ø early establishing the medical rehabilitation programme in order to restore, as much as possible, the original physiological and biomechanical conditions;(29)
- Ø early mobilization;(22)
- Ø standing and assisted walking;
- Ø passive motion;
- Ø physical exercises with weight loading;
- Ø functional electrical muscle stimulation is recommended for the local effect on increasing bone mineral density and muscle strength;
- Ø pulsed ultrasound therapy may represent an osteogenic stimulus, effective in preventing osteoporosis;
- Ø thermotherapy;
- Ø massage therapy. Conclusions:

Osteoporosis after stroke is a known problem, but neglected and insufficiently treated, which leads to the occurrence of severe osteoporotic fractures which worsen the prognosis of these diseases.

It is necessary to establish, as early as possible, prophylactic measures that can reduce bone loss.

Applying a complex programme of medical rehabilitation and antiosteoporotic medical treatment is the optimal strategy in these patients.

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AMT, vol. 20, no. 3, 2015, p. 91

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