ANZBMS Postgraduate Research Scholarship Report

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Date: 1 January 2005- 31 December 2005

Title: Studies of the Pathogenesis and Treatment of Secondary Osteoporosis

There are two main projects the results of which will be summarised separately below.

Part 1:
Project Title: Pathogenesis of Bone Loss in HIV-infected Patients taking Highly Active Antiretroviral Therapy and its Prevention with Zoledronate

Two studies are in progress, while one study has been completed. The completed study was a comparison of the baseline bone density and biochemical markers of bone and calcium metabolism in a cohort of HIV-infected men with those in an age-matched group of healthy men. The results of this study show that there were no differences between the groups in bone density at the lumbar spine and total body, while there was a small reduction in bone density at the total hip in the HIV-infected group. This reduction was explainable by the difference in body weight between the groups (The HIV-infected group had a mean weight of 77.4 kg whereas the control group had a mean weight of 83.4kg). There are at least 20 published studies that report that HIV infection is associated with lowered BMD, and/or higher than expected prevalence of osteopenia or osteoporosis, many of which did not adjust for potential confounders. We hypothesize that the difference between our study and these previous reports is that our cohort of HIV-infected men have received effective treatment (HAART) for at least 20 months longer than in other studies that have reported similar data. Thus participants in this study may have had better nutritional status for a longer period of time (despite having lower body weight than the controls), and have regained more of their body weight that was initially lost with advancing HIV infection, than HIV-infected participants in earlier studies. Weight gain has consistently been shown to be associated with an increase in BMD in various populations, and body weight in our cohort increased by an average of 4.9 kg during 4.3 years of treatment with HAART. Thus we conclude that osteoporosis is not a significant health issue for HIV-infected men receiving HAART. If these results are confirmed by other researchers they represent an important finding.

This study was presented as a poster at the ANZBMS ASM in Perth, where I was awarded the Chris Nordin poster prize. The manuscript has been accepted by Clinical Endocrinology for publication. An abstract describing the study and its results has been attached to this report.

There are 2 ongoing studies. Firstly we recruited 43 men into a prospective, randomised, double blind study comparing the effects of zoledronate (4mg/yr) with placebo in HIV-infected men over two years. The aim of this study is to determine the effectiveness of zoledronate in treating and preventing osteoporosis in HIV-infected men. To date 30 men have completed two years of follow up, with the last man finishing his 2 years of follow up in April. We hope to present the data from this trial later this year at the ANZBMS ASM. The second ongoing study recruited 29 HIV-infected subjects who were not eligible for, or declined to enrol in, the zoledronate intervention study, who were offered a repeat bone density scan 2 years after the screening examination. To date 20 men have had a repeat bone density scan. The age-matched control group will also be re-studied at 2 years. Thus we will be able to compare the rates of change of bone density between the two groups. This comparison will determine whether bone loss is accelerated in HAART-treated HIV-infected subjects. This study will be completed in October this year.

Part 2
Project Title: The relationship between Parathyroid Hormone, Body Weight, Vitamin D and Bone Density.

Previously, results from our group suggested that postmenopausal women with primary hyperparathyroidism are heavier than healthy age-matched controls. We sought to extend this observation by performing a metaanalysis of published studies of primary hyperparathyroidism. We identified 17 studies that reported BMI or body weight in group of people with primary hyperparathyroidism and a control group suitably matched for age and gender. The results of our analyses suggested that on average people with primary hyperparathyroidism were approximately 3.0 -3.5kg heavier than healthy controls. The results were consistent across gender and age. This weight gain is likely to be of clinical significance and may in part account for the reported associations of primary hyperparathyroidism with a number of conditions such as hypertension, diabetes, cholelithiasis, cardiovascular disease, and neoplasia. If so, this suggests that parathyroidectomy in an attempt to reduce the risk of these complications in patients with asymptomatic primary hyperparathyroidism is not justified.

This study was presented as a poster at the ANZBMS ASM in the Hunter Valley, where I received the Chris Nordin poster prize. It was published in the Journal of Clinical Endocrinology and Metabolism [Bolland et al. (2005). "Association between Primary Hyperparathyroidism and Increased Body Weight: A Meta-Analysis." J Clin Endocrinol Metab 90(3): 1525-30] and the abstract from that paper has been attached to this report.

Following on from this study we then sought to determine whether the same relationship between body weight and parathyroid hormone (PTH) levels exists in eucalcemic healthy post-menopausal women. We also sought to determine whether this effect was due to the established inverse relationship between PTH and 25-hydroxyvitamin D (25OHD) levels. We analysed the baseline cross-sectional data of a group of 116 healthy postmenopausal women who volunteered to take part in a study of the effects of thiazides on bone density. We found that PTH was significantly positively correlated with measures of body weight and fat mass, and negatively correlated with 25OHD levels. On multivariate analysis, PTH was positively related to percent body fat, and negatively related to dietary calcium intake and serum phosphate. Adjusting for vitamin D insufficiency or 25OHD levels did not affect the relationship between PTH and fat mass. Therefore we concluded that fat mass is a significant independent determinant of serum PTH levels, and that this relationship is independent of the inverse relationship between 25OHD and fat mass. The relationship between PTH and fat mass might contribute to our earlier observations on the relationship between body weight and primary hyperparathyroidism. We hypothesize that elevated PTH levels may cause increased fat mass by promoting insulin resistance at the adipocyte. Another hypothesis is that increased body weight may lead to lower vitamin D levels and secondary hyperparathyroidism. Over a long period of time sustained stimulation of the parathyroid gland may then lead to adenoma development.

This study has been published electronically in the journal Bone [Bolland et al. (2005). "Fat mass is an important predictor of parathyroid hormone levels in postmenopausal women." Bone. Epub Sept 19]. The abstract from this study has been attached to this report.

We also analysed the relationship between 25OHD, body composition, and bone density in a database of the baseline cross-sectional data of 1606 postmenopausal women recruited for a study of calcium supplementation. We found that 25OHD levels were negatively correlated with body weight. When we correlated 25OHD levels with body composition measures there was no significant correlation with lean mass but 25OHD levels were significantly correlated with fat mass and most strongly with percent fat. There were no significant correlations between 25OHD levels and bone density measured at any site. In addition we found that the major determinants of 25OHD levels were the month of the blood sample, age, percent fat, and activity levels. These four variables accounted for 21% of the variance in 25OHD levels.

This study has been published in Osteoporosis International [Lucas JA, Bolland MJ et al. (2005). "Determinants of vitamin D status in older women living in a subtropical climate." Osteoporos Int 16(12): 1641-1648]. The abstract from this study has been attached to this report.

We have several ongoing projects that have started during the last year and will be completed shortly, including the relationships between 25OHD levels and body composition in men, and the influence of body weight on vitamin D binding protein in men and women. This work will form part of my thesis which I hope to submit later this year.

Acknowledgements:

I would like to thank the Australian and New Zealand Bone and Mineral Society for their generous award of this postgraduate research scholarship. This year has been a very productive year for me and I thank the Society for supporting this research which has led to 3 oral and 6 poster presentations at national and international meetings and 4 papers being published in high impact international medical journals.

Abstracts of submitted and published work.

Title: Bone mineral density is not reduced in HIV-infected Caucasian men treated with highly active antiretroviral therapy.

Abstract

Objective:
Recent studies have reported low bone mineral density (BMD) in HIV-infected patients. Frequently these findings have been attributed to treatment with highly active antiretroviral therapy (HAART). We sought to determine whether BMD in HIV-infected men treated with HAART for at least 3 months is different from that in healthy controls, and, if so, what HIV-related factors might explain this finding.
Design:
Cross-sectional analysis.
Patients:
59 HIV-infected Caucasian men treated with HAART, and 118 healthy community-dwelling controls. Each HIV-infected man was age-matched (within 5 years) to 2 controls.
Measurements:
All participants had measurements of BMD, and bone-related laboratory parameters.
Results:
The mean duration of known HIV infection was 8.5 years, and of treatment with HAART was 52 months. There was no significant difference in mean BMD between groups at the lumbar spine (HIV group: 1.23g/cm^2, controls: 1.25g/cm^2; P= 0.53) or total body (HIV group: 1.18g/cm^2, controls: 1.20g/cm^2; P= 0.09). At the total hip the HIV-infected group had significantly lower BMD than the control group (HIV group: 1.03g/cm^2, controls: 1.09g/cm^2; P=0.01). The HIV-infected group were on average 6kg lighter than the controls. After adjusting for this weight difference, HIV infection was not an independent predictor of BMD at any site (lumbar spine P=0.87; total hip P=0.15; total body P=0.67).
Conclusions:
HIV-infected men treated with HAART are lighter than healthy controls. This weight difference is responsible for a small decrement in hip BMD. Overall, BMD is not significantly reduced in HIV-infected Caucasian men treated with HAART.

Reference: Clinical Endocrinology, in press

Title: Association Between Primary Hyperparathyroidism and Increased Body Weight: A Meta-Analysis

Abstract:

Although primary hyperparathyroidism is frequently asymptomatic, it has been associated with an increased prevalence of hypertension, insulin resistance, dyslipidemia, cardiovascular mortality, and cancer. Previously, we reported that patients with primary hyperparathyroidism are heavier than age-matched controls. Increased body weight could contribute to the association between primary hyperparathyroidism and these extraskeletal complications. We searched MEDLINE for English-

language studies published between 1975 and 2003 that reported body weight or body mass index in subjects with primary hyperparathyroidism and a healthy age- and sex-comparable eucalcemic control group. 17 eligible studies were identified. Subjects with primary hyperparathyroidism were 3.34 kg (95% confidence interval 1.97 to 4.71, $P<0.00001$) heavier than controls in 13 studies reporting body weight. In 4 studies reporting body mass index, subjects with primary hyperparathyroidism had an increased body mass index of 1.13 kg/m^2 (-0.29 to 2.55, $P=0.12$) compared to the controls. Standard mean difference analysis showed that subjects with primary hyperparathyroidism have an increased weight or body mass index of 0.3 standard deviations (0.19 to 0.40, $P<0.00001$) compared to the controls. We conclude that patients with primary hyperparathyroidism are heavier than their eucalcemic peers and that increased body weight may contribute to the reported associations between primary hyperparathyroidism and some extraskeletal complications.

Reference: 1. Bolland MJ, Grey AB, Gamble GD, Reid IR. Association between Primary Hyperparathyroidism and Increased Body Weight: A Meta-Analysis. J Clin Endocrinol Metab 2005;90(3):1525-30.

Title: Fat mass is an important predictor of parathyroid hormone levels in postmenopausal women.

<u>Abstract</u>

Previously we reported that people with elevated parathyroid hormone (PTH) levels due to primary hyperparathyroidism have increased body weight compared to eucalcemic controls. We sought to determine whether the same relationship between PTH and body weight exists in eucalcemic healthy post-menopausal women, and to investigate the relationships between components of body weight, PTH, vitamin D metabolites and metabolic indices.

We performed a cross-sectional analysis of 116 healthy community-dwelling post-menopausal women. Pearson correlation analysis was used to test for univariate linear relationships between variables, and stepwise multiple regression analysis to assess for multivariate relationships.

We found that PTH was significantly positively correlated with body weight, regional and total fat mass, and percent body fat, and negatively correlated with activity levels, 25 hydroxyvitamin D (25OHD), dietary calcium intake, and serum phosphate. On multivariate analysis, PTH was positively related to percent body fat ($P=0.020$; partial $r^2=0.10$) and negatively related to dietary calcium intake ($P=0.041$; partial $r^2=0.03$) and serum phosphate ($P=0.026$; partial $r^2=0.04$). Adjusting for vitamin D insufficiency or 25OHD levels did not affect the relationship between PTH and fat mass. For 25OHD, there were significant positive correlations with lumbar spine BMD and serum albumin, and significant negative correlations with PTH, total fat mass, trunk fat, and pelvic fat. On multivariate analysis, 25OHD was positively related to serum albumin ($P=0.008$; partial $r^2=0.07$) and negatively related to pelvic fat mass ($P=0.014$; partial $r^2=0.05$). Adjusting for PTH levels did not change the relationship between 25OHD and pelvic fat mass.

We conclude that fat mass is a significant independent determinant of serum PTH levels, and that this relationship is independent of the inverse relationship between 25OHD and fat mass. This association between fat mass and PTH might contribute to the association between primary hyperparathyroidism and increased body weight.

Reference: Bolland MJ, Grey AB, Ames RW, Horne AM, Gamble GD, Reid IR. Fat mass is an important predictor of parathyroid hormone levels in postmenopausal women. Bone 2005; epubl Sept 19.

Title: Determinants of Vitamin D status in older women living in a subtropical climate

Abstract:

Studies performed in the Northern Hemisphere and in areas distant from the equator have demonstrated significant seasonal variation in 25-hydroxyvitamin D (25OHD) levels. Whether such variation occurs in a subtropical area such as Australasia is not clear. We performed a cross-sectional study of 1606 healthy, postmenopausal women recruited over a 33-month period. The study had three goals: to determine the normal levels of 25OHD in healthy postmenopausal women living in Auckland, New Zealand; to determine whether seasonal variation of 25OHD occurs at this latitude; and to assess the relationship between 25OHD, biochemical indices, anthropometric variables and bone mineral density (BMD). We found significant seasonal variation in 25OHD levels, with the change in monthly ultraviolet dose from summer to winter being followed 6-8 weeks later by a corresponding change in 25OHD levels. Vitamin D insufficiency was common. During summer, 28-57% of participants had suboptimal vitamin D status, while in winter, the frequency increased to 56-73%. 25OHD levels correlated with participants' age (r=-0.15), weight (r=-0.11), body mass index (r=-0.13), fat mass (r=-0.14), percentage body fat (r=-0.16), physical activity (r=0.10) and the month of blood sampling (all P<0.0001). Collectively, age, fat mass, physical activity, and month of sampling explained 21% of the variance in 25OHD. No significant relationships were noted between 25OHD and BMD at any site. Other variables that showed significant monthly variation were glucose (P=0.002), serum phosphate, alkaline phosphatase, and albumin (all P<0.0001). There was no monthly variation in BMD at the lumbar spine or proximal femur. In conclusion, there is significant seasonal variation in 25OHD levels, even in a subtropical climate. Furthermore, despite generous amounts of sunlight, considerable numbers of women have suboptimal vitamin D status, even in summer. Our findings support the suggestion that vitamin D supplementation should become standard practice in this population of women, particularly during winter.

Reference: Lucas JA, Bolland MJ, Grey AB, Ames RW, Mason BH, Horne AM, Gamble GD, Reid IR. Determinants of vitamin D status in older women living in a subtropical climate. Osteoporos Int 2005;16(12):1641-1648.