Proceedings of the 1st International Symposium on Secondary Causes of Osteoporosis

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Chairmen: Maria Luisa Brandi and **Sol Epstein**

Maria Luisa Brandi, M.D., Ph.D.
Department of Internal Medicine,
University of Florence
Viale G. Pieraccini 6, 50139 Florence, Italy
Ph. +39 055 4296586
Fax +39 055 4296585
E-mail: m.brandi@dmi.unifi.it

Sol Epstein, M.D.
Mount Sinai School of Medicine
New York, NY, USA
Ph. +1 215 345 2867
Fax +1 215 345 2532
E-mail: bonedocsol@aol.com

Introduction and overview

The secondary causes of osteoporosis are frequent but because of the vast numbers of women suffering from postmenopausal and age related bone loss and fractures, its importance is overshadowed despite the fact that these forms of osteoporosis can be potentially devastating. With this in mind the 1st International Symposium on Secondary Causes of Osteoporosis was held in July 2006 in Florence, Italy. The invited speakers were all international authorities on their subject and presented new data derived from their own research and the world literature. There were 6 sessions in all.

The first session covered immune related bone disease and the emerging field of immuno-osteobiology. The topics reviewed included the role of T cells in mediating the action of PTH, the exciting discovery that the osteocytes and their canaliculi are disrupted by glucocorticoid excess which may help explain the poor bone quality in steroid induced osteoporosis. The role of the calcineurin inhibitors on bone in post transplant induced bone disease and the role of the T lymphocytes and new treatment modalities for this devastating form of osteoporosis was discussed. A form of osteoporosis which is emerging as an important consideration for both men and women is cancer therapy with the increasing use of aromatase inhibitors and androgen deprivation therapy for the treatment of breast and prostate cancer. The fracture rate is increased and bisphosphonates are the mainstay of standard of care for the bone problems despite the potential for osteonecrosis of the jaw in these patients.

The second session concentrated on gastrointestinal, rheumatic, renal and neurological diseases.
The inflammatory bowel diseases produce osteoporosis via a variety of mechanisms, including inflammatory cytokines, disturbances of the RANKl/OPG system, malnutrition and Vitamin D deficiency. Rheumatoid arthritis patients have an increased risk of fracture due to steroid medication as well as alterations in the RANKL/OPG system. The risk of fracture is also increased in ankylosing spondylitis. Treatment modalities include bisphosphonates and disease modifying drugs such as anti-TNF therapies. Uremic osteodystrophy and the various metabolic abnormalities relating to PTH, Vitamin D, phosphate retention and the complex interplay resulting in the different types of bone abnormalities and new therapies such as the Vitamin D analogs and calcimimetics were also discussed.
The final topic of this session was the effect of immobilization stroke and spinal cord injuries on bone loss. The severity of bone loss with immobilization is much greater than that seen with post menopausal osteoporosis as are fracture rates. Both trabecular and cortical bone are lost. The main etiology is loss of mechanical stimulation. Therapy is largely still unproven and the studies have not been powered sufficiently to assess fracture rates.

The third session which generated a lot of debate was that which was devoted to “hot” topics which were not well publicized but increased our understanding of osteoporosis in certain populations. Anorexia nervosa has an incidence of osteopenia of 90% and osteoporosis of 40% with a 7-fold increase in fracture rate. Here the main brunt of the disease was on the osteoblast with bone formation impaired although bone resorption is also increased. Etiological factors include a GH (growth hormone) resistant state, estrogen deficiency, calcium and vitamin D abnormalities as well as hypercortisolism and nutritional/regulated hormones. The treatment is difficult and no therapy has been shown to be ideal in reversing the bone loss. The role of anabolics, estrogen and IGF1 singly or in combination was discussed.
Weightlessness (lack of gravity) during space flight have intrigued bone researchers particularly as space flights are becoming more common, and of longer duration. The principal cause appears to be loss of mechanical signals to the skeleton. This loss occurs despite 2 hours exercise per day. A novel approach maybe to exert low magnitude/high frequency loading regimens via mechanical devices. These appear to be effective in delivering signals to the bony skeleton as well as to the muscular components of the skeleton.
The role of idiopathic hypercalciuria, osteoporosis and the role of cytokines such as IL-1, IL-6, and TNF alpha in the pathogenesis were discussed. The type of osteoporosis is one of increased bone resorption. Thiazide diuretics are still the mainstay of treatment to reduce the hypercalciuria.
Vitamin D plays an integral role in skeletal integrity yet more than 50% of postmenopausal women worldwide and 97% of hospitalized patients in some countries have Vitamin D levels below 30 ng/ml (75 nmol/L). This level by consensus is considered sufficient or adequate. The other functions of Vitamin D were discussed (eg, in relationship to falls, musculoskeletal integrity and immunity, etc.).

Session 4 included osteoporotic fractures in men. These are an important public health problem. The fracture burden is about 1/3 that of post menopausal osteoporotic women. The morbidity and mortality may exceed that of their female counterparts with hip fractures. Gender affects on the anatomy of

the skeleton plays a role with men having thicker cortices and larger bones. Osteoporosis in men is often idiopathic but is also multifactorial with the role of the sex steroids now beginning to be clarified. BMD still remains an integral part of the identification of men at risk for fracture. Despite tools for measuring BMD few men are diagnosed and treated for osteoporosis.
The last talk of this session was an extremely comprehensive presentation of the practical impact of genetic disorders of bone. Diseases such as osteogenesis imperfecta, skeletal dysplasias, hypophosphatemia, MEN 1, MEN 2, and disorders of the calcium sensor receptor producing hypo- and hyper-calcemia. The diagnostic tools such as mutational analysis have assisted the physician in guidance of treatment (eg, DNA diagnosis for prophylactic thyroidectomy in MEN 2).

Sessions 5 and 6 were devoted to new drugs for the treatment of osteoporosis.
The data of the bisphosphonates used in extended dosing intervals were discussed. The binding affinities and potency in relation to inhibition of key enzymes in the mevalonic acid pathway was shown for zoledronic acid. The relationship to osteonecrosis of the jaw in the clinical trials was also discussed. Ibandronate results from the compliance trials were presented and the implications for monthly versus weekly administration debated. The protocol for the head to head trial (MOTION) of alendronate versus ibandronate was also shown.
The inhibition of the RANK-RANKL/OPG pathway has been utilized to develop drugs which inhibit RANKL in order to suppress bone turnover and bone resorption. Denosumab (Amgen 162; RANKL monoclonal antibody given every 6 months by sc injection) has successfully completed phase 2 studies and shown impressive gains in BMD at all sites. Phase 3 fracture trials are ongoing.
The holy grail in terms of treating osteoporosis for Vitamin D has been to develop specific bone sparing or forming analogs which do not produce bone resorption and hypercalcemia. The vitamin D receptor is the target of many initiatives to try and fulfill this role. The vitamin D knockout models have been used to try and explain all the actions of vitamin D but as yet there are still many unanswered questions especially at the molecular level. New analogs such as ED 71,2 MD and MV2 are currently being investigated for their treatment in osteoporosis. The results of the new SERM-bazedoxifene from phase 2 and 3 studies were shown with the emphasis on uterine sparing properties while preserving BMD. Anabolic therapies such as PTH 1-34 and 1-84 were discussed in relation to fracture reduction and combination therapy with either estrogens, raloxifene and bisphophonates. Other osteogenic peptides such as hPTH 1-31 and PTHrP 1-36, nasal oral and dermal preparations were mentioned as potential therapeutic options.
Strontium ranelate is not approved in the USA for the treatment of osteoporosis but is used in other countries. The data on fracture reduction from the pivotal trials, pharmacokinetic and pharmacodynamic data on this drug was presented. The last talk of this session was a presentation of the development of small molecules such as alpha V beta integrin, and cathepsin K to inhibit bone resorption. Knockout animal models which develop osteosclerosis led to exploration of the potential of these compounds for treating humans with osteoporosis. Cathepsin K inhibition produces bone resorption inhibition in animal models whilst sparing bone formation. Human studies are ongoing with cathepsin K and preliminary results show significant reduction of markers of bone resorption and little or no change in formation markers.

The meeting concluded after this talk.