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: 1630 - 1800, Tuesday 24 Oct 2006

Oral Abstracts

4C (Clinical) - Clinical studies, bone mass, density, and quality

O43

Intrinsic bone quality in fragility hip fracture patients: altered mineralisation and damage accumulation

J.S. Kuliwaba, P. Sutton-Smith and N.L. Fazzalari.
Bone and Joint Research Laboratory, Division of Tissue Pathology, Institute of Medical and Veterinary Science and Hanson Institute, and Discipline of Pathology, The University of Adelaide, Adelaide, Australia.

Bone strength is determined by a number of inter-related variables, including bone mass, geometry, and bone quality. Bone quality consists of bone turnover, microarchitecture, mineralisation, matrix composition, and damage accumulation. This study aimed to identify material and structural factors that contribute to bone quality in fragility hip fracture patients (Fx) and age-matched controls (C). Intertrochanteric bone cores were obtained from patients undergoing hemi-arthroplasty surgery for a non-traumatic subcapital femoral fracture (7f, 5m, mean age 80 [67-91] years), and from controls at autopsy (9f, 4m, 77 [65-88] years). Samples were

resin-embedded for quantitative backscattered electron imaging of the degree of mineralisation, and morphometric assessment of bone architecture, resorption, and microdamage. Trabecular bone volume, architectural parameters, and indices of bone resorption were not different between groups. Both groups showed normal distributions of percent calcium; however, the fracture cohort was less mineralised (mean % calcium: Fx:24.2%, C:24.9%). Linear microcrack parameters were similar between groups. Whereas diffuse damage was increased in bone from fracture patients (DxV/BV[%]: Fx:1.51(0.19-4.67), C:0(0-0.33), $p<0.01$ [median(quartiles)]). The ratio of damage (cracks and diffuse) density to resorption site density was higher in the fracture group compared to controls (Mdx.Dn/Rs.Dn: Fx:0.44(0.10-0.86), C:0(0-0.31), $p<0.01$), which is suggestive of an unrepaired microdamage burden in the fracture cohort. Collectively, these data suggest that increased fragility fracture risk is associated with under-mineralisation and damage accumulation rather than changes in bone architecture. Inclusion of bone material property data together with other bone quality measures may hold the key to better fracture risk assessment and treatment efficacy.

O44

Relationship between antero-postero cortical thickness trabecular architecture and ultimate failure strength in the L2 and L3 vertebral bodies

A. Badiei[1,2], H. Tsangari[1], R. Davies[1], M.J. Bottema[3] and N.L. Fazzalari[1,2,]
[1]Bone and Joint Research Laboratory, Division of Tissue Pathology, Institute of Medical and Veterinary Science and Hanson Institute, Adelaide, Australia. [2]Discipline of Pathology, School of Medical Sciences, University of Adelaide, South Australia. [3]School of Informatics and Engineering, Flinders University, South Australia.

The aim of this study was to investigate the relationship between vertebral cortical thickness, trabecular architecture and bone failure strength.

A para-sagittal slice and a central cube were taken from the L2 and L3 vertebra of 8 post-mortem cases (3 females and 5 males, mean age 59.8±18). A semi-quantitative method was used to determine the cortical thickness (Ct.Th) and architectural parameters, bone volume fraction (BV/TV), trabecular thickness (Tb.Th), trabecular separation (Tb.Sp) and trabecular number (Tb.N). Ultimate failure strength (UFS) of cubes was obtained by uni-axial compression to failure.

There was no statistically significant difference between any architectural and mechanical measures of the L2 and L3 vertebral bodies or between males and females. We found no relationship between the posterior, central and anterior architectural parameters. Mean values revealed that the BV/TV in the central region (9.72 ± 2.1) was lower compared to the anterior region (11.72 ± 3.4) and posterior regions (11.95 ± 4.7). For posterior, central and anterior regions BV/TV decreased with age ($p < 0.02$, $p < 0.02$ and $p < 0.07$, respectively) and Tb.Sp decreased with increasing BV/TV ($p < 0.001$, $p < 0.001$ and $p < 0.001$, respectively). A positive relationship, approaching significance, was also found between Ct.Th and Tb.Th in the posterior region ($p < 0.07$). With respect to the central cube, UFS was shown to decrease with age ($p < 0.001$) and increased with an increase in BV/TV ($p < 0.002$).

This study shows that relationships between UFS, trabecular architecture and vertebral Ct.Th exist. This highlights that assessment of strength should not be limited to assessment of trabecular architecture alone but include vertebral Ct.Th.

O45

Annual intravenous zoledronate increases bone density in HIV-infected men

M.J. Bolland[1], A. Grey[1], A.M. Horne[1], S. Briggs [2], M.G. Thomas[2], R.B. Ellis-Pegler[2], A.F. Woodhouse[2], G.D. Gamble[1] and I.R. Reid[1]
[1] Department of Medicine, University of Auckland, Auckland, New Zealand;
[2] Department of Infectious Diseases, Auckland Hospital, Auckland, New Zealand.

While many cross-sectional studies of HIV-infected people have shown high rates of osteopenia or osteoporosis, there are few trials of treatment or prevention of bone loss in this disorder. Recently, annual administration of intravenous zoledronate has been shown to increase bone mineral density (BMD) in post-menopausal women with osteoporosis. Whether the same benefits occur in men or HIV-infected people is not known.

We performed a 2-year randomised, controlled trial of HIV-infected men who had taken highly active anti-retroviral therapy (HAART) for >3 months. 43 men with BMD T score at hip or spine < -0.5 were randomised to receive either annual administration of 4mg zoledronate (n=21) or placebo (n=22). All men received 400mg calcium supplements daily and 50,000u cholecalciferol monthly. BMD was measured every 6 months at the lumbar spine, total hip and total body.

Both the zoledronate and placebo treated-groups had increases in BMD at 2 years from baseline at the lumbar spine. At the total hip and total body, BMD increased in the zoledronate-treated group but not the placebo group. The between-groups difference in the percentage change from baseline at 2 years was 6.2% (P<0.001) at the lumbar spine, 4.6% (P<0.001) at the total hip, and 2.8% at the total body (P<0.001).

We conclude that annual administration of zoledronate is a potent and effective therapy for the prevention or treatment of bone loss in HIV-infected men. The current data also provide the first controlled trial evidence that annual administration of zoledronate prevents bone loss in men.

O46

Long-term remission following treatment of Paget's disease with oral alendronate

N.J. Harrison, K.M. Sanders, M.A. Kotowicz and G.C. Nicholson.
Department of Clinical and Biomedical Sciences: Barwon Health, The University of Melbourne, Geelong, Victoria 3220, Australia

The long-term remission rates and predictors of relapse of Paget's disease after initial oral bisphosphonate have not previously been reported.

We followed 22 patients with moderately-severe Paget's disease enrolled in 1993-4 in a randomized, placebo-controlled trial of oral alendronate 40mg daily for 6-12 months.[1] Mean baseline ALP was 580u/L (range 187-1449). Relapse was defined as ALP increasing >2.5 times post-treatment nadir, or >120u/L, or clinical relapse with pagetic bone pain. Non-responders were excluded (n=3).

Forty-seven percent remained in remission at mean follow-up of 72 months (range 18-153). Sixty-four percent (n=7/11) treated for 6-months relapsed, compared with only 38% (n=3/8) treated for 12-month (p=0.26). All patients who relapsed had subsequent relapses.

In the group treated for 6-months, with ALP <460u/L, probability of relapse was predicted by baseline ALP: the probability of remission at 30, 64 and 75-months was 71%, 54% and 27% respectively. With ALP >460u/L, the probability of remission at 18-months was 67% but all had relapsed by 30-months. The time to relapse was greater with baseline ALP <460u/L (Kaplan-Meier, p=0.02). The nadir ALP did not predict time to relapse (p=0.80).

Our results show that treatment of Paget's disease with alendronate for 6-12 months results in long-term remission in half the patients. Longer remission may occur in patients receiving 12-months treatment. With 6 months treatment, time to relapse is delayed with baseline ALP <460u/L. Patients who relapse, do so recurrently.

[1] Reid IR *et al.* 1996 Am J Med 101:341-8

O47

A single dose of zoledronic acid 5 mg achieves more sustained biochemical remission vs daily 30 mg risedronate in patients with Paget's disease

M. Hooper[1], P. Miller[2], J. Brown[3], W. Fraser[4], D. Hosking[5], I. R. Reid[6], P. Hunt[7], D. Levitt[8], C. M. Diaz[9], M. Stone[10], A. Morales[11], J.E.F.Del Pino[12], Y. Saidi[13], G. Su[14] J. Pak[14], J. Krasnow[14], K. Zelenakas[14], K. Lyles[15].
[1]University of Sydney, Sydney, Australia, [2]Colorado Center for Bone Research, Lakewood, CO, USA, [3]Le Centre Hospitalier Universitaire, Sainte-Foy, PQ, Canada, [4]Royal Liverpool Univ Hospital, Liverpool, United Kingdom, [5]Nottingham City Hospital, Nottingham, United Kingdom, [6]University of Auckland, Auckland, New Zealand, [7]Christchurch Hospital, Christchurch, New Zealand, [8]Groote Shuur Hospital, Cape Town, South Africa, [9]Fundation Jimenez Diaz, Madrid, Spain, [10]Llandough Hospital, Penarth, United Kingdom, [11]Hospital Ramon y Cajal, Madrid, Spain, [12]Hospital Universitario, Salamanca, Spain, [13]Novartis Pharma AG, Basel, Switzerland, [14]Novartis Pharmaceuticals Corp, East Hanover, NJ, USA, [15]Duke Univ & Medical Center, Durham, NC, USA.

Length of remission was assessed for an extended observation period (EOP).after a single 15-min infusion of zoledronic acid (ZOL) 5 mg or risedronate (RIS) 30 mg/d for 60 days in Paget's disease following 6-month core data from 2 randomized controlled trials (Reid I et al. *NEJM* 2005;353:898-90).

Of 169 ZOL and 125 RIS patients eligible for entry, 152 ZOL and 115 RIS responders (≥75% reduction in serum alkaline phosphatase [ALP] excess or its normalization) entered EOP and had ALP tested regularly. Time to first loss of therapeutic response, time to first partial disease relapse (≥50% increase from ALP measurement at month 6 and at least 1.25 × ULN) and complete disease relapse (ALP level returned within 20% of baseline value) were evaluated.

After a mean period of 26 months from study drugs administration, 57/115 RIS patients lost therapeutic response compared to only 3/152 ZOL patients (P<.0001). Further, 49/115 and 9/115 RIS patients had partial and complete disease relapse compared to only 3/152 (P<.0001) and 0/152 (P<.001) ZOL patients, respectively.

A single ZOL 5-mg infusion shows longer duration of effect in terms of reduction in ALP than RIS. Treatment efficacy was sustained in most ZOL patients, compared to the substantial number of RIS patients who either lost therapeutic response or had partial or complete disease relapse. Hence, a single ZOL 5-mg dose offers potential for multi-year biochemical remission in Paget's disease.

O48

Higher Serum 25(OH)D concentrations are related to larger BMD increases with alendronate therapy for osteoporosis

P. Lee, P.G. Colman and P. R. Ebeling
Dept. Diabetes and Endocrinology, The Royal Melbourne Hospital, Parkville 3050, Victoria, Australia

Bisphosphonate treatment studies included daily calcium supplements and corrected low serum 25(0H)D concentrations. However, the serum 25(OH)D concentration for optimal bone health is unclear.

We performed a prospective cohort study to examine the influence of baseline serum 25(OH)D concentrations on changes in BMD during alendronate therapy at the spine, total hip and femoral neck over 11 to 14 (median 12) months.

172 women and 11 men with osteoporosis aged 27-87 years who had been treated with alendronate for 12 to 28 months were studied. The majority (96%) also received calcium (mean daily dose 667 mg), while 69% received vitamin D_2 (ergocalciferol) supplements (mean daily dose 1180 IU). All patients had baseline serum 25(OH)D concentrations between 50 and 120 nmol/L (mean 69 nmol/L). Baseline fracture prevalence was spine (82%); hip (29%); humerus (4%) and distal radius (2%). Baseline mean spinal, total hip and femoral neck T-scores were -1.9, -1.8, and -2.5, respectively.

Changes in spinal BMD ranged from -2% to +15% and were strongly positively related to baseline serum 25(OH)D concentrations ($r=0.80$, $p < 0.05$). No such relationship existed at the total hip. Changes in femoral neck BMD ranged from -8 to +16% and were only positively related to baseline serum 25(OH)D concentrations in those patients with a baseline 25(OH)D > 80 nmol/L ($r=0.57$, $p < 0.05$).

Conclusion: Higher serum 25(OH)D concentrations improve spinal BMD responses to bisphosphonate therapy. This may relate to an improved calcium supply to bone, but further studies are required to determine mechanisms.

O49

The association between vitamin D stores and bone mass in older adults: the Tasoac Study

C. Ding[1], V. Parameswaran[2], J. Burgess[2] and G. Jones[1]
[1]Menzies Research Institute, University of Tasmania, Hobart, Australia; [2]Diabetes and Endocrine Services, Royal Hobart Hospital, Liverpool St, Hobart, Australia

Objective: To describe the associations between vitamin D stores and lifestyle factors, muscle strength and bone mass in male and female older adults.

Methods: A total of 976 randomly selected subjects (mean age 62 years, range 50-80, 50% female) was measured at baseline and approximately 2 years later. Spine, and hip bone mineral density (BMD) was measured by DXA. Vitamin D stores were assessed by serum 25-hydroxyvitamin D3 [25 (OH) D3] at baseline and follow-up.

Results: The mean 25(OH) D3 level at baseline was 53 nmol/l (range: 13, 119) and was significantly associated with age, female sex, BMI, sun exposure, self-reported activities, as well as hip (P=0.009) and spine BMD (P=0.023). Change in 25(OH) D3 over 2 years (mean +6.2, range: -46, +82) was associated with lower limb muscle strength (P<0.001), and % change in hip (+0.03% per nmol/l, P=0.02) but not spine BMD (P=0.32).

Conclusions: Vitamin D is mainly obtained from outdoor activity in older adults, and its insufficiency is common and associated with higher body weight and weaker muscle strength. Furthermore, vitamin D stores and their change are important for preservation of bone mass.

O50

The ROSI study (risedronate in adults with osteogenesis Imperfecta type 1): improved BMD but high fracture rate persists

E.L. Duncan[1], L.A. Bradbury[1], S. Barlow[2], F. Geoghanen[2], P. Schofield[3], J.A.H. Wass[2], R.G.G. Russell[2] and M.A. Brown[1].
[1]University of Queensland, Brisbane, Australia, [2]Nuffield Orthopaedic Centre, Oxford, United Kingdom, [3]Proctor and Gamble, Basingstoke, United Kingdom.

Osteogenesis Imperfecta type I ('mild' OI) is an inherited disease of bone fragility, with decreased type I collagen synthesis. IV bisphosphonates improve BMD and fracture rates in children with severe OI. This study assessed oral bisphosphonates in adults with mild OI.

OI type I patients were recruited from the Nuffield Orthopaedic Centre (Oxford UK) and by self referral. Eligibility included age>18 years, exclusion of other causes of osteoporosis, and contraception in fertile women. Risedronate was prescribed (5mg daily or 35mg weekly) for 24 months. BMD was assessed at lumbar spine (LS) and total hip (Hologic DXA) at 0 and 24 months. LS results were excluded if marked degeneration or fracture was present. A careful fracture history was taken. Bone turnover markers (serum P1NP, bone-specific ALP) were assessed at baseline and 6 monthly. BMD results were analysed by paired t-test; bone turnover results by repeat measurements ANOVA.

35 patients were recruited; 26 (10 male, 16 female) completed the study. Average baseline age was 41.3 years. Baseline mean LS BMD was 0.820g/cm^2 (t-score=-2.22) with improvement (3.4%) at 24 months (p=0.015). Baseline mean BMD at total hip was 0.849g/cm^2 (t-score=-0.927) with no significant change at 24 months (p=0.56). P1NP fell 47% (p=0.008).

Six major fractures were recalled in the 5 years preceding the study (5% incidence). During the study, 9 major fractures occurred (17% incidence).

Oral bisphosphonates improve BMD and suppress bone turnover in mild OI. However, the high fracture rate observed suggests that this may not be clinically significant in these patients.