Combined Meeting of the
3rd IOF Asia-Pacific Regional Conference on Osteoporosis *and the*
16th Annual Meeting of the ANZ Bone & Mineral Society
~ 22-26 October 2006, Port Douglas, Australia ~
www.anzbms.org.au/asm/asm2006

SESSION TIME: 0815 - 1000, Wednesday 25 Oct 2006

Invited Plenary Abstracts
Plenary Lectures 5 - Epidemiology, Pathogenesis and Cancer

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Epidemiology of fractures – known and unknown

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Which fractures are osteoporotic in nature?
Hip, vertebral and forearm fractures are the classic osteoporotic fractures. However, it is increasing being recognized that many other fractures could be osteoporotic. In the Dubbos Study, fracture of the ankle, rib and humerus were frequent and was found to be associated with low bone mineral density. In Mr and Ms Os(Hong Kong) , fractures occurred in many sites and most of these were found to be associated with osteoporosis.

Are fractures in Asian Lower than Caucasians?
The incidence of hip fractures are definitely lower in Asians than Caucasians. According to the Asian Osteoporosis Study, the incidence of hip fracture in developed Asian countries was around 80% of these observed in American Caucasians, while the incidence of hip fracture in developing Asian countries was only 50% of than in America Caucasians. In contrast to hip fracture, the prevalence of vertebral deformity is as high in Asians (14%) as in Caucasians (12%-19%).

Why is hip fracture less frequent in Asians than Caucasians?
Despite the lower incidence of hip fracture in Asians, bone mineral density is around 20% lower in Asian than Caucasians. The reasons why hip fracture is less frequent in Asians is hence unknown. Difference in hip morphometry, tendency to fall and muscle strength are possible explanations.

Are osteoporotic fracturesbecoming less frequent around the world?
There is some evidence that hip fracture is becoming less frequent in the West. In Ontario, Canada, hip fracture incidence began to decrease in the 20 century, reaching a rate of 33 per 10,000 in 2005. However, in Asia, including Singapore and Hong Kong, the incidence rates of hip fracture has remained static after an exponential increase. These different changes could be due to more comprehensive diagnosis and treatment of osteoporosis in the west.

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Goodbye T and Z, Welcome to the absolute risk on the Y-axis

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Osteoporosis is described as 'a disorder characterised by low bone mass and micro-architectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk'. From an operation view osteoporosis has been defined in terms of bone mineral density (BMD), namely a BMD that lies 2.5 SD or more below the average value for young healthy women. Diagnostic thresholds have been best validated for femoral neck BMD using dual energy X-ray absorptiometry. A diagnostic test has clinical value if it provides information that is useful to direct intervention strategies or inform on prognosis. In this context, the risk of fracture increases approximately 2 to 3-fold for each SD decrease in femoral neck BMD. There are, however, well recognised limitations to the use of T-scores. The first is that the test lacks sensitivity over most ranges of assumptions. Thus, at acceptable specificity, the majority of patients who will fracture would be designated to be at low risk at the time of testing. Secondly, the performance characteristics of the test varies with age. For any BMD, fracture risk is much higher in the elderly than in the young. For example, in men and women at the threshold of osteoporosis (T-score = -2.5 SD), the 10-year probability of hip fracture ranges from 1.4 to 10.5% depending on age. A third limitation is that the predictive value of BMD tests at the hip vary according to the Z-score. For the prediction of any osteoporotic fracture, the risk increases by 2.0/SD with a Z-score of -3, but the gradient of risk is 1.3 with a Z-score of +3. These limitations can be partially resolved by taking account of factors that influence fracture probability. The use of fracture probability as the clinical metric also permits the consideration of prognostic risk factors over and above that provided by BMD and age. Independent risk factors include a prior fragility fracture, a parental history of hip fracture, the use of glucocorticoids, rheumatoid arthritis, smoking and excessive alcohol consumption. If these risk factors are to be used, their multiplicity demand the use of fracture probability as the measurement of clinical relevance. In addition, the output from multiple techniques and sites for BMD assessment (all with different gradients of risk) can be standardised. The acceptance of fracture probabilities in clinical practice will render T-scores and Z-scores less relevant.

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Pathogenesis of bone fragility

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At the microscopic level, osteoporotic bone is normally mineralized but reduced in volume. There is a generalized thinning of trabecular elements with the total loss of some trabeculae. The combination of less bone and disrupted micro-architecture greatly reduces the strength of osteoporotic bone. Loss of bone is sometimes pathological, but more commonly occurs as a normal part of the ageing process. With age, the efficiency with which osteoblasts refill resorption cavities is reduced, and there is also an increase in bone resorption, probably resulting from hypogonadism. There is an increase in fracture risk with age which is partly independent of BMD.

Whether or not an individual develops osteoporosis depends on their peak bone mass, their rate of loss of bone in later life, and their longevity. Probably the strongest influence on peak bone density is genetic, though the major genetic contributors remain to be determined. Genetic mechanisms probably underlie the significant racial differences in fracture incidence, and might involve differences in bone architecture as well as BMD. Body weight is an important influence on bone density throughout life, heavier people having greater bone mass. This is probably mediated via hormonal mechanisms and by direct skeletal load. The role of calcium intake in determining bone density is limited, and vitamin D deficiency, which is common in older individuals may also contribute to reduced bone mass. Physical activity contributes only moderately to the differences in bone density that exist in postmenopausal women.

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Cancer + Bone - new frontier in drug discovery in oncology

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Inhibitors of bone resorption have changed the way in which we think about cancer bone disease, clarified our understanding of the interactions that occur between cancer cells and osteoclasts in the bone microenvironment, and become major drugs in the field of oncology, with sales in the range of $3 billion dollars US and increasing. Bisphosphonates are the drugs most commonly used, and are likely to dominate this field for the next few years until approval is obtained for other agents that specifically interfere with RANK ligand effects on osteoclasts. However, with the widespread use of resorption inhibitors, new issues arise. The most prominent at this time is the issue of osteonecrosis of the jaw (ONJ), which appears to be predominantly bisphosphonate associated and was unknown as a complication 5 years ago, despite widespread use of these drugs in patients with cancer for almost 30 years. Our field's approach to the ONJ issue has been slow, and as a result there is danger that overreaction to its possibility as a side effect may lead to patients not being treated with these agents when they need them as life saving therapeutics. An interesting question unanswerable at present is whether ONJ is a specific association of bisphosphonates, or whether it is a complication of osteoclast inhibition by any means. Resorption inhibition invariably reduces tumor burden in bone, independent of the mechanism. This has important implications for the management of patients with advanced cancer, and emphasizes the importance of this form of therapy directed at the host in patients with widespread metastatic disease. The reduction in tumor burden is due to impaired release from remodeling bone of factors that promote tumor growth and aggressive behavior, such as TGFb. These issues and others relevant to cancers that metastatize to bone will be reviewed during this presentation.