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Studies of the Pathogenesis and Treatment of Secondary Osteoporosis

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A thesis submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy, Faculty of Medical and Health Sciences, The University of Auckland, 2006.
Abstract:

Background:

Osteoporosis commonly affects older men and women. Frequently, it is caused or exacerbated by a disease or treatment (termed secondary osteoporosis). The aim of this thesis is to explore aspects of the pathogenesis and treatment of three conditions that may cause or contribute to osteoporosis: human immunodeficiency virus (HIV) infection, primary hyperparathyroidism (PHPT), and vitamin D insufficiency. Each of these conditions is potentially linked to bone metabolism via associations with nutritional status, which in turn is a key regulator of bone mass and fracture risk.

Methods:

Eight studies were performed:

2. Two-year randomised controlled trial of the effects of annual zoledronate on BMD in HIV-infected men.
3. Longitudinal comparison of the change in BMD over two years in HIV-infected men not receiving skeletal therapy and controls.
7. Cross-sectional analysis of the effects of fat mass and seasonal variation on diagnosis of vitamin D sufficiency.
**Results:**

1. HIV-infected men were 6.3 kg lighter than controls, and after adjustment for this weight difference, did not have lower BMD than controls.
2. Annual intravenous zoledronate caused substantial increases in BMD in HIV-infected men over two years.
3. HIV-infected men did not have accelerated bone loss over time compared to controls.
4. Patients with PHPT are on average 3.1-3.3 kg heavier than age-matched controls.
5. Fat mass is an important determinant of parathyroid hormone levels.
6. The major determinants of 25OHD levels in men and women are surrogate measures of ultraviolet-B exposure, and fat mass, but men have higher 25OHD levels throughout the year than women.
7. Thresholds for diagnosis of vitamin D sufficiency vary by season and amount of fat mass.
8. Vitamin D binding protein does not mediate the relationships between 25OHD and age, gender or weight.

**Conclusions:**

Uncomplicated HIV infection is not associated with low BMD at baseline or accelerated bone loss over time. There are important relationships between body weight and PHPT, and among fat mass, parathyroid hormone and 25OHD that have significance both for the pathogenesis of PHPT and vitamin D sufficiency, and for the clinical diagnosis and treatment of these conditions.
Preface:

Osteoporosis affects a significant number of older men and women. Osteoporosis is defined by the WHO as “a systemic skeletal disease characterised by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fractures” [1]. In Caucasian populations, approximately 50% of post-menopausal women and 20% of men older than 50 years will experience at least one fragility fracture in their remaining lifetime [2]. In Caucasian populations, the lifetime risk for fragility fracture of the hip is 14% for women and 3% for men, and for fragility fracture of the spine is 28% for women and 12% for men [3]. In the majority of cases of osteoporosis, the bone loss is due to the normal ageing process, in which case it is termed primary or idiopathic osteoporosis. However, in up to 20-30% of post-menopausal women, 50% of pre-menopausal women, and more than 50% of men, osteoporosis is caused or exacerbated by a disease or treatment, in which case it is termed secondary osteoporosis [4]. Currently, there are more than 50 recognised causes of secondary osteoporosis [4]. Since there are very large numbers of people affected by osteoporosis and many of these cases of osteoporosis will be due to secondary causes, secondary osteoporosis is a significant health issue.

In 2000, Tebas et al. published the first report which suggested HIV or treatment of HIV with antiretroviral agents may cause osteoporosis [5]. In contrast, PHPT has been recognised to cause osteoporosis since the earliest descriptions of patients with osteitis fibrosa cystica [6], and vitamin D deficiency has also been known for many years to cause osteopenia and osteomalacia [7]. PTH and vitamin D are essential hormones in calcium homeostasis, and their roles in calcium metabolism are interlinked [8, 9]. Therefore, diseases with abnormal levels of serum PTH are likely to impact upon vitamin D metabolism, and, conversely, diseases with abnormal levels of serum vitamin D metabolites are likely to impact upon parathyroid gland function. Thus, in any consideration of PHPT or vitamin D insufficiency, it is important to consider the roles of PTH and vitamin D and its metabolites. Recent evidence has suggested that both PHPT and vitamin D insufficiency are associated with increased body weight. Since body weight is a major determinant of BMD and an important risk factor for osteoporotic fractures [10], and both PHPT and vitamin D insufficiency are important causes of secondary osteoporosis, it is important to explore the role of body weight in the pathogenesis of PHPT and vitamin D insufficiency.
The purpose of this thesis is to explore aspects of the pathogenesis and treatment of secondary osteoporosis in association with three conditions: HIV, PHPT and vitamin D insufficiency. In Chapters 1-4, I will review the association between HIV and osteoporosis, and then report and discuss the results of a cross-sectional study and a longitudinal study of BMD in HIV-infected men in comparison to age-matched healthy controls, and an intervention study on the effect of the potent bisphosphonate zoledronate on BMD in HIV-infected men. In Chapters 5-10, I will review the relationship between PTH, vitamin D, body weight and BMD, and then report and discuss the results of five studies that explore aspects of the relationships between PTH and body weight, vitamin D metabolites and body weight, and the determinants of PTH and vitamin D metabolites in a variety of population groups.
Acknowledgements:

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I am lucky to have worked with so many other outstanding colleagues. Anne Horne co-ordinated the HIV trial, and her enthusiasm and professionalism ensured the study ran without any hitches. Our collaborators in the HIV trial were Rod Ellis-Pegler, Mark Thomas, Simon Briggs, and Andrew Woodhouse. Mark and Rod started the project by suggest HIV-related bone disease as a link between the specialities of Endocrinology and Infectious Diseases. The idea snowballed from there, and Mark, Rod and Andrew gave it their fullest support, and Simon managed to track down and recruit everyone possible.

Ruth Ames, Diana Wattie, Barbara Mason, and Anne Horne form the clinical arm of our group, and their kindness and professionalism make it a very enjoyable place to work, as well as ensuring that the studies run without hitches. Thanks especially to Barbara to always dealing cheerfully with my requests for yet more data. I would also like to thank Jill Cornish, Dorit Naot and the other members of the laboratory arm of our group for putting up with me in their work space, and for their enthusiastic support of these and our other shared projects.

I would like to acknowledge the generous financial support I have received from the Australia and New Zealand Bone and Mineral Society in the form of a post-graduate scholarship to carry out this research, travel grants to attend their annual scientific meetings and present data from this research, and prizes from those meetings.

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Table of Contents:

Chapter 1: HIV and Osteoporosis .......................................................................................... 1
  Background history of HIV and AIDS: ............................................................................. 1
  Osteoporosis prior to the use of HAART: ....................................................................... 2
  Osteoporosis in the HAART era: ..................................................................................... 3
    Cross-sectional studies: .............................................................................................. 3
    Longitudinal studies: ................................................................................................. 14
  Bone turnover markers and calcitropic hormones: ......................................................... 16
  Pathogenesis of bone loss in HIV infection: ................................................................. 19
  Clinical fractures in HIV infection: ................................................................................ 23
  Treatment of osteoporosis in HIV infection: ................................................................. 25
  Conclusion: ................................................................................................................... 27

Chapter 2: A cross-sectional analysis of bone mineral density in HIV-infected men treated with HAART .......................................................................................... 28
  Introduction: .................................................................................................................. 28
  Methods: ....................................................................................................................... 28
    Subjects: ...................................................................................................................... 28
    Measurements: .......................................................................................................... 29
    Statistics: .................................................................................................................... 30
  Results: .......................................................................................................................... 30
  Discussion: ..................................................................................................................... 36

Chapter 3: Annual zoledronate increases bone mineral density in HAART-treated HIV-infected men: a randomised controlled trial ........................................... 40
  Introduction: .................................................................................................................. 40
  Methods: ....................................................................................................................... 41
    Participants: .................................................................................................................. 41
    Protocol: ....................................................................................................................... 41
    Measurements: .......................................................................................................... 42
    Statistics: .................................................................................................................... 43
  Results: .......................................................................................................................... 43
  Discussion: ..................................................................................................................... 47

Chapter 4: Bone mineral density remains stable in HAART-treated HIV-infected men over two years ............................................................................................. 50
  Introduction: .................................................................................................................. 50
  Methods: ....................................................................................................................... 50
    Subjects: ...................................................................................................................... 50
    Measurements: .......................................................................................................... 51
    Statistics: .................................................................................................................... 51
Chapter 5: The relationships between bone mineral density and parathyroid hormone, vitamin D, and body weight .......................................................... 60

Introduction: ..................................................................................................................... 60
PTH: .................................................................................................................................. 60
The effects of PTH on BMD and fractures: .......................................................... 61
Vitamin D: ........................................................................................................................ 63
The effects of vitamin D on bone turnover, BMD and fractures: ......................................... 64
The relationship between PTH and Vitamin D: ............................................................... 67
The effects of body weight and body composition on bone turnover, BMD and fractures: ...... 68
Conclusion: ....................................................................................................................... 70

Chapter 6: The relationship between primary hyperparathyroidism and body weight .......................................................... 71

Introduction: ..................................................................................................................... 71
Methods: ........................................................................................................................... 72
Study Selection: ........................................................................................................ 72
Statistics: ...................................................................................................................72
Results: ............................................................................................................................. 73
Discussion: ....................................................................................................................... 77

Chapter 7: Fat mass is an important predictor of parathyroid hormone levels in post-menopausal women .......................................................... 82

Introduction: ..................................................................................................................... 82
Methods: ........................................................................................................................... 82
Results: ............................................................................................................................. 84
Discussion:....................................................................................................................... 87

Chapter 8: Determinants of vitamin D status in middle-aged and older men and in older women .......................................................... 91

Introduction: ..................................................................................................................... 91
Methods: ........................................................................................................................... 92
Participants: ............................................................................................................... 92
Measurements: ..........................................................................................................93
Statistics: ...................................................................................................................93
Results: ............................................................................................................................. 94
Women: .....................................................................................................................94
Men: ..........................................................................................................................96
Comparisons between the women and men: ............................................................. 98
Discussion: ................................................................................................................... 100

Chapter 9: The effects of seasonal variation of 25-hydroxyvitamin D and fat mass on diagnosis of vitamin D sufficiency.............................................................. 106

Introduction: ................................................................................................................... 106
Methods: ......................................................................................................................... 106
Participants: ................................................................................................................... 106
Measurements: ............................................................................................................. 107
Statistics: ....................................................................................................................... 107
Results: ........................................................................................................................... 108
Discussion: ...................................................................................................................... 112

Chapter 10: Age-, gender-, and weight-related effects on levels of 25-hydroxyvitamin D are not mediated by vitamin D binding protein....... 116

Introduction: ................................................................................................................... 116
Methods: ......................................................................................................................... 117
Participants: ................................................................................................................... 117
Measurements: ............................................................................................................. 117
Statistics: ....................................................................................................................... 118
Results: ........................................................................................................................... 118
Discussion: ...................................................................................................................... 120

Conclusions to Chapters 5-10: ............................................................................................ 124

References: ..................................................................................................................... 127
List of Tables:

Table 1.1: Cross-sectional studies of BMD in HIV-infected patients prior to use of HAART ... 4
Table 1.2: Cross-sectional studies of BMD in HIV-infected adults in the HAART era........... 11
Table 1.3: Studies of HIV-infected adults that report bone turnover markers.................... 18
Table 2.1: Baseline characteristics of HIV-infected group and control group.................... 31
Table 2.2: Clinical characteristics of HIV-infected group............................................. 32
Table 2.3: Calcitropic hormones and bone-related laboratory parameters of HIV-infected
    group and control group.......................................................................................... 33
Table 2.4: Baseline characteristics of HIV-infected group in the presence or absence of
    lipodystrophy........................................................................................................... 36
Table 3.1: Baseline anthropometric, BMD, biochemical parameters and other
    characteristics of the groups.................................................................................. 44
Table 3.2: HIV-related clinical characteristics of the groups........................................... 44
Table 4.1: Characteristics of the study groups at baseline and two years.......................... 52
Table 4.2: Clinical characteristics of HIV-infected group............................................. 53
Table 6.1: Studies of patients with PHPT and eucalcaemic controls presenting data on body
    weight...................................................................................................................... 74
Table 6.2: Studies of patients with PHPT and eucalcaemic controls presenting data on BMI.. 75
Table 7.1: Descriptive and biochemical characteristics of the study group....................... 84
Table 7.2: Pearson’s correlations between vitamin D metabolites, PTH, and other variables .. 85
Table 7.3: Predictors of PTH and 25OHD in multivariate regression models...................... 87
Table 8.1: Descriptive and biochemical characteristics of the study group....................... 94
Table 8.2: Mean levels of 25OHD by age range............................................................ 95
Table 8.3: Frequency of low 25OHD levels by month of sampling ................................... 96
Table 8.4: Pearson’s correlations between 25OHD and other variables............................ 97
Table 8.5: Predictors of 25OHD levels in multivariate regression models........................ 97
Table 8.6: Studies from Europe and USA that report 25OHD levels in cohorts of men....... 101
Table 9.1: Baseline characteristics of the study populations ........................................... 108
Table 9.2: The minimum 25OHD level required to have a predicted nadir 25OHD more
    than 50 nmol/L, by month of measurement .......................................................... 110
Table 9.3: The effect of fat mass on seasonal variation of 25OHD levels............................ 111
Table 10.1: Biochemical and anthropometric characteristics of the study groups............. 119
Table 10.2: Pearson’s correlations between DBP, 25OHD, and other variables.............. 120
List of Figures:

Figure 1.1: Factors that may contribute to low BMD in HIV-infection ................................. 23

Figure 2.1: Distribution of unadjusted BMD for HIV-infected group and control group at the lumbar spine, total hip, and total body ................................................................. 34

Figure 2.2: Mean BMD and 95% CI at the lumbar spine, total hip, and total body adjusted for body weight in HIV-infected group and controls .................................................. 34

Figure 3.1: Flow of subjects through the study ........................................................................ 42

Figure 3.2: The effects of 4 mg annual zoledronate or placebo on BMD at the lumbar spine, total hip, and total body in HIV-infected men ......................................................... 46

Figure 3.3: The effects of 4 mg annual zoledronate or placebo on bone turnover markers in HIV-infected men ..................................................................................................... 47

Figure 4.1: The change in BMD from baseline at the lumbar spine, total hip, and total body in HIV-infected men and controls ............................................................................. 47

Figure 6.1: Weighted mean difference in body weight in studies of PHPT and eucalcaemic controls that present data on body weight .............................................................. 75

Figure 6.2: Weighted mean difference in BMI in studies of PHPT and eucalcaemic controls that present data on BMI .............................................................................................. 76

Figure 6.3: Standard mean difference in studies of PHPT and eucalcaemic controls that present data on weight or BMI ...................................................................................... 76

Figure 7.1: Relationship between PTH and fat mass ................................................................ 85

Figure 8.1: Monthly variation of UV dose and 25OHD levels .................................................... 95

Figure 8.2: The relationship between 25OHD and fat mass ....................................................... 99

Figure 9.1: Sine curve of best fit for 25OHD in the cohort of women (N=1606) with measured mean monthly 25OHD for comparison ................................................................. 109

Figure 9.2: Sine curve of best fit for 25OHD in the cohort of men (N=378) with measured mean monthly 25OHD for comparison ................................................................. 109

Figure 9.3: The effect of fat mass on seasonal variation of 25OHD levels in men and women .......................................................................................................................... 112

Figure 10.1: DBP levels in men and women .............................................................................. 119
List of Publications:

**Chapter 2:**


**Chapter 3:**


**Chapter 4:**


**Chapter 6:**


**Chapter 7:**

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. 2006; 38:317-21

**Chapter 8:**

Bolland MJ, Grey AB, Ames RW, Mason BH, Horne AM, Gamble GD, Reid IR.
Determinants of vitamin D status in older men living in a subtropical climate. Osteoporos Int. 2006; 17:1742-8

**Chapter 9:**


**Chapter 10:**

Abbreviations:

1,25(OH)₂D  1,25-dihydroxyvitamin D  
25OHD  25-hydroxyvitamin D  
AIDS  Acquired immunodeficiency syndrome  
ALP  Alkaline phosphatase  
ANCOVA  Analysis of covariance  
ANOVA  Analysis of variance  
BMC  Bone mineral content  
BMD  Bone mineral density  
BMI  Body mass index  
bsALP  Bone specific alkaline phosphatase  
CI  Confidence interval  
CTx  β-C-terminal telopeptide of type I collagen  
CV  Coefficient of variation  
DPD  Deoxypyridinoline  
DXA  Dual energy x-ray absorptiometer  
ELISA  Enzyme linked immunosorbent assay  
GGT  γ-Glutamyl transferase  
HAART  Highly active antiretroviral therapy  
HIV  Human immunodeficiency virus  
NIH  National Institutes of Health  
NNRTI  Non-nucleoside reverse transcriptase inhibitor  
NRTI  Nucleoside reverse transcriptase inhibitor  
NTx  N-telopeptide of type I collagen  
OC  Osteocalcin  
OPG  Osteoprotegerin  
PHPT  Primary hyperparathyroidism  
PI  Protease inhibitor  
PTH  Parathyroid hormone  
PYD  Pyridinoline  
RANK  Receptor activator of nuclear factor κβ  
RANKL  Receptor activator of nuclear factor κβ ligand  
RIA  Radioimmunoassay  
SD  Standard deviation  
SEM  Standard error of the mean  
UV  Ultraviolet  
WHO  World Health Organisation