**SESSION TIME:** 0815 - 0930, Thursday 26 Oct 2006

# Oral Abstracts
## *7 - Emerging therapies*



**O84**

### Accelerated fracture healing in osteoprotegerin deficient mice

N. Ota[1], N. Kosaki[1], K. Horiuchi[1], H. Ikegami[1], J. Takito[1], T. Kimura[2], Y. Okatada[2], H. Takaishi[1], Y. Toyama[1]
*Departmens of 1 Orthopaedic Surgery and 2 Pathology, Keio University, School of Medicine, Tokyo, Japan*

Osteoprotegerin (OPG) is a decoy receptor for RANKL and acts as a negative regulator of bone resorption. It has previously been shown that OPG is highly expressed in fracture bone, indicating possible involvements of OPG in bone healing process. To further investigate the roles of OPG in fracture healing, we generated a fracture model and analyzed the healing process in OPG-deficient mice (OPG-/-). A transverse osteotomy was done in the mid-diaphysis of the tibia in 8-week-old OPG-/- and wildtype mice (WT) and bone healing was assessed radiologically and histologically. Notably, fracture healing process was significantly accelerated in OPG-/- compared to that in WT. On X-rays, callus became apparent at around day 10 and bone union by day 21 in WT, while in OPG-/- fracture callus was evident even at day 4 and bone union was completed by day 14 in all specimens. Bone remodeling was nearly completed by 4 weeks post-fracture in OPG-/-, meanwhile it took as long as 8 weeks in WT. Histologically, there was a significant acceleration in bony callus formation which was apparent on and after day 4 in OPG-/- and a higher number of TRAP-positive multinuclear cells in fracture site throughout the fracture healing process compared to that in WT. These results indicate that lack of OPG leads to an accelerated fracture healing and that OPG plays essential roles, not only in the homeostasis of bone physiology, but also in the regulation of callus formation and remodeling during fracture healing.

**O85**

## The PPAR-gamma agonist rosiglitazone decreases bone formation and reduces bone density

A.Grey, M. Bolland, G.Gamble, D. Wattie, A. Horne and IR Reid
*University of Auckland, Auckland, New Zealand*

Laboratory and animal studies suggest that peroxisome-proliferator-activated receptor-gamma (PPAR-gamma) signalling negatively regulates osteoblastic bone formation and bone density. Thiazolidinediones (TZDs), which are PPAR-gamma agonists, are widely prescribed to patients with disorders characterized by insulin resistance. Human data on the skeletal effects of TZDs are currently available only from observational studies containing small numbers of TZD users.

We performed a 14 week randomized, placebo-controlled trial in 50 healthy postmenopausal women, to assess the effects of the specific PPAR-gamma agonist rosiglitazone on biochemical markers of bone formation. Participants were randomly assigned to receive rosiglitazone 8mg/day (n=25) or placebo (n=25).

The osteoblast markers procollagen type I N-terminal propeptide and osteocalcin declined by 13% ($p<0.005$ vs placebo) and 10% ($p=0.04$ vs placebo), respectively, in the rosiglitazone group. These changes were evident by 4 weeks, and persisted for the duration of the study. There was no change in the serum β-C-terminal telopeptide of type I collagen, a marker of bone resorption ($p=0.9$ vs placecbo). Total hip bone density fell in the rosiglitazone group (mean change from baseline rosiglitazone -1.9%, placebo -0.2%; $p <0.01$); the change in lumbar spine bone density was not significantly different between groups (mean change from baseline rosiglitazone -1.2%, placebo -0.2%; $p=0.13$).

These data provide evidence that PPAR-gamma agonists exert detrimental skeletal effects. Fracture risk assessment and skeletal monitoring should be undertaken in patients for whom TZD treatment is prescribed. Skeletal endpoints should be added to, or included in, long-term studies of TZD use.

**O86**

## Prevention of bone loss in acute spinal cord patients over one year with alendronate: randomised double-blind placebo controlled study

N.L. Gilchrist [1], C.P. Frampton [2], R.R. Acland[3], R.L. March[1], P. Maguire[1], A. Heard[1], P. Reilly[1] and K. Marshall[3]
*Canterbury Geriatric Medical Research Trust, Christchurch, New Zealand[1], Associate Professor/Biostatistician, Department of Medicine, Christchurch School of Medicine, Christchurch Hospital, New Zealand[2], Burwood Spinal Injuries Unit, Christchurch, New Zealand[3]*

The aim of the study was to document the effect on bone mass loss in acute spinal cord injury patients using oral alendronate 70mg once weekly having commenced within 10 days of acute spinal cord injury and administered for a period of 12 months. Between March 2001 and February 2004, males and females, 18 – 55 years presenting to the Burwood Hospital, Spinal Injury Unit, Christchurch, New Zealand with acute spinal cord injury (C4 – L2, ASIA scores A – D) were randomly assigned to enter a prospective double blind placebo controlled study to compare the safety and efficacy of oral alendronate 70mg once weekly. Additional calcium or vitamin D was not administered. Vitamin D deficiency was corrected. Data was collected at baseline 3, 6, 12 and 18 months (bone mineral density, total body and regional areas, hip, lumbar spine and ultrasound at calcaneous). Weight body mass index and adverse events were collected. Bone mineral density loss was prevented at the total body site (>7% and at the regional site, pelvis >15%, trunk >4%, legs >7%, arms >3%). No significant loss was observed at the spine. All areas at the hip demonstrated prevention of bone loss, total >16%, femoral neck >16%, trochanter >20%, femoral shaft >15%. In conclusion this is the first study to use once weekly oral alendronate in patients with acute spinal cord injury soon after the acute event. Bone loss was prevented in most bone sites measured and occurred over 12 months with oral alendronate 70mg per week.

**O87**

## Zoledronic acid inhibits both the osteolytic and osteoblastic components of osteosarcoma lesions but increases lung metastases in a mouse model

A. Labrinidis, L.M. Thai, V. Liapis, S. Hay, D.M. Findlay and A. Evdokiou
*Discipline of Orthopaedics, University of Adelaide, Royal Adelaide Hospital, and Hanson Institute, Adelaide, South Australia*

Osteosarcoma (OS) is the most common primary malignant tumour of bone and is associated with the formation of osteolytic and/or osteoblastic lesions. The objective of this study was to evaluate the efficacy of ZOL in the development, progression and metastatic spread of OS, using an established model of direct transplantation of OS cells within the tibial marrow cavity of mice. The effect of ZOL on bone and tumour growth was analysed by radiography, micro-CT and histology. Mice transplanted with K-HOS human OS cells and left untreated showed extensive osteolysis in the area of cancer cell transplantation and new bone formation in the form of bone spicules extending from the periosteum. In contrast, treatment with ZOL at 100 g/kg/dose, once weekly for five weeks prevented the formation of osteolysis and significantly reduced the amount of new bone formation. Micro-CT analysis showed a significant increase in trabecular density and cortical thickness in the ZOL-treated animals. Despite the protective effects of ZOL on OS-induced bone remodeling, ZOL had no effect on tumour burden in the surrounding soft tissue. Importantly, we found that the incidence and severity of lung metastases in the ZOL-treated animals, was significantly greater. This is the first report to show that ZOL protects the skeleton from bone destruction by OS. However, our findings that ZOL treatment may promote metastasis of OS cells from bone to lung is of major concern and warrants further investigation.

**O88**

## Circulating 25-hydroxyvitamin D below 80nmol/L causes osteoporosis in an animal model

P.H. Anderson[1], R.K. Sawyer[1], A. Muliabrahimovic[1], B.K. May[1], P.D. O'Loughlin[1,2], H.A. Morris[1]
*[1]Endocrine Bone Research, Hanson Institute & [2]Division of Clinical Biochemistry, Institute of Medical and Veterinary Science, Adelaide, SA, 5000, AUSTRALIA*

The association between increased risk of hip fracture and a low vitamin D status has long been recognised although the level of vitamin D required to maintain bone strength is controversial. To determine the circulating 25-hydroxyvitamin D (25D) level required for the maintenance of bone, we generated 6 groups of Sprague-Dawley rats with stable, mean 25D level ranging from 11 nmol/L to 118 nmol/L. Vitamin D depleted animals were fed various levels of vitamin D (0ng-500ng/d) with 0.4% Ca for 4 months before being killed at 7 months of age for serum biochemistry and bone histomorphometry analyses. Proximal femora structure was analysed by μCT and distal femora histomorphometry was analysed using sagittal 5μm undecalcified sections. Fasting serum calcium, PTH and phosphate levels were normal in animals with low 25D levels. Evidence of osteomalacia was seen only in animals with 11(±0.7) nmol/L 25D, with elevated serum ALP, increased osteoid surface and delayed osteoid maturation time (OMT) compared to animals fed higher levels of vitamin D. In animals fed between 50 and 500ng/d vitamin D, trabecular bone volume (BV/TV) was positively related to circulating 25D ($R^2$=0.51, P<0.001), but not to $1,25(OH)_2D_3$ levels. Animals fed between 50 and 100ng/d vitamin D (mean 25D <80nmol/L) had lower BV/TV and both osteoid surface and osteoclast surface were elevated compared to animals fed higher vitamin D. While osteomalacia occurs at extremely low 25D levels, less severe depletion of vitamin D causes osteoporosis. For animals fed adequate dietary Ca, a circulating 25D above 80nmol/L is required to prevent bone loss.