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Immobilization osteoporosis : a review

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SUMMARY *Bone mass is not only subject to systemic hormonal homeostatic mechanisms, but also to local mechanical influences. The importance of the mechanical balance of bone has been more recently stressed by the research on the effect of weightlessness on bone, and by the introduction of the concept of "mechanostat" in the pathogenesis of osteoporotic conditions. Immobilization osteoporosis has clinical (fractures, sometimes hypercalcemia, urinary lithiasis) and radiological features. Immobilization has an effect on bone modeling and remodeling, through an increased activation of remodeling loci, and a decrease of the osteoblastic stimulus. This leads directly to a local reduction in bone mass, the increased activation multiplying the effect of the deficit in bone formation. The prevention is based on exercise if the load is applied intermittently for a daily period. It seems also that muscle weight is an important determinant of bone mass. There is a potential for recovery during the active early phase of immobilization osteoporosis that may disappear in the subsequent late (about six months) inactive phase. Permanent losses could be prevented by appropriate measures, pharmacology or exercises, applied during the first months of immobilization. No recovery has been demonstrated after the inactive phase has been reached, whatever the treatment. The cumulative effect of repeated periods of immobilization remains hypothetical.*

Key words : Osteoporosis, Immobilization, Disuse.

INTRODUCTION

Immobilization has long been known to result in hypercalcaemia and hypercalciuria (1-7). A marked reduction in skeletal mass accompanies prolonged immobilization, so that poliomyelitis, spinal cord injury, and other forms of muscular paralysis are regularly associated with "disuse" or "immobilization" osteoporosis. Immobilizations due to less acute diseases, however, are also accompanied by some progressive atrophy of bone. A cross-sectional survey of 139 young men immobilized with fractured legs or prolapsed discs showed a loss of 2% of total body calcium per month (8). The mineral loss from the 4th lumbar vertebra of 13 teenage women during the 3 to 6 weeks following surgery for scoliosis was 8% per month (9). Male and female patients subjected to 27 days of bed rest during the treatment of a sciatica averaged a 0.9% loss in mineral content of the lumbar vertebrae per week (10). Bed-rest studies of healthy men have been used as the ground-based simulation of weightlessness for evaluation of the mineral metabolism during space flights. For instance, 3 healthy young men confined to bed-rest for 36 weeks dem-

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onstrated a 4.2% loss in total body calcium; after 18 to 24 weeks, the loss of bone mass in the central os calcis was respectively 25.1%, 33.3%, and 49.5% (11). These results have been confirmed in middle-aged men (12).

It has been admitted since a long time that bone is affected by local and systemic factors. Up to now, more emphasis has been placed upon the systemic hormonal controls and their regulations. In reality, the local mechanical forces in the form of gravity and muscle contraction affect also bone cell function. The bones subjected to altered loading regime respond by modifying either their architecture or the quality of their tissue (13). The renewed interest in immobilization osteoporosis and more generally in the effect of mechanical forces on bones stems from the concept of a feedback relation between the mechanical usage, the architecture, and the biology of a bone (13,14). The mechanical usage has an effect on bone growth, modeling, remodeling, and mass. This has been observed clinically in paralyzed adults (5) and in chronically immobilized children (15).

Immobilization osteoporosis has been extensively studied recently because of similarities with the bone changes observed in humans or animals submitted to microgravity experimentally or during space flights. Unfortunately, the experimental methods used to produce immobilization vary from casting to nerve and tendon sectioning, in different species. In clinical studies, the duration and cause of immobilization as well as the age and sex of the patients are not comparable. Some studies include only acute cases of immobilization with or without paralysis, while others deal with gradual sedentarity, a term whose definition is sometimes unclear. Immobilization of a segment of limb is often used, as well as the immobilization of the whole body. These methodological differences certainly introduce some discrepancies in the literature. Nevertheless, it is possible to present here the commonly established features of immobilization osteoporosis.

Clinical and radiological aspects

1) The most striking clinical symptom is the occurrence of *fractures* of the long bones, without trauma or following a mild trauma usually not associated with fractures in normal subjects. These fractures have been observed for instance when paralyzed patients undergo a passive range of motion by the therapist. Various figures have been given for the incidence of such fractures in paralyzed patients: 2%, 4%, and 5.9% respectively in three series of the literature (16,17,18). It is difficult to assess the role of sedentarity in bone involution and increased incidence of fractures observed in old adults. A reduced global mobility may have a protective effect against vertebral crush fractures. In another way, no correlation seems to have been found between repeated periods of immobilization during life and the appearance of a senile or post-menopausal osteoporosis.

Pathological bone fractures are particularly frequent in children with physical handicaps and/or mental retardation (15). The effect of immobilization on bone modeling is marked (19,20) and sometimes associated with severe hypercalcaemia.

2) Immobilization *hypercalcaemia* is associated with the usual symptoms of hypercalcaemia from other origins (21,22). It occurs mainly in patients with high rates of bone turnover, including children, adolescents, and pagetic patients (23). It has been observed also in immobilized adults, but in a milder degree, the serum calcium being in the upper normal range (24).

3) The loss of urinary calcium from immobilization has been associated with the development of *renal stones* (1,25,26). Nevertheless, several other factors which could increase the risk of development of renal stones, such as urinary infection, impaired drainage, increased phosphate excretion, high urinary pH, are also associated with immobilization.

4) A variety of radiological changes of the immobilized long bones have been described

(27,28,29). They have been divided by Jones (27) into four groups: generalized or diffuse osteoporosis, speckled osteoporosis, linear epiphyseal or subcortical translucent bands, lamellation and scalloping of the cortices. Several of these patterns are frequently present together in the same patient. The radiological changes are dependent on the age of the patient, the extremes of ages and particularly the youngest patients being more likely to present with the patterns described above. The duration of immobilization has a positive correlation with the radiological changes.

The radiological aspects of immobilisation osteoporosis are very similar to those of Sudeck's atrophy or Reflex Sympathetic Dystrophy Syndrome. They sometimes mimic a malignant involvement of the bone (28).

Of particular interest are the cortical radiological changes (27,29). Described initially as "lamellation" (27), they have been studied in depth in the acetabular roof (29). A double cortical line was frequently found in the acetabulum of spinal cord injured patients: 92.5% of cases 20 to 104 weeks after the onset of immobilization, the interval being shorter in younger (mean = 44 weeks) than in older patients (mean = 62 weeks). A double cortical line was also observed in other bones, as well as in non-paralytic immobilized bones. The radiological appearance of a double cortical line is the traduction of a severe intra-cortical bone loss. It probably demonstrates a marked trabecular and cortical weakness of the bones, which should prevent the patient and the therapist from any forced range of motion or any trauma even minimal.

Mineral and endocrine responses to immobilization

1) A prolonged immobilization has long been known to result in hypercalciuria. This has been observed in healthy immobilized persons (11,30,31) where the high urinary calcium concentrations peaked at 6 or 7 weeks after the initiation of bed-rest and persisted throughout bed-rest periods as long as 36 weeks. The 24-hour urinary calcium excretion was also markedly elevated in paralyzed subjects (5,7,32) with a mean value of 314 mg or 8 mmol per 24 hours (32). A urinary calcium loss was observed during several Gemini, Skylab and Soyuz space flights (33).

Serum calcium values in immobilized subjects are usually normal (5,32), but they are frequently in the high normal range (32,34) in adults. In young adults, adolescents and children, however, immobilization, whatever its cause, leads frequently to hypercalcaemia (21,22) when the kidney is not capable of excreting a massive load of resorbed calcium.

There is also an elevation of the fecal excretion of calcium (11,31). This is probably due to a deficient absorption of calcium during the acute development stage of immobilization (35). After about 12 months, the excretion of calcium returns to normal, even if the patient remains immobilized. It is assumed that a chronic, stable stage has then been reached (35).

2) The urinary excretion of *hydroxyproline* is increased and peaks at about 7 or 8 weeks of immobilization (5,11,12). A rise in urinary hydroxyproline was noted also during the Skylab space flights (36). The urinary excretion of the non-collagenic organic phase of the bone matrix is increased after spinal cord injury (37).

3) Serum phosphorus values are in the high-normal range or markedly elevated in immobilized animals or patients (5,32,38,39), as well as the renal phosphorus threshold (32). During the first week of immobilization, however, there might be a slight decrease followed by a significant increase thereafter (39).

4) In parallel, there is an initial increase in the secretion of parathormone, especially during the first post-operative week when surgery has been performed (39). After 2 or 3 weeks of complete immobilization, the parathormone level markedly decreases even to undetectable levels (32).

5) The low levels of the mean plasma 1,25 dihydroxyvitamin D (32) confirm the suppression of the parathyroid-1,25 dihydroxyvitamin D axis as a result of the resorption of bone mineral.

6) Norepinephrine, but not epinephrine, was significantly increased during bed-rest (40). The urinary excretion of cortisol was normal (41). If baseline glucose and insulin levels remained normal in bed-rest studies, the administration of a glucose challenge provoked an exaggerated insulin response (40,42).

These various endocrine factors may intervene at least partly in the modifications of bone metabolism observed during immobilization. It may even be possible that the bone cells respond differently to normal hormonal levels during immobilization.

The mechanisms of bone loss

Quantitative bone histological data were obtained for the first time from iliac crest biopsies from 28 immobilized spinal cord injured patients (5). They were completed in subsequent studies (34) in order to form an homogenous series of 63 patients. Trabecular bone volume of the immobilized patients was less than that of the control subjects. It decreased by an average of 33% prior to the 25th week of immobilization. After this time, the trabecular bone volume became constant at a new, lower, steady state value. The osteoclastic resorption increased during the first 16 weeks of immobilization, then returned to normal values at about 40 weeks. The osteoblastic bone formation was initially greatly decreased and rose back to normal values in 8 to 10 weeks.

An histomorphometric study was carried out in iliac bone samples taken from 21 immobilized volunteers before and after 120 days of bed-rest (43). It shows the same cellular modifications (increased resorption and decreased formation) as in paraplegic patients, but without a decrease in the trabecular bone volume.

The same pattern has been observed in the bone of immobilized dogs (44,45) and singularly in primates (46) over an almost similar period of time of about 7 months. Phasic changes have even been described (45,47) with a rapid initial loss of bone during the first 6 weeks followed by a slower but longer lasting bone loss, and eventually by the maintenance of a reduced bone mass (inactive phase).

The stable amount of bone reached after about 6 months of immobilization in several human and animal studies (5,45,46) corresponds probably to the minimum amount of bone mechanically necessary. Such an observation has been made in handicapped non-walking children by Nishiyama (15). At the end of their growth, these children level off their bone mineral density at 25 to 30% below that of age-matched controls. Thus the difference between the initial and the remaining bone masses (= the bone loss) is probably the equivalent of the amount of bone normally acquired during growth under normogravity and regular frequency of loading and exercise (Fig. 1).

The osteoblastic activity or recruitment in the trabecular bone measured by the mineral apposition rate was markedly reduced or even ceased in immobilized paraplegic patients (5) as well as in immobilized monkeys (48,49). It has been estimated that about 30% of the immobilization-induced bone loss in rats is due to increased bone resorption, and about 70% to decreased bone formation (50).

It appears that bone activation is the first phenomenon in the cellular events, probably in relation to a local increase in hydrostatic pressure similar to hypergravity (51), and/or to the suppression of a direct, mechanical repressing effect on the osteoclasts (14,52). This leads logically to hyperresorption. In contrast, the absence of mechanical forces, first hypothesized by Albright (1), results in diminished bone formation, and leaves the bone resorption activity temporarily unop-

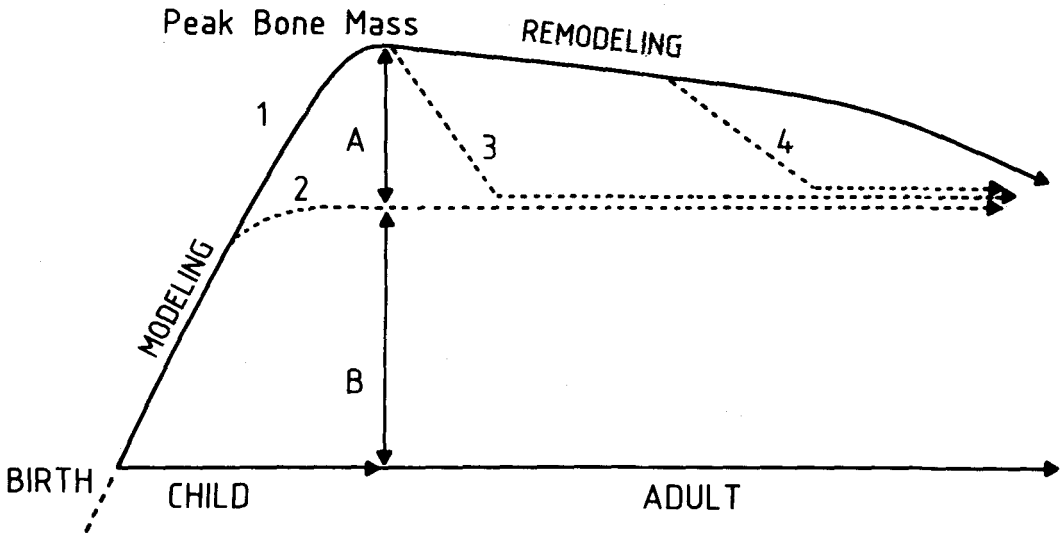

Fig. 1: Comparison of the evolution of the bone mass during life.
A = amount of bone acquired through weightbearing and against gravity
B = minimal amount of bone necessary for the structural maintenance of the human body.
1: normal gain of bone during growth
2: non-walking child
3 and 4: patterns of immobilization bone loss in adults.

posed. A new steady state is reached when bone formation again re-equilibrates the resorption, apparently after 5 to 6 months.

There are several modulating factors to this general pattern: 1) Cortical bone responds much more slowly to immobilization, with thinning and porosity gradually increasing after only 3 to 6 months of immobilization (29), then becoming the major component of the fragility of the immobilized bone. 2) The loss of bone is related to the age of the patient (5,53) or of the animal (45): it is higher in young than old immobilized subjects reaching a maximum of 50% over 6 months in adolescents. 3) Every bone has been modeled in shape and mass during growth according to its future function and particularly its antigravital requirements. Consequently, immobilized bones undergo site-specific losses, greater in weightbearing bones. 4) Besides the duration of immobilization, its intensity and acuteness play a role in the rate of the bone loss. Acute osteoporosis is observed in spinal cord injury patients; a gradual sedentarity or a bed-rest of healthy non-paralyzed subjects will have obviously slower although similar effects on the cell kinetics and loss of bone (43,53). 5) Finally, it should be pointed out that the biomechanical competence of a bone depends not only on bone mass, but also on the three-dimensional architectural distribution of bone tissue (54). The stereology of the immobilized human bone remains practically unknown. It is likely that unloading will alter the disposition of the trabeculae and thus be another trigger of the cellular modifications directly or through piezo-electricity.

Reversibility, prevention, and treatment

The potential for recovery of the immobilization bone loss has been denied in some studies (9,55), but observed by other authors (10,11). In immobilized, then remobilized dogs, Jaworski and Uhthoff (56) noted a marked but incomplete reversal of the bone loss, more pronounced in younger dogs. Their observations apply only to remobilization incurred during the active phase of im-

mobilization osteoporosis (before 6 months). The potential for recovery probably does not exist in the inactive, established, immobilization osteoporosis. Consequently, it is logical to infer that remobilization is the most adequate preventive treatment during the first 3 or 6 months of immobilization.

Bone is constantly stimulated by *muscle contraction* and *weight-bearing*, and responds proportionally to the magnitude of the mechanical stresses imposed. Exercise intervention preventively or curatively during the first months of immobilization should thus include muscle strengthening and skeletal loading.

It has been demonstrated that there is a relationship between bone mineral density and the strength and size of relevant muscles, for instance in the spine (57,58) or the forearm (59). The use of intense exercises during bed-rest, however, has not satisfactorily prevented immobilization bone loss (11).

A dynamic intermittent load applied for a short daily period resulted in a substantial increase in bone mass in the avian ulna (60). Weightbearing exercise was able to reverse the negative calcium balance and bone loss induced by immobilization in rats (61). The absence of longitudinal weightbearing on the skeleton accounted for its demineralization in humans subjected to bed-rest (62).

Consequently, it has been widely reported during the past fifteen years that physical activity associating muscle exercises and weightbearing had a positive effect on bone mineral content (63-67). Exercises could prevent the age-associated loss of bone mineral content in animals (68) and the osteoporosis observed in women with anorexia nervosa (69).

The difficulties lie in the application of relevant combined exercises to a population of elderly and/or bedridden patients, or to patients presenting with an association of cardio-vascular or respiratory and locomotor ailments or even to younger patients with multiple traumas (70,71). Moreover, the type, intensity, duration, and frequency of the exercises have not been accurately determined yet. An important progress for the precise prescription of exercise would be the knowledge of the relative effect of exercise directly on the bone cells, or indirectly through either muscle strengthening, modifications of the bone flow or hormonal changes (Fig. 2).

When physical activity or graduated exercises are not possible, other ways of prevention and early treatment are suggested. Electrical muscle stimulation, for instance, increases the bone turnover rate and prevents the bone loss as well as the erosion and fibrillation of the cartilage in cast-immobilized rabbits (72). Another possibility is to use a pharmacologic preparation to prevent the loss of bone calcium. The administration of pharmacological doses of synthetic salmon calcitonin (100 MRC units every 2 days for 100 days) prevented significantly the loss of

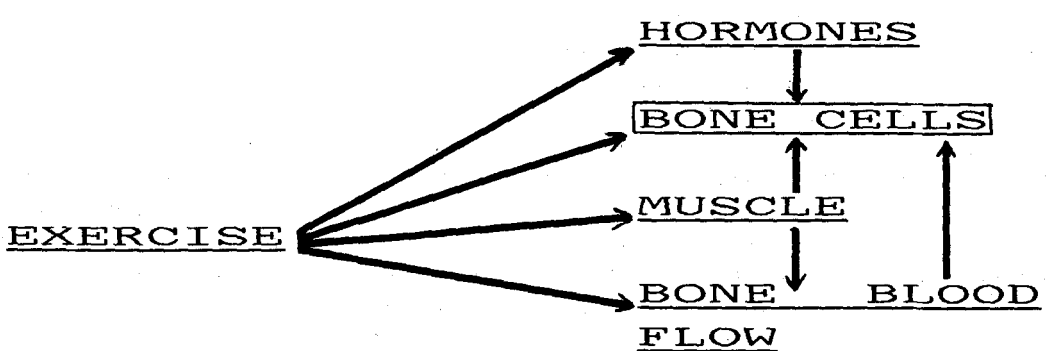

Fig. 2: Hypothetical direct or indirect impacts of exercise on bones.

trabecular bone and the increase in blood calcium and urinary calcium and hydroxyproline without side effects (73,74). Similar results were reported with the use of biphosphonates (75). Clodronate was the most effective of these compounds (34,76,77), but is not commercially available presently. Etidronate was active at a dose of 20 mg/kg/d, but this dose level was subsequently associated with the development of osteomalacia (75,78).

It is then suggested that the early administration (before 1 to 2 weeks after onset) of 100 MRC units of salmon calcitonin daily or every two days for 2 to 3 months is presently a safe way of reducing or even preventing the bone loss associated with acute immobilization. This treatment can also prevent or treat immobilization hypercalcaemia which is now an acknowledged complication of the acute immobilization of young patients in intensive care units.

In conclusion, immobilization osteoporosis is a more widely recognized entity, not only in its acute forms, but also in gradually sedentary or hypoactive subjects. Studies on bone and calcium metabolism in humans should take into account the level of activity of the subjects taken in the study, in order to improve the homogeneity of the samples. The submission of humans to microgravity, or weightlessness, during space flights and soon within orbital stations for longer periods, cast a new light (33,49,71,79) on this field.

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