J Musculoskel Neuron Interact 2001; 2(2):181-186

Hylonome

Abstracts from the 6th International HEL.I.OS. Seminar

(Hellenic Institution of Osteoporosis)

15-16 December 2001, Athens, Greece

The Influence of Hormonal Events and of the Way of Life in Female Puberty on Bone Mass

G. Mastorakos

The succession of hormonal events taking place during female puberty are not as yet fully understood. However, their physiologic outcome is the change of the young girl to a young woman. The main event of this phenomenon is the menarche, which follows the development of cyclic activity of the hypothalamic-pituitary-gonadal axis.

During that period of life, apart from sexual steroids, many factors influence bone mineral metabolism. They include nutrition, vitamin D_3 and calcium intake, physical activity and the effect of other hormones such as calcitonin, parathormone, prolactin and growth hormone. The role of estrogens is pivotal. Primary or secondary amenorrhea, oligomenorrhea or even irregularity of menstrual cycles may develop during puberty, resulting in lower body mass due to lack of sufficient estrogenization. The latter is also encountered in situations such as anorexia nervosa, excessive athletic training and GnRH analogue treatment of precocious puberty. The racial, ethnic and geographical factors influence to a certain extent the development of bone mass during adolescence.

From Puberty to Menopause Bone Metabolism in Pregnancy and Lactation and Bone Mass Maintenance

N.G. Goumalatsos

Achieving maximum bone mass just after puberty and its maintenance until the menopause are significant risk factors for osteoporotic fractures. During the reproductive years, maximum bone mass is maintained with appropriate nutrition and exercise except in pathological conditions (premature menopause, drugs, endocrine disorders, etc.).

Pregnancy and lactation are conditions of high bone turnover aiming towards offering approximately 30 gr of calcium to the fetal skeleton. During pregnancy, intestinal absorption of calcium and its renal excretion are increased; however, ionized serum calcium remains constant. PTHrP, which is produced by the mother and the fetus, is increased and plays multiple roles in calcium homeostasis. Oestrogens, prolactin, HPL and IGF-1 directly or indirectly influence bone metabolism. The reliability of studying biochemical indices of bone turnover is limited in pregnancy because of the alterations in plasma volume, glomerular filtration, creatinine clearance and fetoplacental unit contribution. Bone density is slightly increased or not influenced, as shown by bone densitometry. Administration of corticosteriods, magnesium and heparin decrease bone density in pregnancy but this effect is reversible after delivery.

During lactation, the daily calcium requirements of the neonate (200-400 mg) are covered by calcium recruitment from the maternal skeleton. This is mainly achieved through PTHrP which, in combination with the decrease in oestrogens, reduces calcium renal loss and redirects it to the mother's milk. There is a reduction in bone mass in the whole skeleton of approximately 4-6% after 6 months' lactation, which is fully reversible after lactation ceases.

In rare cases there is temporary osteoporosis, mainly in the iliac bones, during pregnancy and lactation, although these two important reproductive events do not constitute risk factors for osteoporosis in menopause.

Bone in The Advanced Menopause: is There a Place for Hormone Replacement Therapy?

N. Tsakalakos

The estrogen deficiency caused by the menopause has very important short- and long-term consequences for the health of postmenopausal women. While short-term use of hormone replacement therapy (HRT) is very effective in the management of the acute climacteric symptoms, the long-term and possibly lifelong use of HRT for the prevention and treatment of the chronic consequences of the menopause (osteoporosis, risk of cardiovascular disease and possibly Alzheimer's disease) presents many difficult problems.

HRT is considered an established approach in the prevention and treatment of postmenopausal osteoporosis. Many short-term and some long-term studies of HRT with bone density (BMD) as a primary endpoint have shown significant efficacy. Moreover, observational studies have indicated a significant reduction in the occurrence of spinal and non-spinal fractures with HRT. However, there are still no large prospective clinical studies of HRT having fractures as the primary outcome. Thus, the efficacy of HRT in the prevention of osteoporotic fractures remains uncertain.

In elderly osteoporotic women, the position regarding the usefulness and efficacy of HRT is even more uncertain. Some studies have shown that HRT is effective in preserving BMD in elderly women, while more recent studies have indicated that the effect of HRT on women 75 years and older is negligible. The same controversy exists with the data on the effect of HRT on fracture risk in elderly women. Most studies, however, agree that current HRT users showed the best results for reduction of fractures and conclude that in order for HRT to be effective in the reduction of fracture risk, it should start early (within 5 years of menopause) and continue for many years (more than 10) and perhaps for the duration of the patient's life. However, long-term HRT use presents many problems, the most important of which is the high discontinuation rate, especially among elderly women. It is known that about 50% of women either do not fill their prescription or if they do, they stop taking it within a year, while more than $^2/_3$ of women on HRT discontinue treatment within 2 years of starting it. This poor compliance is due mainly to the fear of breast cancer and the presence of vaginal bleeding.

Until the effectiveness of HRT in reducing osteoporotic fractures is clarified and compliance is improved, treatments other than HRT should be the first choice for elderly women with osteoporosis. One very good alternative to the HRT approach is raloxifene, a second generation SERM (Selective Estrogen Receptor Modulator), which, as very well-designed large clinical trials have shown, has estrogenic effects on bone (reduction of vertebral fracture risk) and on cardiovascular risk factors, while having anti-estrogenic effects on the breast (reduction of breast cancer risk) as well as the endometrium (no stimulation, no increase in endometrial cancer). Recent studies have shown that the compliance of women on raloxifene is much more satisfactory than for HRT or alendronate (Kaiser Permanente Data). Thus, treatment with raloxifene offers an important opportunity for

elderly women for protection from osteoporotic fractures and perhaps from other chronic non-skeletal consequences of the menopause.

Adverse Effects of Hormone Replacement Therapy: Myth and Reality

Dr. I. Lambrinoudaki

Hormone replacement therapy (HRT) is invaluable for the relief of climacteric complaints, the prevention of postmenopausal urogenital atrophy, osteoporosis, cardiovascular disease and possibly Alzheimer's disease. The use of HRT in Greece is, however, quite low when compared with other western countries, probably because women are afraid of the possible adverse effects associated with HRT. The main untoward effects attributed to HRT are weight gain, thromboembolic disease and endometrial as well as breast cancer.

HRT use may be associated with 1-2 kg of weight gain, which can be prevented by a moderate reduction of salt intake. On the contrary, HRT prevents long-term muscle loss and fat tissue increase associated with the menopause. The relative risk for venous thromboembolism is increased with HRT. Absolute figures, though, are low. The annual risk for postmenopausal women not on HRT is 0.23%, while the respective percentage for those on HRT is 0.60%, much lower than the risk for osteoporosis or heart disease. Women on combined estrogen-progestin preparations have no increased risk for endometrial cancer. On the other hand, prolonged HRT administration for more than 5 years may be associated with a slightly increased risk of breast cancer. Absolute figures again suggest that this increase may be clinically not important: 45 out of 1,000 postmenopausal women who do not take HRT will develop breast cancer, while the respective figure for women who use HRT for longer than 10 years is 51. HRT users tend to develop better differentiated cancers with a more benign clinical course. The mortality, thus, from breast cancer does not differ between users and non-users.

In conclusion, the benefits associated with HRT outweigh the risks. The clinician, however, should handle each case with caution and review the history and risk factors carefully. The decision for HRT represents an attitude towards life and should be met by the clinician and the woman in common, after thorough discussion.

Fracture Syndrome an Overlooked Clinical Entity

P.J. Boscainos

Every musculoskeletal trauma and fractures in particular, result in a change in the mechanical environment and an activation of healing mechanisms, aiming at the restoration of structure and function, through a biological process that begins with locally released inflammation agents and results in remodeling. In the long term this process has an overall effect on the musculoskeletal system and its consequences depend on factors related to the patient, the extent of the lesion and the treatment modality.

Fracture syndrome consists of the whole of the biological consequences in the musculoskeletal system, in the early healing phase until the late phase after rehabilitation and represents a complication in the treatment and immobilization of fractures.

These consequences have been studied in clinical and laboratory settings in patients and animal models and affect the bone, the articular cartilage, the muscles and tendons as well as the joints and ligaments. Most frequently, the result of these complications in functional ability and quality of life is poor and usually irreversible, while the socioeconomic cost is overwhelming. Fracture syndrome, particularly in elderly patients, increases morbidity as well as mortality.

Comprehension of the pathophysiology and the mechanisms involved is essential in the prevention and treatment of fracture syndrome. The rate of onset of fracture syndrome, and the long and usually problematic rehabilitation necessitates increased vigilance by the clinician and in most cases a multi-disciplinary collaboration.

Surgical Management of The Osteoporotic Spine

G. Kapetanos

If spinal surgery is very difficult and demanding work even for the experts, it is obvious that the surgical management of the osteoporotic spine and its instrumentation is a real challenge for the orthopaedic surgeon.

Nowadays in everyday practice, the orthopaedic surgeon is very often faced with the necessity of more aggressive treatment for different conditions of the osteoporotic spine.

The three main conditions are:

1. Traumatic fractures in elderly people, since they are more active than in former years,
2. Reconstructive spinal surgery in osteoporotic patients with spinal stenosis, discopathies, instability, olisthesis etc., since these people insist on quality of life, and
3. Osteoporotic fractures when they cause constant incapacitating pain, severe deformity and very rare late neurological signs. These kinds of fractures are the cause of serious morbidity and poor quality of life. Therefore, not only prevention but also treatment/ correction would be of great benefit.

It is well-known today that if the BMD of vertebrae is below 0,450 gr/cm^2, any instrumentation is difficult to apply and rather unstable. Therefore, we have to increase the BMD preoperatively or modify our technique and materials (the dimensions and depth of the screws, the use of a short and powerful system with hooks etc.) in order to achieve a stable instrumentation.

In addition, we have to correct the deformity, to relieve the pain and mainly to prevent a generalized disorganization/instability of the spine.

We can manage this today by vertebroplasty-kyphoplasty of the fractured vertebra. This vertebral augmentation is better achieved now by transpedicular injection in the vertebral body of some structural material like polymethyl-methacrylate (PMMA), bone mineral cement, other osteoconductive materials (Norian) or by the systematic and local use of different osteoinductive growth factors (TGF-β, BMP-2, BMP-3). This latest concept, although promising, has no serious supportive data at present. It seems that the mot effective and safest method at the moment is kyphoplasty using transpedicularly PMMA (bone cement) in the special plastic bag.

Physical Therapy After Acute Immobilization

A. Kapsabelis, PT

The deleterious effects of immobilization are known and generally accepted. As a result of immobilization, biological tissues lose a great part of their mechanical abilities and especially their strength within a very short period of time. Atrophy of type I fibers and a reduction in power, strength and neuromuscular co-ordination are observed in muscles. Bone mass is reduced and bone microarchitecture is disordered. Cartilage suffers necrosis in loading surfaces and fibrin transformation in deeper surfaces, which cause secondary arthritis and adhesions. Collagen tissues (ligaments, tendons) become less flexible and strong. The reduced flexibility of collagen tissues, the adhesions and the limitation in the lubrication of the joint cause joint stiffness.

The effects of acute immobilization after trauma or operation can be managed by physical therapy focusing on early controlled mobilization. Dynamic splinting, interrupted and continuous passive motion (CPM) and active exercise can accomplish early controlled mobilization. The goals of dynamic splinting are the elongation of collagen fibers and a reduction in joint stiffness based on creep and tense relaxation phenomena. CPM accelerates the restoration of cartilage defects and wound healing, reduces adhesions and increases passive joint motion. Active exercises consist of isometric, stretching, isotonic concentric and eccentric, open and close chain, isokinetic and neuromuscular facilitation. Their goals are an increase in active joint motion, muscle power and strength, neuromuscular co-ordination and bone strength. Co-operation with the doctor and careful assessment of the patient are necessary before planning the physical therapy program. It is essential that the patient participate actively in the program, which must be holistic, painless, safe and fast.

Variability of Biochemical Markers of Bone Turnover and Factors That Influence

C.J. Miras

Biochemical markers of bone metabolism have made it possible to assess the relationships between bone turnover, bone mass and loss. Also, the

evaluation of treatment success and the effectiveness of new drugs can be achieved much more rapidly because biochemical markers do not have limitations posed by bone densitometry or bone biopsy.

However, a number of pre-analytical and analytical factors interfere in the measurement of bone turnover markers. Inter-laboratory variation has been noted for almost all markers of bone turnover and the results cannot be compared among laboratories. This variability can be considered as a major problem of both practical and scientific concern. Pre-analytical factors that influence bone marker measurements are age, gender, growth, diet: diurnal or day to day variation, seasonal rhythms, menstrual and menopausal status, body mass index, physical activity, and way of life. Endocrine disorders, malignant disease, renal and hepatic function and certain medications (corticoid, heparin) and others have to be considered.

Analytical variations in laboratory techniques or the instability of reagents and calibrators have all been found to be of great importance and need standardization for assay precision and accuracy, with inter- and intra-laboratory quality control.

We have proposed a reference range for markers of bone turnover using blood collected from transfusion banks and checked with standard conditions. For inter-laboratory evaluation, separate reference ranges to cover the differences in levels and age-related changes have been established for men and women who are healthy and free from any pre-analytical influencing factors. Since blood from children and old people was more difficult to obtain, for everyday standardization, we relied more or less on bibliographical data.

New Developments in Biochemical Bone Markers

P. Dimou

Biochemical bone markers correlate on the one hand with the estimation of bone turnover rate and on the other with the management of the treatment of osteoporosis and the other metabolic bone diseases. They help mainly with the diagnosis and treatment of the 30% of early postmenopausal women with high bone turnover (FAST BONE LOSERS).

In these cases, the measurement of bone mass is not sufficient because two or three measurements are necessary in order to predict what the biochemical markers can accomplish in 3 or 6 months.

The problem with bone markers is in specificity and sensitivity. This problem can be surpassed with two methods of higher specificity and sensitivity (like chemiluminence assay and new commercial Elisa Kits), which measure the markers in serum, not in urine, where we have to face the known problems of urine collection and creatinine excretion.

Newer markers are now available (traced in serum for bone formation, like osteocalcin, bone alkaline phosphatase and propeptides of type I), as well as for bone resorption, like collagen cross links (total pyridinolines, free pyridinolines, cross-linked N and c-telopeptides).

Recently TRAP 5b was expressed in bone resorbing osteoclasts and secreted into the circulation. Thus, serum TRAP 5b has been considered a potentially useful marker of bone resorption rate.

Bone TRAP can be used to identify individuals with the condition of increased bone resorption rate. Bone TRAP is especially useful in monitoring the efficacy of anti-resorptive treatment (HRT, SERMs, Bisphosphonates) of bone disorders such as osteoporosis, Paget's disese and cancer bone metastases.

Clinical Use of Biochemical Markers of Bone Remodeling

J. Stepan

The issue is the value of any marker or panel of markers, for ascertainment in an individual patient of the risk of fracture, the extent of bone loss, or the response to therapy. Numerous sources of biological variability, namely static factors such as age, gender, menopausal status, disease or recent fracture can be accounted for by using appropriate reference ranges. Dynamic factors such as menstrual or exercise effects can be minimized by standardizing conditions under which samples are taken. However, several sources of variability such as circadian, circaannual, geographical and genetically determined cannot easily be reduced. The interpretation of markers is further complicated by factors known to influence both bone loss and fracture such as corticosteroids and immobilization, that reduce bone formation though not necessarily decreasing bone resorption. The markers offer little practical information for estimating BMD level in individual women and cannot be used as a surrogate measure to predict bone mass and therefore to diagnose osteoporosis. The available data do not indicate that measuring the individual serum and urine markers of the bone turnover can accurately predict rates of bone loss at the spine and hip over a 3-year period in the individual with sufficient accuracy to be used in clinical practice. An association of markers to fracture rates is apparent in some but not all studies. Markers can be used to monitor the response to therapy, and statistical models recently developed should be tested in other cohorts. The main factor affecting clinical utilization of biochemical markers is absence of standardization of assays. Large interlaboratory variations were reported for the current markers. There are currently no accepted criteria for defining a high bone turnover in terms of young adult reference values or age-matched reference values. Thus, the acceptance by clinical practice of biochemical markers for assessment of bone turnover in individual patients requires a better characterization of the markers and an improved precision and standardization of the assays.

Calcium, Vitamin D and its Metabolites

R. Rizzoli

Adequate calcium intake is mandatory for the maintenance of bone homeostasis. During growth, particularly before puberty, there is a positive correlation between calcium intake and bone growth. It is not only bone mass that appears to be affected by calcium but also bone size, as indicated by the results of intervention studies. The positive influence of calcium supplements could last longer than the duration of the dietary modification suggesting, at least for certain kinds of calcium salts, that such a supplement can modify the bone tracking throughout growth. From the second decade on, bone mineral mass remains relatively stable up to the menopause in women. During middle adulthood, there appears to be a slight positive relation between calcium intake and bone mass. After menopause, calcium cannot be substituted for hormone replacement therapy, but calcium appears to sensitize bone to the effects of sex hormones. In the elderly, calcium and vitamin D insufficiencies are frequently encountered. Not only are calcium intake and exposure to the sun reduced, but the intestinal capacity to absorb calcium and the ability of the skin to synthesize vitamin D in response to UV light are diminished in the elderly. These phenomena are associated with compensatory secondary hyperparathyroidism, which causes deleterious effects on bone, particularly the cortical envelope, and also on muscle function. Calcium and vitamin D supplements have been shown to significantly reduce the incidence of hip fracture in elderly people living in nursing homes. Preventive effects of calcium and vitamin D on non-vertebral fractures have also been reported in ambulatory patients living in the community. Besides bone itself, muscle function could be favorably influenced by vitamin D. The serum levels of the active metabolite of vitamin D, calcitriol, decrease with age. However, the results regarding possible prevention of osteoporosis and/or low energy fracture by the administration of calcitriol are far from being consistent and unanimous. With age, the decrease in calcitriol could be an appropriate response to increased bone resorption, rather than being a causal factor for osteoporosis. Finally, the therapeutic window between the stimulation of intestinal absorption and of bone resorption is very narrow. Needless to say, calcitriol and other 1-alpha derivatives are of significant therapeutical benefit in patients with chronic renal failure.

Clinical Efficacy of Calcitonin Treatment in Osteoporosis

J.D. Ringe

Osteoporosis is a common problem among postmenopausal women and patients on long-term corticoid treatment and is associated with significant morbidity, mortality and cost, primarily resulting from osteoporotic fractures. Salmon calcitonin given by subcutaneous injection was the first effective antiresorptive treatment used in these conditions.

This peptide hormone binds to specific surface-receptors of osteoclasts

and thereby inhibits bone resorption. An average decrease of biochemical markers of bone resorption of 30-40% can be found in treated patients and with long-term application, an increase in bone mineral density (BMD) can be observed. Independent of these specific effects on bone turnover and bone mass, calcitonin has an interesting analgesic potency, which was documented in various skeletal and non-skeletal pain syndromes.

The intranasal formulation of salmon calcitonin offers a more convenient and better tolerated alternative to the parenteral application of the hormone. Showing a comparable antiresorptive and analgesic potency, the rate of adverse events is significantly lower. Accordingly, the patient's acceptance and compliance is augmented. The application of the hormone using a nasal spray has produced favorable results in the prevention and therapy of postmenopausal and corticoid-induced osteoporosis. In our own study we compared injectable and intranasal salmon calcitonin in patients with corticoid-induced osteoporosis. We found an equipotent efficacy in terms of BMD and pain reduction for both adopted therapeutic regimens.

In several therapeutic trials of established postmenopausal osteoporosis, early effects on skeletal pain were reported and the changes in BMD amounted to +2 to +3% per year. In a limited number of studies of relatively short duration (1 to 2 years) a decreasing tendency in the incidence of vertebral fractures was reported.

The Prevent Recurrence of Osteoporotic Fractures Study (PROOF) is a large multicenter 5-year study with adequate statistical power to confirm the effect of calcitonin nasal spray on vertebral fracture events in postmenopausal women. 1255 postmenopausal women with established osteoporosis were randomized to receive 100, 200 or 400 IU salmon calcitonin nasal spray or a placebo for 5 years. All patients were treated with 1000mg calcium and 400 IU vitamin D per day. In all three calcitonin groups the rate of new vertebral fractures was reduced, however reaching statistical significance only in the 200 IU dosage group with a 36% reduction in patients with new fractures ($p=0.03$). The rate of hip fractures was 3% in the placebo group and was reduced to 1.6% in the 200 IU group, i.e. a reduction of 48%.

There was an interesting discrepancy between this significant antifracture efficacy and the significant but rather small increases in BMD values. It is supposed that small changes in bone mass at mechanically relevant sites of spongy bone architecture may lead to rather high increases in bone strength, i.e. bone quality is of higher importance than just bone quantity.

Salmon calcitonin is a physiological inhibitor of osteoclasts without toxic side effects and should be kept within our increasing choice of therapeutic options for the different types of osteoporosis.

Developments in the Use of Bisphosphonates in the Management of Osteoporosis

S. Papapoulos

Animal and human studies have demonstrated that daily administration of bisphosphonates leads to the suppression of bone turnover that reaches a plateau within the first 6 months of treatment and remains at the same level for years, despite the continuous administration of the drug. These changes are associated with increases in bone mineral density at all skeletal sites, improvement in bone strength and reduction in fracture risk.

Alendronate and risedronate given daily have been shown by randomized controlled trials and meta-analysis to significantly reduce the risk of fractures, including those of the hip. The question is whether the same total dose given at longer intervals, that can improve patient convenience, can induce the same response. According to current knowledge of bone biology this interval should not exceed 15 days, the life span of the osteoclast. Animal data provided strong support for that and this principle was tested in a large clinical study in which alendronate was given to osteoporotic women once weekly at a dose of 70 mg instead of 10 mg/d. Over two years, the changes in bone turnover and in BMD induced by the two regimens were the same. Until now, attempts to give bisphosphonates at less frequent intervals have generally failed to show antifracture efficacy. In developing such regimens, mainly with injectable bisphosphonates, which provide a therapeutic option for a number of patients, issues related to the dose and dosing interval need to be addressed.

The most important is the reversibility of the effect on bone remodeling following a single administration by the time of the next dosing. Available data indicate partial or complete reversal of the effect does not offer skeletal protection. This issue is currently explored in clinical studies and can lead to the development of efficacious intermittent regimens providing the physician with additional options in the management of patients with osteoporosis with bisphosphonates.

Treatment of Osteoporosis: SERMs

D. Agnusdei

The relevance of hormone replacement therapy (HRT) in the treatment of the short- and long-term complications of the menopause has become clearly evident. This treatment, however, has been associated with the emergence of complications, namely breast cancer and endometrial neoplasia. These side effects have led to research in the direction of tissue-specific effects leading to the evolution of selective oestrogen receptor modulators (SERMs). Tamoxifen was the first SERM employed in the prevention of breast cancer recurrence. Although anti-oestrogenic to the breast tissue, tamoxifen was found to maintain bone mass and preserve a favourable lipoprotein profile. Tamoxifen, however, led to endometrial stimulation with consequent polyp formation and hyperplasia.

Raloxifene is a SERM and it has recently been approved for the prevention of non-traumatic vertebral fractures in postmenopausal women at increased risk of osteoporosis. Acting as an oestrogen agonist in the skeleton, in postmenopausal women raloxifene decreases bone turnover within premenopausal range and fully prevents early and late postmenopausal bone loss. More importantly, raloxifene was also shown to prevent new vertebral fractures in one of the largest studies ever performed, the Multiple Outcomes of Raloxifene Evaluation (MORE), a placebo-controlled, double-blind randomized trial of 7,705 postmenopausal women with osteoporosis. The enrolled osteoporotic women had a mean age of 66.5 years with a hip or spine T-score ≤ -2.5 and/or prevalent vertebral fractures, and they were assigned to receive either a placebo or 60 mg or 120 mg of raloxifene. All the women were provided with supplemental calcium (500 mg/day) and vitamin D (400 IU/day). After 4 years, raloxifene 60 mg (the marketed dose) reduced the risk of new vertebral fractures by 36% (RR 0.64, 95% CI 0.53, 0.46; $p<0.001$) in women without prevalent baseline fractures and by 34% (RR 0.66, 95% CI 0.55, 0.81; $p<0.001$) in women with prevalent baseline fractures compared with the placebo. The reduction in vertebral fracture risk observed for the 120 mg dose in both women with and without prevalent baseline fractures was similar. There was no difference in the proportion of women reporting non-traumatic, non-spine fractures among those receiving raloxifene vs. the placebo. BMD at the hip and spine increased in raloxifene users by 2-3% compared with the placebo after 48 months ($p<0.001$). Raloxifene therapy lowered (cumulative effect) the incidence of multiple vertebral fractures by 75% and the incidence of clinical vertebral fractures by 68% within the first year of treatment. This antifracture efficacy was maintained through to the fourth year and fracture incidence was significantly lowered at each yearly interval.

In the osteoporosis prevention study, raloxifene significantly decreased LDL-Cholesterol, while maintaining unaltered both serum total HDL-C and serum triglyceride levels. Raloxifene also lowered the levels of lipoprotein (a) and fibrinogen, both biochemical markers of cardiovascular risk. These effects of raloxifene will be addressed in a specific cardiovascular outcomes trial: the Raloxifene Use for the Heart (RUTH) trial. The incidence of Estrogen-Receptor positive (ER+) breast cancer was lowered by 84% after 4 years of raloxifene therapy as compared with the placebo (3.7% vs. 0.6%), but the incidence of ER- breast cancer was the same in the two groups (0.4%). Therefore, raloxifene therapy for 4 years maintains BMD in healthy postmenopausal women and reduces the risk of new vertebral fractures by about half in postmenopausal women with osteoporosis, while improving the lipid profile and lowering breast cancer risk.

In the future, with further pharmacological manipulation, more modern SERMs may be able to reduce both the short- and long-term complications of the menopause and simultaneously reduce the incidence of neoplasia such as breast and uterine carcinoma.

Male Osteoporosis: An Underestimated Socio-Medical Problem

J. Stepan

Fragility fractures in men are a public health problem. The differing

incidence of fractures across time, from country to country, between genders and races is poorly understood and needs to be studied prospectively to determine whether differences in the incidence of falls, severity of trauma, or differences in fragility are responsible. In the Czech Republic, in 1997, out of 320 000 men over the age of 70, an estimated 39% had osteoporosis. The prevalence of spine fractures is about half that of women. About one third of all hip fractures occur in men. Hospital discharges for hip fracture in men increased over a 30 - year period by 15-fold. Population aging explained half of this increase in men. The relative risk for spine and hip fracture conferred by a 1 SD lower BMD, or by a prevalent fracture, is similar in men and women. Higher mortality and fewer falls may contribute to the lower incidence of fractures in men than in women. The structural components that determine the breaking strength of bone (bone size, periosteal apposition, cortical porosity and trabecular architectural disruption) are favourable in men. An accelerated bone loss, cortical thinning and porosity, trabecular thinning, and loss of connectivity during aging in men is particularly due to exposure to risk factors, hypogonadism and illness. The problem of osteoporosis in men remains unrecognized by doctors, the public, health authorities and pharmaceutical companies. The use of calcium and vitamin D supplementation, and testosterone in men with proven hypogonadism appears to be reasonable intervention. The antifracture efficacy of drugs used in women remains to be established in men. In conclusion, an increase in incidence rates above that due to population aging may increase future fracture rates and the public health burden of fractures in men still further.

Therapeutical Management of Osteoporosis in Men

G. Trovas

Osteoporosis in men is more common than many realize. Applying the WHO criteria for osteoporosis, 47% of men aged 50 and above have osteopenia at the femoral neck and 6% have osteoporosis, which is responsible for one-third of all osteoporosis-related hip fractures. Men are not routinely evaluated for osteoporosis risk factors and as a result are undiagnosed and under treated. Osteoporosis prevention consists of adequate calcium and vitamin D intake, avoiding smoking, excess alcohol etc., fall prevention, exercise, and treatment of secondary causes.

To optimize therapy for primary osteoporosis in men, it is crucial to establish criteria for effective treatment. Information on specific therapies is now available for alendronate, PTH, calcitonin and fluoride in male osteoporosis.

Management of Musculoskeletal Pain Due to Inflammatory Degenerative Causes and Post-Operative Pain

K. Malizos

Pain is the unpleasant sensory and emotional experience associated with actual tissue damage or an experience described as such.

As a common characteristic of inflammation, surgical tissue trauma and arthritis, pain is the result of released mediators and cytokines such as Interleukin-1, Bradykinin, substance and prostagladins, acting both locally and systemically through blood circulation. They induce a cascade of local and systemic neuro-endocrine, metabolic and neuro-immunologic responses.

In addition to the biological interactions, pain also initiates psychological processes. Pre-emptive analgesia is essential for the management of post-operative pain, the reduction of cardiovascular complications, morbidity and cost.

NSAIDS are routinely used for the management of arthritis and inflammatory pain, and post-operative and acute pain.

Opioids are mainly used for post-operative pain management but present side effects such as nausea, vomiting, dizziness and disorientation in 25% of the patients. Use of NSAIDS for the management of post-operative pain reduces the dosage and side effects of opioids.

In cases of moderate pain, NSAIDS may be used as a single therapy and in cases of severe pain, as an adjunct. The most common complications are from the GI system and the kidneys.

The recent development of COX-2-inhibiting molecules gave new possibilities for increased usage without a concomitant parallel increase in side effects, reduced or fewer gastric reactions, no interference with platelet activity and equal effectiveness as with older NSAIDS. Coxibes have been successfully utilized in osteoarthritis, inflammatory arthritis and acute pain and in post-operative pain control. Rofecoxib has proved effective in post-operative pain management, limiting the use of opioids without the unwanted effects of older NSAIDS.

The new coxibes for IV use, now on trial, may decisively change our approach to the control of acute and post-operative pain.

Management of Pain in Osteoporotic Patients

G.P. Lyritis

Musculoskeletal pain, common in osteoporosis, is one of the most frequent symptoms for which medical assistance is sought. Osteoporosis represents one of the main causes of back pain in postmenopausal women. On the other hand, in the same population, non-osteoporotic vertebral deformities are seen as often as osteoporotic ones, and they are also the main cause of back pain. In women up to 60 years old, back pain was found mostly to be due to degenerative disorders of the spine. The differential diagnosis for pain in osteoporotic patients is extensive, but individualizing the patient work-up begins with a careful clinical history, appropriate radiographic examination and possible bone scan, computed tomography and magnetic resonance imaging. In more than half of the cases of chronic pain related to muscle-skeletal syndromes, the pain is in the region of the head and back. Osteoporosis-related fractures have important health consequences for older individuals, including disability and increased mortality. Clinical or sub-clinical vertebral fractures are a common cause of acute back pain, but it is surprising that most of these patients do not receive anti-osteoporotic treatment. In fact, in a retrospective study, only 18% of medical records indicated that fracture patients had been prescribed anti-osteoporotic medication. Back pain in the majority of these patients is treated with prolonged bed rest, local and systemic analgesia and bracing. The elongation of bed rest in these patients results in an increase in bone loss (identified by the increase of hydroxyproline excretion), muscle weakness and joint stiffness. Another interesting aspect is that as most of the osteoporotic vertebral fractures occur in high bone turnover patients, post-fracture immobilization is an additional risk factor of increased bone loss. A better approach in the management of musculoskeletal pain in osteoporotic patients combines the anti-resorptive effect of an anti-osteoporotic agent with analgesia caused directly by the anti-osteoporotic treatment, or with the combination of a pure analgesic agent. This regime increases the compliance of the osteoporotic patient to long-term treatment and prevents the disuse due to painful attacks, especially of the spine. Pain in the spine in osteoporotic patients is a result of an acute vertebral collapse or a gradual loss in height of the osteoporotic vertebrae in consequent attacks. On the other hand, patients with existing osteoporotic fractures of the spine have constant pain due to mechanical reasons. In man, calcitonin alleviates the pain associated with bone disorders. The analgesic effect of calcitonin has been observed in animal experiments in different studies. Intracerebroventricular administration of 8 IU/kg salmon calcitonin raised the pain threshold in rabbits subjected to electrical stimulation of the dental pulp. This analgesic effect of salmon calcitonin reaches a peak at 90 minutes and appears to be sustained on repeated dosing, whereas the effect of equipotent doses of morphine (10 mg/kg) tends to decline with repeated administration. The effects of calcitonin and morphine together are additive, although they have been shown *in vitro* to act at different receptors. In patients with intolerable chronic pain, a single injection of salmon calcitonin via the subarachnoid route achieved pain control within a few minutes (10). The explanation of the analgesic effect of calcitonin is still not clear. The analgesic activity of salmon calcitonin (subcutaneous or intranasal) has been demonstrated in several prospective clinical trials, in patients suffering different painful skeletal conditions, including recent non-traumatic osteoporotic vertebral fractures. The mechanism of the analgesic effect of calcitonin is not clear. It is possible that specific binding sites for salmon calcitonin (sCT) exist in the brain. Another explanation is that changes in descending serotonergic modification on the sensory transmission mediated by C afferents contribute to the analgesic effects of calcitonin on pain in osteoporotic patients. From the clinical point of view, the analgesic effect of calcitonin is beneficial throughout the whole period of medical treatment of osteoporotic patients. Salmon calcitonin in a daily dose of 100 IU subcutaneously or 200 IU

intranasally dramatically reduces back pain ($p<0.0005$) after a recent osteoporotic vertebral fracture and promotes the early mobility of patients. The finding that subcutaneously or intranasally administered salmon calcitonin effectively controls severe pain in osteoporotic patients with a recent vertebral fracture, allowing them earlier mobility in combination with a reduction in urinary hydroxyproline excretion, and a limitation of the considerable bone loss that may occur during prolonged bed rest, makes this therapeutic scheme attractive.

The Treatment of Painful Bone Metastases

V. Barbounis

The pain from metastatic bone lesions poses one of the most important problems for patients and one of the most difficult problems for the oncologist. Every year more than 1,000,000 new cases are presented. Thirty-three to 66% of these will develop devastating pain. In the vast majority of cases, bone metastases cause only morbidity and they do not threaten the life of the patients, while destroying the quality of their lives.

The treatment of the pain due to bone lesions comprises various different therapeutic modalities, such as:

a) systematic administration of analgesics and painkillers,
b) chemotherapy and/or hormonotherapy,
c) surgical operation,
d) radiotherapy, and
e) administration of bisphosphonates.

Analgesics offer transient alleviation of the pain but they lack permanent effect. Chemotherapy or hormonotherapy are directly correlated with the chemosensitivity or hormonosensitivity of the underlying neoplasia. When such sensitivity is present, these modalities have satisfactory results for a period of time.

Surgical intervention itself is able to offer an improvement in function as, to some degree, can analgesia. Radiotherapy possesses the ability to diminish the pain in the body area in higher degree than the previous modalities. However, it has the disadvantage of being a local treatment without systemic results in the rest of the skeleton. This latter fact can be circumvented effectively with the intravenous administration of some redionuclides, such as strontium etc.

Bisphosphonates are the most promising treatment for metastatic bone disease. They are stable analogs of inorganic pyrophosphates. They disturb bone resorption and inhibit the action of osteoclasts. They are administered mainly by the IV route. The data from large randomized trials have proved that in combination with chemo or hormonotherapy, they are superior to chemo/hormonotherapy alone in the treatment of metastatic bone pain for a number of solid tumors or myeloma. They significantly reduce the need for radiotherapy and orthopaedic operations. In the majority of the trials, pamidronate was used, while zoledronate is the most active agent of the group with significant antineoplastic properties.

Physical Therapy in Musculoskeletal Pain

D. Sfetsioris

The clinical rationale for pain relief is based upon empirical observation and integration of information from basic and applied sciences. There are many clinical applications based on the knowledge of the gate theory and the central modulation of pain. Many techniques can stimulate receptors that send information to the dorsal horn through large myelinated fibers, leading to partial or complete inhibition of nociceptive input.

The stimulation of "trigger" points, motor points, and acupuncture points is considered responsible for eventual activation of PAG and descending inhibition of nociceptive input. Behavior modification seems to be efficient in the control of pain.

There are many techniques, which can be reasonably used by the physical therapist to deal with the problem of pain. Massage, mobilization techniques, electrotherapy, relaxation, and biofeedback are some of the physical therapy modalities, which are commonly used in everyday practice. In the past, their use was justified on an empirical basis. The physiology of nociception now permits us to justify their use in a more scientific way and to explain their high success rate in the management of pain.

Although heat and cold are known to relieve pain in a variety of conditions, the underlying mechanisms were obscure. In recent years, it seems that some mechanisms accounting for local neuralgic and vascular changes in response to the thermal agent can be responsible for such analgesic effects. A decrease in sensory nerve conduction, an alteration in neuronal activity of the endings of the muscle spindle, the counterirritation theory, the generalized relaxation, vascular changes, and somatovisceral reflex arcs can be used to explain thermal effects on pain.

The physical therapist can use his skills and his means to reduce or to control the sensation of pain in order to establish the more appropriate conditions for his essential goal, which is always the restoration of function. For that purpose, primary consideration should be given to individualization of the treatment program.

Nutritional Aspects in the Rehabilitation of Elderly Fractured Patients

R. Rizzoli, M.D.

Among the determinants of osteoporosis in the elderly, nutritional deficiencies certainly play a major role. A variety of evidence also leads to the conclusion that protein intake far below RDA could be particularly detrimental for both the acquisition of bone mass and the conservation of bone integrity with aging. Various studies have come to the conclusion that either a deficient or an excessive protein supply could negatively affect the balance of calcium. In a prospective study carried out on more than 40,000 women in Iowa, higher protein intake was associated with a reduced risk of hip fracture. In a longitudinal follow-up in the frame of the Framingham study, the rate of bone mineral loss was inversely correlated with dietary protein intake. Altogether, these results indicate that a sufficient protein intake is mandatory for bone health. Thus, whereas a gradual decline in calorie intake with age can be considered as an adequate adjustment to the progressive reduction in energy expenditure, the parallel reduction in protein intake may be detrimental for maintaining the integrity and function of several organs or systems, including skeletal muscles and bone. Experimental and clinical studies suggest that dietary proteins, by influencing both the production and action of growth factors, particularly the Growth Hormone (GH) – Insulin-like Growth Factor (IGF) system, could control bone homeostasis. Protein restriction has been shown to reduce IGF-1 plasma levels and to render target organs less sensitive to IGF-1. Even a simple oral dietary preparation that normalizes protein intake can improve the clinical outcome after hip fracture, in association with an increase of IGF-1 and even of IgM concentrations. Protein undernutrition can be associated with alterations of cytokine secretion, such as interferon gamma, tumor necrosis factor alpha, or transforming growth factor beta. The modulation by nutritional intake of cytokine production and action, and the strong implication of various cytokines in the regulation of bone remodeling suggest a possible role of certain cytokines in the nutrition-bone link. In conclusion, there is a large body of evidence linking nutritional intake, particularly protein undernutrition and replenishment, to bone homeostasis and osteoporotic fractures. Several mechanisms, among them the growth hormone-IGF-1-target organ axis and various cytokines, are likely to be implicated. This should be strongly considered in the management of elderly patients with osteoporotic fractures.