Studies of the Pathogenesis and Treatment of Secondary Osteoporosis

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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:

1. Cross-sectional comparison of bone mineral density (BMD) in HIV-infected men and age-matched controls.
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.
4. Meta-analysis of body weight in patients with PHPT.
5. Cross-sectional analysis of the relationship between parathyroid hormone and body weight in post-menopausal women.
6. Cross-sectional analysis of the determinants of 25-hydroxyvitamin D (25OHD) in post-menopausal women and middle-aged and older men.
7. Cross-sectional analysis of the effects of fat mass and seasonal variation on diagnosis of vitamin D sufficiency.
8. Cross-sectional analysis of the relationship between vitamin D binding protein and body weight in older men and women.

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.

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Chapter 3:

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Chapter 6:

Bolland MJ, Grey AB, Gamble GD, Reid IR. Association between primary hyperparathyroidism and increased body weight: a meta-analysis. J Clin Endocrinol Metab. 2005; 90:1525-30

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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

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Chapter 9:

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Chapter 10:

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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