2006 IOF+ANZBMS Combined Meeting

*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:** 1400 - 1530, Wednesday 25 Oct 2006

# Oral Abstracts

## *6C (Clinical) - Other clinical issues*



---

**O75**

## The synergy of TNF related molecules RANKL, TNFα, and TWEAK in osteoclast formation *in vitro* and expression of these in human tissues associated with bone loss near orthopaedic implants

C. Holding[1], D.M. Findlay[2], T. Zheng[3], T. Ueno[1], A.S.S.K. Dharmapatni[1], G.J. Atkins[2] and D.R. Haynes[1]
*[1]Department of Pathology, The University of Adelaide, North Terrace, Adelaide, South Australia, 5000, Australia. [2]Department of Orthopaedics and Trauma, The University of Adelaide, North Terrace, Adelaide, South Australia, 5000, Australia. [3]BIOGEN, Cambridge, MA. USA.*

The aim of this study was to, firstly, determine the expression of the TNF related molecules, RANK, RANKL, TNFα, TWEAK AND FN14 (TWEAK receptor), in human bone loss in peri-implant osteolysis and, secondly,

determine if these molecules could enhance the ability of RANKL to induce osteoclast resorption of mineralised tissue in vitro. Tissue was obtained from zones of peri-prosthetic osteolysis from 11 patients undergoing revision of total hip prosthesis, identified preoperatively by high resolution spiral multislice CT. Synovial tissue from 10 patients with osteoarthritis undergoing primary hip replacement was used as control tissue. Immunohistochemical analysis of formalin fixed tissue sections demonstrated that RANK, RANKL, TNFα, TWEAK and FN14 were strongly expressed by large multinucleated cells containing polyethylene wear debris in revision tissues. Control tissue did not express or only very weakly expressed the same molecules. A strong statistical correlation ($p < 0.02$) was found between volume of bone loss, polyethylene wear debris, RANK, RANKL and TNFα expression. TWEAK expression was significantly increased in the peri-implant tissues ($p = 0.001$). Importantly, *in vitro* studies using a model of osteoclast formation from human blood monocytes revealed that RANKL and TNFα synergise to increase the volume of bone resorbed, by more than 7 fold, when compared to the effect of either cytokine treatment alone. TWEAK also enhanced bone resorption. This suggests that the interaction of other TNF related molecules, such as TNFα and TWEAK, with RANKL may promote osteoclast activity in human bone loss diseases.

**O76**

## Vitamin D insufficiency defined by serum 25-hydoroxyvitamin D and parathyroid hormone before and after oral vitamin D load in Japanese subjects

R. Okazaki[1], H. Ochiai[1], N. Tsugawa[2], T. Sugimoto[3], M. Miura[4], H. Kaji[5] Y. Fujii[6], M. Shiraki[7], T. Okano[2] and T. Matsumoto[8]

*[1]Teikyo University School of Medicine, Ichihara; [2]Kobe Pharmaceutical University, Kobe; [3]Shimane Univ. School of Medicine, Izumo; [4]Mitsubishi Kagaku Bio-Clinical Laboratories Inc. Tokyo; [5]Kobe University Graduate School of Medicine, Kobe ;[6]Fujii Clinic, Kobe; [7]Research Institute and Practice for Involutional Diseases, Misatomura; [8]University of Tokushima Graduate School of Medical Science, Tokushima, Japan*

Although vitamin D insufficiency is regarded as a risk factor for osteoporotic fractures, there is a wide range in proposed serum 25(OH)D levels for vitamin D insufficiency. In order to determine the threshold serum 25(OH)D level to maintain normal calcium availability without elevation in serum PTH among subjects with various calcium intake, relationship between serum 25(OH)D and PTH levels along with changes in PTH levels were examined before and after 400 IU/day vitamin D3 supplementation for 4 to 6 months without calcium supplementation. Among 82 ambulatory Japanese subjects with 67.2 ± 12.4 years, 56 subjects were examined between June and July, and 26 subjects between February and March. The results demonstrated that either serum intact or bio-intact PTH was over the upper reference range in 24 out of 82 subjects (29.3%) with serum 25(OH)D below 25 ng/mL, that none of the subjects with serum 25(OH)D over 25 ng/mL showed elevated serum intact or bio-intact PTH. In addition, vitamin D3 supplementation caused a significant reduction in serum intact or bio-intact PTH levels among subjects with baseline serum 25(OH)D below 20 ng/mL, and 63% of subjects with serum 25(OH)D between 20 to 25 ng/mL also showed a reduction in serum PTH after vitamin D3 supplementation. In contrast, mean serum PTH levels were almost stable after vitamin D3 supplementation in subjects with serum 25(OH)D over 25 ng/mL. These results demonstrate that the threshold serum 25(OH)D level for vitamin D insufficiency in majority of Japanese subjects can be defined as 25 ng/mL.

**077**

## Vitamin D status, parathyroid hormone levels and predictors of falls risk in well women aged 47-80 years

N. El Haber[1,2], K. Hill[2] and J.D.Wark[1]

*University of Melbourne Department of Medicine and Bone & Mineral Service, Royal Melbourne Hospital[1], Public Health Division, National Ageing Research Institute[2], Melbourne, Australia.*

Vitamin D status is a determinant of falls and fracture risk in frail older people but the mechanism of this effect is uncertain and its relevance to healthy older people remains unclear. We studied 25-hydroxyvitamin D (25-OHD), parathyroid hormone (PTH) levels, and clinical and laboratory tests of gait, balance and lower limb strength in 119 well, community-dwelling women aged 47 – 80 years residing in Melbourne (38° south). Associations of 25-OHD and PTH levels with outcome measures were investigated by regression analysis and

by comparing groups divided by tertiles of both 25-OHD (<53, 53-75, >75 nmol/L) and PTH (<3.5, 3.5-4.9, >4.9 pmol/L) using ANOVA. 25-OHD was independently related to R and L step test (ST) performance, double support duration (DSD; Clinical Stride Analyzer), maximal activity score and adjusted activity score. PTH was associated positively with DSD, but not independently of 25-OHD. R and L ST performance increased by 12.0% and 13.5% respectively, in the highest compared with the lowest 25-OHD tertile. DSD increased by 12.7% comparing lowest and mid-tertiles with the highest 25-OHD tertile, indicating gait impairment at lower 25-OHD levels. These findings reveal an important relationship between vitamin D status and validated predictors of falls risk in community-dwelling older women. The public health significance of this association requires further study.

**O78**

## Quality of life following low trauma fracture

Y. Selecki
*Bone and Mineral Research, Garvan Institute of Medical Research, Darlinghurst, NSW, Australia*

There have been few studies measuring quality of life following all types of low trauma fracture.

The SF36 questionnaire and its two summary mental and physical health component scores enabled examination of the long term impact of low trauma fracture. It also enabled comparison with the impact of other common diseases. One hundred and eight subjects with low trauma fractures and 70 matched controls completed questionnaires at baseline, three months and twelve months.

**At baseline** the physical component scores were lower in the fracture group than controls (mean difference - 3.74 p=0.008) but there was no difference in mental health scores (- 0.96 p=0.44).

**At three months** the physical health component score difference widened (8.08 p<0.0001). Mental health scores deteriorated in fractures versus controls (3.43 p=0.02).

**By one year** both the physical and mental scores in the fracture group improved. However, although the mental health scores returned to baseline values (1.32 p=0.34), the physical health scores remained lower than baseline values

(- 4.85 p <0.0001) and lower than the 12 month control group (- 6.34 p=0.0001).

Subjects show resilience to the mental health effects of low trauma fractures but physical difficulties affecting quality of life after fracture persist one year after fracture. These effects are comparable to those of myocardial infarction (5.30) and stroke (8.10).

**O79**

## Statin and fracture risk

N.D Nguyen, C.Y. Wang, J.A. Eisman and T.V. Nguyen
*Bone and Mineral Research Program, Garvan Institute of Medical Research, Sydney, Australia*

Despite observational studies have suggested that statin use may be associated with reduced fracture risk, the association is controversial. This study utilized the Bayesian approach to combine existing evidence and update the association with consideration of potential publication bias.

Data on the association between statin use and fracture incidence from 11 observational studies and 4 from randomized clinical trials (RCTs) were synthesized by both Empirical Bayesian analysis and fully Bayesian random-effects meta-analysis models. Sensitivity analyses were carried out to estimate the effect of potential bias on the observed association. The heterogeneity of effect sizes was assessed by the coefficient of inconsistency.

Empirical Bayesian analysis indicated that statin use was associated with a reduction in hip fracture risk (OR=0.57, 95% credible interval: 0.46-0.71) and for non-vertebral (0.69, 0.63-0.74). These results were comparable with results from the fully Bayesian random-effects meta-analysis only for hip fracture (0.56, 0.42-0.73), but not for non-vertebral fracture (0.77, 0.58-1.03). The probability that statin use reduces fracture risk by at least 20% was 0.995 for hip fracture and 0.61 for non-vertebral fracture. Under the assumption that bias

over-estimates the true OR by 20%, there is still a probability of 0.97 that statin use reduces hip fracture risk by at least 20%; however, the effect on non-vertebral fracture was uncertain with a probability of 0.27.

Results of this analysis suggest that statin use is associated with reduced risk of hip fracture, but the association between statin use and non-vertebral fracture risk remains uncertain.

**O80**

## Does a fracture interfere with long-term pattern of bone loss: Geelong Osteoporosis Study

E.N. Merriman, J.A. Pasco, M.J. Henry, G.C. Nicholson, M.A. Kotowicz
*The University of Melbourne, Department of Clinical and Biomedical Sciences: Barwon Health, Victoria, Australia.*

Both peak bone mass and age-related bone loss contribute to bone strength and fracture risk. We aimed to determine differences in rates of bone loss in postmenopausal women with and without incident fracture. Medication use was documented by self-report. Biennial BMD measurements (Lunar DPX-L) were performed over a period of 6 years in 437 women aged 50+ yr enrolled in the Geelong Osteoporosis Study. Incident fractures (all causes) were confirmed radiologically. Annualised rates of bone loss were calculated using linear regression. BMD was measured at the spine (SP), femoral neck (FN), whole body (WB) and ultradistal forearm (UD).

There were 100 incident fractures among 83 cases (spine (27), hip (9), wrist (9), other (55)). Fracture cases were older (median (IQR): 70.8 (64.5–77.0) vs 65.5 (59.4–72.9) yr), but there were no differences in weight, height, glucocorticoid use or osteoporosis therapy. The table lists values for baseline BMD and annualised rates of change in BMD. Women with fracture had consistently lower baseline BMD at all sites, but showed no difference in overall rates of bone loss.

These results confirm that low BMD predisposes to fracture but a fracture does not affect the overall pattern of bone loss in the population over time. This analysis does not exclude the possibility of short-term changes before or after fracture.

| | Baseline BMD ($g/cm^2$)* | | | Rate of change in BMD ($g/cm^2/yr * 10^{-3}$)# | | |
|---|---|---|---|---|---|---|
| | **Frac** | **No frac** | **P** | **Frac** | **No frac** | **P** |
| **SP** | 1.04 ± 0.02 | 1.09 ± 0.01 | 0.050 | 4.6 ± 1.4 | 4.2 ± 0.7 | 0.8 |
| **FN** | 0.81 ± 0.01 | 0.86 ± 0.01 | 0.001 | -4.5 ± 1.2 | -3.7 ± 0.6 | 0.6 |
| **WB** | 1.05 ± 0.01 | 1.09 ± 0.01 | 0.009 | -0.9 ± 0.7 | -0.8 ± 0.3 | 0.8 |
| **UD** | 0.27 ± 0.01 | 0.29 ± 0.01 | 0.006 | -1.4 ± 0.6 | -1.3 ± 0.3 | 0.9 |

**age-adjusted* *#age- and therapy-adjusted*

**O81**

## New type of bone resorption marker (Tartarate resistant acid phosphatase 5b: TRACP5b) is useful for the detection of patients who respond to risedronate treatment

T. Miki, H. Naka, H. Masaki, A, Tamura, Y. Tomiyoshi, Y. Imanishi, M. Inaba and Y. Nishizawa
*Osaka City University Graduate School of Medicine, Osaka, 8585 Japan*

**Background:** Compliance of treatment is one of the key factors to reduce osteoporotic fracture. The early detection of patients who respond to treatment may contribute to good compliance. We investigated usefulness of new type of TRACP5b measurement for the early detection of the treatment, and compared with other metabolic markers of bone in postmenopausal osteoporotic women who started to risedronate treatment.

**Methods:** Risedronate was administered orally to 35 women, and the metabolic markers of bone (BAP, TRAP5b, NTX(sNTX and uNTX), urinary βC-TX(uCTX), and urinary DPD (uDPD) ) were measures before, 1, 3, 6, and 12th month. L2-4BMDs were measured before, 6, and 12 months.

**Results:** Resorption markers were reduced by 20-50% during the first 6 months. The formation markers were reduced by 30-40% during the 3-6th months. L2-4BMD were increased 4% and 6% at 6th and 12th month. The percentage of the patients showed more than minimum significant changes were 76%(TRACP), 66%(sNTX), 59%(uNTX), and 50%(uCTX) at 1st month. Those of 3rd months were 84%, 75%, 80%, and 63%, respectively. The correlations of L2-4BMD increase at 6th month and the suppression rate of TRACP5b were –0.419($p<0.05$) at 1st month, and –0.365($p<0.05$) at 3rd month. Those of L2-4BMD with BAP were –0.336($p<0.05$) at 3rd month and –0.387($p<0.05$) at 6th month. The relations of other markers with BMD were not significant.

**Conclusion:** The high detection rate of responder by TRACP5b at 1st month and the significant positive correlation with L-BMD change suggest that TRACP5b measurement contributes to good compliance.

**O82**

## Depression and bone mineral density in a community sample of men: Geelong Osteoporosis Study

F.N. Jacka, J.A. Pasco, M.J. Henry, L.J. Williams, M.A. Kotowicz, G.C. Nicholson and M. Berk
*The University of Melbourne, Department of Clinical and Biomedical Sciences: Barwon Health, Victoria, Australia.*

Previous research in psychiatric and community samples has demonstrated reduced bone mineral density (BMD) in individuals with both clinical depression and depressive symptoms, although the findings are equivocal. This study aimed to investigate the association between self-reported depression and BMD in a community sample of men aged 20-96yr enrolled in the Geelong Osteoporosis Study. A self-report questionnaire based on DSM-IV criteria was utilised to determine lifetime prevalence rates of depression within the study sample at baseline. Those currently taking oral glucocorticoids, testosterone or bisphosphonates were excluded from the analysis (n=23) resulting in a sample of 1279 men.

In this sample 155 men (12%) reported a lifetime history of depression (LHX). There were no differences in age, weight, height or unadjusted BMD at the femoral neck between the depressed and non-depressed men ($p=0.08$, 0.34, 0.41 and 0.13 respectively), but unadjusted BMD at the PA-spine was significantly lower in those with a LHX ($1.254 \pm 0.187$ vs $1.293 \pm 0.194$ g/cm$^2$, $p=0.017$). Age, weight and smoking-adjusted BMD was 2.8% lower at the PA spine ($1.255 \pm 0.015$ vs $1.292 \pm 0.006$ g/cm$^2$, $p=0.025$), and 3.0% lower at the femoral neck ($0.971 \pm 0.011$ vs $1.001 \pm 0.004$ g/cm$^2$, $p=0.007$) in those with a LHX compared to those non-depressed. Adjusting for SSRI use did not affect these relationships.

These data are consistent with previous findings of diminished BMD in people with depressive disorders and symptoms and suggest that depression may be a risk factor for reduced BMD in community-dwelling adult men.

**O83**

## Interaction between micromechanical strength at the trochanter and hip geometry

A.C. Jones[1], R.M.D. Zebaze[2], E. Seeman[2] and M.A. Knackstedt[1]
[1]*Department of Applied Mathematics, RSPhysse, Australian National University, Canberra 0200, Australia*
[2]*Austin Hospital, University of Melbourne, Heidelberg 3084, Melbourne, Australia*

To advance our understanding of pathogenesis of bone fragility at the trochanteric site, we studied the association between material stiffness (measured by nano-indentation), and tissue mineral density (measured by backscattered electron imaging), and the geometric properties of the hip (neck-shaft angle, FN width and FN axis length (FNAL) – all measured directly) in 9 specimens from cadavers (mean age $65.4 \pm 18$). Material and stiffness were assessed in a 1mm x 0.5mm area situated on the lateral aspect of the greater trochanter (~ 50 indentations areas per specimen). In each specimen, at each indentation area, we determined the tissue mineral density (TMD) and the Young's modulus (E; measure of mechanical competency).

In each specimen, E and TMD were normally distributed. There were no relationships between E and age, TMD and age. There was only a moderately strong correlation between E and TMD (r = 0.65). Solely, FNAL showed a significant but negative relationship with the material (TMD) and mechanical strength (E), respectively r= -0.75 and -0.42.

Within the constraint of the small sample size, we inferred that at the trochanteric region: (i) There is a large variation in stiffness and material properties within an individual (ii), Tissue mineralization accounts for only a moderate proportion of the variance in tissue mechanical strength, (iii) The longer the FN, the weaker the TMD and stiffness at the trochanter. Further studies are needed to understand this relationship.