

**THE UNIVERSITY OF HULL**

**The treatment of postmenopausal osteoporosis**

being a Thesis submitted for the Degree of Doctor of  
Medicine in the University of Hull

by

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May, 2008.

This thesis is dedicated to my wife, Louise, for her love  
and support during both my MD and all of our time together.  
I also dedicate it to my children, Sophie and Ava, for all the love,  
joy and trouble they bring to my life.

## **Thesis summary.**

**Introduction:** Osteoporosis is a skeletal condition in which bone strength is compromised leading to a propensity to fragility fractures. Osteoporotic fractures have significant consequences for both the individual, due to the resulting morbidity and mortality, and for society in terms of resource implications. Fortunately, in recent years there have been an increasing number of treatments available. This thesis aims to investigate current topical areas regarding the treatment of osteoporosis.

**Method:** This thesis contains 5 different studies with different methodologies. One is a reanalysis of data previously collected as part of a prospective osteoporosis screening and follow up study. Three studies are derived from clinical databases at our centre. The final study is a prospective study specifically conducted as the centrepiece for my MD.

**Results:** 1): Routine VFA screening detects vertebral fractures in 20% of women attending for DXA, the majority of which have osteopenia in whom the presence of a fracture may directly effect their treatment. Targeted VFA screening only detects around 10% of women who have vertebral fractures. 2): A short course of HRT has prolonged benefit in terms of BMD. 3): Prior bisphosphonate use does not result in blunting of the BMD response to teriparatide. 4): The BMD response to strontium ranelate is blunted by prior bisphosphonate use for the first 6 months of therapy at the spine and for 12 months at the hip and heel. 5): Vertebroplasty using Cortoss cement reduces pain from vertebral fractures with results comparable to those achieved with PMMA vertebroplasty.

**Conclusion:** Osteoporosis is a disease with an increasing number of treatment options. While modern treatments are all proven to reduce fractures in treatment naïve women their place in the overall treatment of women with osteoporosis is less well studied. This thesis provides further insight into areas such as improving fracture risk assessment in order to guide treatment initiation, initial treatment options, the effects of switching between treatments and finally the treatment of vertebral fractures which occur as a result of osteoporosis.

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## **Acknowledgements**

The two and a half years I have spent in research in order to gain this MD have provided me with a wealth of experience and knowledge which will benefit my future career as a rheumatologist and I am extremely grateful to all those who have made this possible.

Particular thanks must be said to Dr Doherty who created the research post for me, helped me turn my research ideas in to reality and provided me with the benefit of her expertise in the field of metabolic bone disease. I am also very grateful to Sue Steel whose scientific knowledge of osteoporosis and bone densitometry was vital for my research and complemented perfectly the clinical knowledge of Dr Doherty. I am also deeply appreciative of the all help I received from the research nurses, Karen Stubbs and Val Sutton, and from the bone densitometry technicians, receptionists, secretaries and porters at the bone centre. I would like to thank Vicki Lowthorpe from pharmacy for dispensing countless boxes of strontium ranelate and Ian Hanning from biochemistry for analysing the bone turnover markers. I am grateful to Eugene McCloskey from the Academic Unit of Bone Metabolism in Sheffield for acting as my external supervisor and providing me with an independent opinion on my work. Finally I would like to thank Professor Atkin and the endocrinology registrars for their support during my research period.

## **Format of thesis**

This thesis examines the clinical aspects of the treatment of osteoporosis. In order to maintain a focus on postmenopausal osteoporosis other areas of osteoporosis, such as male osteoporosis and glucocorticoid-induced osteoporosis, are not covered in this thesis. The first three chapters provide an overview of the literature on postmenopausal osteoporosis to set the scene for the research studies, which follow in chapters 4 to 8. Chapter 1 defines osteoporosis and covers the epidemiology and pathophysiology. Chapter 2 discusses in turn the different treatments available for osteoporosis including current topical issues and areas studied later in this thesis. Chapter 3 provides information on means of monitoring the response to treatment, which are used in my research. Chapters 4 to 8 are my research studies, which have all been published, with the exception of my strontium study has been submitted for publication. As these studies do not necessarily follow on from each other these chapters are ordered to reflect different stages of the treatment process, starting with fracture risk assessment followed by initial treatment options then the effects of switching between treatments and finally the treatment of painful vertebral fractures. Chapter 9 begins by summarising my conclusions before discussing my findings in the context of current osteoporosis management. I have also used Chapter 9 to review recent developments relevant to the areas of osteoporosis studied in this thesis, which have emerged since my papers were published.



### **Approval and funding of research undertaken.**

The prospective strontium study and the reanalysis of the previous HRT study were both approved by the local research ethics committee. The teriparatide, vertebroplasty and vertebral fracture assessment studies were clinical audits performed as part of a clinical service review within our department, which were approved by the local audit committee.

My research was funded in part by an educational grant from Servier Laboratories, France. For the strontium study Servier Laboratories provided the strontium ranelate and ProStrakan provided Adcal D3 as the calcium supplement. The remainder of my research was supported by internal departmental research funds.

## **Declaration of the author's participation in the work submitted.**

The composition of this thesis, including the literature reviews and the design, interpretation and writing up of all the studies contained within, are the sole work of the author after advice from Dr S M Doherty and Ms S A Steel. I collected the data for the vertebroplasty study and teriparatide study and performed the vast majority of the study visits for the strontium study with the remainder being done by Mrs Karen Stubbs and Mrs Valerie Sutton, Osteoporosis research nurses.

I also had help with the following aspects of my studies:

Vertebral fracture assessment study: The data was recorded onto the Lunar Prodigy database by the bone densitometry technicians at the time of each patient's visit and I had help from Mr Jonathan Thorpe in extracting this data from the 3 Lunar Prodigies and collating it into one single database.

HRT study: The database, which I reanalysed was originally created by Purdie et al (1996) and I had help with the statistics for the reanalysis from Mirella Bottazzi.

Teriparatide and strontium studies: All bone markers were measured by Dr Ian Hanning, Consultant Biochemist, Hull Royal Infirmary. Bone densitometry was performed by the bone densitometry technicians at the Centre for Metabolic Bone Disease. I also had statistical support from Mr Eric Gardiner for the analysis of the strontium study.

Vertebroplasty study: The actual vertebroplasties were performed by Dr Damien Taylor, Consultant Radiologist, Hull Royal Infirmary.

**Chapter 1:**  
**An introduction to postmenopausal**  
**osteoporosis.**

## **Chapter 1.1:**

### **Definition of osteoporosis.**

Osteoporosis is a skeletal condition in which bone strength is compromised leading to a propensity to low trauma (fragility) fractures, which are the clinical manifestation of the disease. While the bone tissue itself is histologically normal, there is a reduction in the amount of bone and deterioration in the structure of the bone leading to a reduction in bone strength. This is reflected in the 1993 Consensus Development Conference definition of osteoporosis as “a systemic skeletal disease characterised by low bone mass and microarchitectural deterioration of bone tissue leading to enhanced bone fragility and a consequent increase in fracture risk” (Anon 1993).

While this is a pathologically correct definition, it has limitations in clinical practice. Bone microarchitecture is difficult to image routinely and bone mineral density (BMD), as measured by dual energy x-ray absorptiometry (DXA), is used as a surrogate for bone mass. As such the World Health Organisation (WHO) has proposed a BMD cut off 2.5 standard deviations (sd) below the average peak adult BMD as a means of defining osteoporosis (Kanis 1994). This led to the development of the “T score” which expresses a patient’s BMD in terms of the number of standard deviations above or below the average peak adult BMD (based on data for 20-29 year olds from the NHANES III database) (Kanis 2002). Defining osteoporosis as a T score of -2.5 or less identifies approximately 30% of the postmenopausal female population as osteoporotic which is

approximately equivalent to the life time risk of osteoporotic fracture (Kanis 1994). Table 1.1 demonstrates the WHO thresholds for bone mineral density.

Table 1.1. WHO diagnostic categories for BMD (Kanis 1994).

<b>Diagnostic category</b>	<b>Description</b>	<b>T score</b>
<b>Normal</b>	BMD is not more than 1 sd below young adult mean value	$T \geq -1.0$
<b>Osteopenia</b>	BMD is between 1 and 2.5 sd below young adult mean value	$T < -1.0$ to $> -2.5$
<b>Osteoporosis</b>	BMD is 2.5 or more sd below young adult mean value	$T \leq -2.5$
<b>Established osteoporosis</b>	BMD is 2.5 or more sd below young adult mean value and a prevalent fragility fracture	$T \leq -2.5$

The limitation of the T score definition of osteoporosis is that fragility fractures do occur in women with osteopenic or even normal BMD. Furthermore, not all patients with a T score diagnosis of osteoporosis will suffer a fracture in the near future. This is illustrated in 2 population studies by Siris et al (2004) and Schuit et al (2004). In both of these studies, although the risk of fracture was higher in those women with a T score below -2.5, most fractures occurred in women with osteopenia due to the larger number of women in this category of BMD.

As discussed later, there are many factors affecting bone strength and the propensity for fracture, which increase the risk of osteoporotic fracture independent of the patient's BMD. As such there is currently a move towards using both BMD and clinical risk factors to estimate an individual's risk of fracture. The WHO has recently produced an

algorithm, which estimates the 10-year probability of fracture for both men and women (Kanis et al 2008). In the future, the T score definition of osteoporosis may become less important and it is likely that treatment decisions will be based on absolute fracture risk rather than the current BMD based threshold for intervention.

## **Chapter 1.2:**

### **Epidemiology of postmenopausal osteoporosis and the consequences of osteoporotic fracture.**

#### **Prevalence of low BMD.**

The WHO definition of osteoporosis is solely based on low bone mineral density compared to the peak adult bone mass of young healthy adults. Prior to the menopause, BMD remains fairly constant and within the population BMD is normally distributed. The prevalence of osteoporosis in the population prior to age 50 is approximately 0.5% and the prevalence of osteopenia is 15% (Kanis 2002). After age 50 bone loss occurs and the prevalence of osteoporosis then increases exponentially with age. Osteoporosis affects 5-8% of women aged 50-60 and in women aged over 85 the prevalence is more than 60% (Kanis 1994). This data is based on femoral neck BMD which is the recommended site for the diagnosis of osteoporosis. The prevalence of osteoporosis will vary if other skeletal sites are used. In one study the prevalence of osteoporosis varied from 12% to 31% depend on the skeletal site assessed by DXA (Arlot et al 1997). In a study of Hull's local population, 9% of women aged 60-70 had osteoporosis and 39% had osteopenia based on femoral neck BMD (Ballard et al 1998). If spinal BMD was used then 20% and 36% of the population was defined as osteoporotic and osteopenic respectively.

### **Epidemiology of osteoporotic fractures.**

The clinical significance of osteoporosis lies not in low BMD but in the resulting low trauma fractures. The classical osteoporotic fractures are those of the wrist, spine and hip although fractures of the humerus, rib, lower leg, pelvis, hand, and clavicle have also been shown to be attributable to low BMD (Seeley et al 1991). In the same study fractures of the ankle, elbow, finger, and face were not associated with BMD.

### **Vertebral fractures.**

Vertebral fractures are the commonest osteoporotic fractures, are strongly associated with low bone mineral density and are often considered the hallmark of osteoporosis. They account for almost half of the 1.5 million osteoporotic fractures which occur annually in the USA with an incidence almost 3 times that of hip fractures (Riggs and Melton 1995). Data from Rochester, Minnesota demonstrates that the prevalence of vertebral fractures increases from 11% in women aged 50-59 to over 54% in those aged over 80 (Melton et al 1993). The overall prevalence of vertebral fracture was 20-25% for all women aged over 50. The same study demonstrated that the incidence of vertebral fracture also increases with age with an incidence of 5.8 and 37.7 per 1000 person years for women aged 50-54 and 85-89 respectively. Similar changes in the prevalence and incidence of vertebral fractures with age has been demonstrated in European women (Ismail et al 1999, Felsenberg et al 2002).



Despite the high prevalence of vertebral fractures it has been reported that only one third of women with vertebral fractures are aware of their presence (Melton et al 1993). In addition to this, vertebral fractures are often ignored or missed by medical professionals. One study looking at the prevalence of fractures on lateral chest X-rays, taken for reasons other than osteoporosis, demonstrated that only 50% of fractures were noted on the x-ray report and only 19% of those patients with a fracture received treatment (Gehlbach et al 2000). Finally, even when vertebral fractures are specifically looked for it has been demonstrated that around 34% of vertebral fractures visible on plain x-ray are not identified by radiologists (Delmas et al 2005).

#### Vertebral fractures predict future fracture risk.

It is important to know if a woman has a vertebral fracture, as it is a predictor of future fracture independent of BMD and thus an indication for treatment. Without bone protective treatment, the relative risk (RR) of suffering a new vertebral fracture is 2.6 in the presence of 1 vertebral fracture and this increases further if there is more than 1 (RR 5.1) or more than 2 (RR 7.3) prevalent vertebral fractures (Lindsay et al 2001). Furthermore, in the same study almost 20% of untreated women who sustained a vertebral fracture suffered another vertebral fracture in 1 year. It has also been demonstrated that vertebral fractures predict non-vertebral fractures independent of BMD. Two large epidemiological studies suggest that a prevalent vertebral fracture increases the risk of future hip (RR 1.9 and RR 4.5) and non-vertebral fracture (RR1.6 in each study) (Black et al 1999, Ismail et al 2001). Neither of these studies demonstrated an

increase in risk of wrist fracture after correcting for BMD. Again, in these studies the risk of future hip and non-vertebral fracture increased with the number of prevalent vertebral fractures.

*Research topic: Given the implications of a prevalent vertebral fracture on the risk of future vertebral and non-vertebral fractures and that, despite their high prevalence, most women with vertebral fractures are unaware of them how should we screen women for vertebral fractures? This is studied in chapter 4 of this thesis.*

Vertebral fractures are associated with considerable mortality.

Population studies suggest that survival is reduced by about 20% over 5 years in patients presenting for medical attention due to vertebral fractures (relative survival 0.81) (Cooper et al 1993). An increase in mortality after a clinical vertebral fracture was also demonstrated when data from the Fracture Intervention Trial was pooled. A clinical vertebral fracture was associated with a 9-fold increase in the age-adjusted risk of death (Cauley et al 2000). The mechanism behind the increased mortality associated with vertebral fractures remains unclear. It may be that vertebral fractures are not independently linked to an increase risk of death, but instead reflect poor underlying health status and co-morbidities. Against this is the fact that adjusting for age and several common co-morbidities did not significantly affect the relative risk of mortality in the study by Cauley et al (2000).

### Vertebral fractures cause significant morbidity.

The pain from an acute vertebral fracture varies from no or minimal symptoms to severe pain requiring hospitalisation. Pain from the acute fracture often settles over a period of weeks however many patients are left with chronic pain. Chronic pain may in part be due to persistent instability due to non-union of the fracture (Heini 2005). A fracture may also alter the mechanics of the spine resulting in the abnormal transmission of force through the vertebral column and abnormal strain on the facet joints and paraspinal ligaments/muscles, which may contribute further to the development of chronic pain after a fracture. This morbidity was demonstrated by Nevitt et al (2000) who reported an increased incidence of severe back pain, limited daily activity and requirement for bed rest over a 3 year period after a vertebral fracture.

Apart from pain, vertebral fractures have other consequences. Increased thoracic curvature, the “dowagers hump”, may result in painful crowding of the ribs and a decline in lung function. A 9% reduction in vital capacity for each thoracic vertebral fracture has been demonstrated (Harrison et al 2007). Compression of the abdomen can result in gastro-oesophageal reflux, early satiety and weight loss. There may be psychological consequences including impaired body image, loss of self-esteem, a fear of future fracture and depression. Overall, vertebral fractures result in a reduction in the quality of life and this has been demonstrated in a case control study. Hall et al (1999) reported that women with vertebral fractures have a reduction in both the physical and mental

components of the SF36 quality of life assessment when compared to patients without fracture.

### **Wrist fractures.**

Wrist fractures are predominantly associated with a fall onto an outstretched hand in women with low bone mineral density who are otherwise relatively healthy and active and have good neuromuscular function (Kelsey et al 1992). Overall about 17% of women over 50 in the UK will suffer a wrist fracture during their life (Van Staa et al 2001). The incidence of wrist fracture increases with age until around age 65 when it plateaus with an incidence of around 7.5-9 fractures per 1000 person years (Kelsey et al 1992). Wrist fractures are associated with an increased relative risk for subsequent fracture of the wrist (RR 3.3), spine (RR 1.7) and hip (RR 1.9) (Klotzbuecher et al 2000). Unlike other osteoporotic fractures, wrist fractures are not associated with an increase in mortality (Cooper et al 1993, Van Staa et al 2001). In the short term, wrist fractures are associated with pain and impaired function and can be complicated by reflex sympathetic dystrophy which has been reported to occur in up to 10-20% of cases (Zollinger et al 2007, Zollinger et al 1999). However, in the long term over 80% of patients with a wrist fracture have a good functional recovery (Rikli et al 1998, Kaukonen et al 1988).

### **Hip fractures.**

Hip fractures are often considered the most devastating consequence of osteoporosis. The lifetime risk of hip fracture for women aged over 50 is around 11-17% (Kanis 1994, Van

Staa 2001). In the US it is estimated that 250,000 hip fractures occur per year making hip fractures more common than either stroke or breast cancer (Riggs and Melton 1995). Three-quarters of all hip fractures occur in women and the overall incidence of hip fracture for women in the UK is 1.7 per 1000 person years (Van Staa 2001). The incidence of hip fracture is low before age 70 after which it increases rapidly and by age 90 the incidence is around 20 per 1000 person years (Van Staa 2001). The increasing incidence with age is not only due to declining BMD but also due to an increased risk of falling. 90% of hip fractures are the direct consequence of a fall and around 50% of women aged over 85 suffer a fall each year (Cummings and Melton 2002). With increasing age and frailty there is a decline in neuromuscular function, which leads to an increased risk of falling. Furthermore, such women are more likely to land on their hip when they do fall as they are less able to use their hands to protect themselves. Therefore they suffer a hip fracture rather than fracturing their wrist (Nevitt and Cummings 1993). Finally, hip fractures are associated with future fracture with an increased relative risk for both subsequent vertebral (RR 2.5) and hip fracture (RR 2.3) (Klotzbuecher et al 2000).

Hip fractures are associated with significant mortality.

Similar to clinical vertebral fractures, hip fractures have been shown to reduce survival by about 20% over 5 years (relative survival 0.82) (Cooper et al 1993). However, in contrast to vertebral fractures where survival diverged from normal in a gradual and increasing manner, the excess mortality due to hip fracture in this study was greatest in the first 6 months. A high mortality rate early after hip fracture was also reported by

Center et al (1999) who demonstrated that 20% of women died within 1 year of hip fracture but over the subsequent 4 years only a further 12% died. Again, the role the hip fracture plays directly in the mortality rate is debateable as hip fracture may occur in older more frail women with more co-morbidity who are thus more likely to die independent of the fracture. However, the high early mortality rate with hip fracture suggests that hip fracture may contribute more directly to mortality rate than vertebral fractures. This is again supported by Cauley et al (2000) who demonstrated a 6 fold increase in death following a hip fracture which persisted even after adjustment for age and common co-morbidities.

#### Social and economic consequences of hip fractures.

Hip fractures often have dire consequence, even for those women who survive. By one year 40% are unable to walk independently, 60% have difficulty with at least one essential activity of daily living and 27% enter a nursing home for the first time (Cooper 1997). Overall around half of women who were previously independently living in the community require admission to residential homes or increased help with activities of daily living after a hip fracture (Cummings and Melton 2002).

Osteoporosis requires significant medical and social resources. It has been estimated that in 2000 osteoporosis cost the UK around £1.7 billion and hip fractures account for approximately 80% of the total costs of osteoporotic fracture (Dolan and Torgerson 1998). Over the period of a year, the estimated cost of a hip fracture requiring residential

care is around £30,000 pounds (Kanis et al 2002). 1 in 5 orthopaedic beds in UK hospitals are occupied as the result of hip fracture. After a hip fracture visits to medical outpatient's departments are increased 3 fold and on average women make an extra 9 visits to their GP in the year after a hip fracture (Dolan and Torgerson 1998).

**Chapter 1.3:**  
**Basic bone physiology and the pathophysiology**  
**of postmenopausal osteoporosis.**

**Normal bone tissue.**

Bone is a complex tissue consisting of inorganic mineral, organic matrix and cells. The majority (90%) of the organic matrix is type 1 collagen with the remaining 10% comprising of noncollagenous proteins such as Osteocalcin, Osteopontin, Osteonectin and bone sialoprotein. Type 1 collagen has a triple helical structure but, unlike type 1 collagen in other connective tissues, in bone the collagen fibres have unique covalent intra and intermolecular cross-links which render the collagen completely insoluble. Calcium phosphate hydroxyapatite crystals bind to the type one collagen to provide strength and rigidity. Through its strength and rigidity, bone serves 3 main functions: it acts as a lever to facilitate mobility; it provides protection for the internal organs and bone marrow; and it has an important role in the homeostasis and storage of mineral ions, particularly calcium, magnesium and phosphate.

There are 3 cell types in bone. Osteoclasts are large multinucleated cells of macrophage origin derived from the haemopoietic stem cells. Osteoblasts and osteocytes are derived from mesenchymal cell lineage. Osteoclasts remove bone while osteoblasts synthesize new bone matrix and their actions are coupled to allow the normal turnover of bone.

Osteocytes were originally osteoblasts, which became embedded within lacunae in the



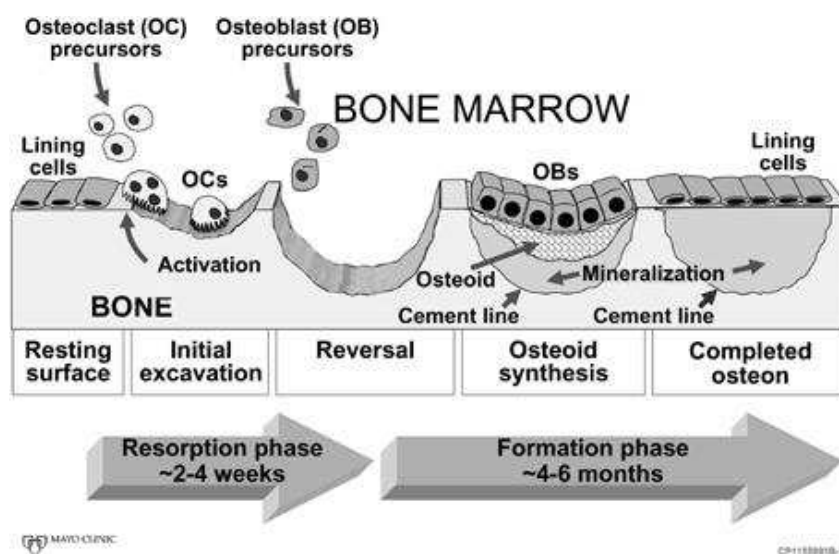
bone structure. Osteocytes are in contact with each other and the lining cells on the bone surface via long cellular processes rich in microfilaments, which form a large network of thin canaliculi throughout the entire bone matrix. Within the osteocyte lacunae and canaliculi, in between the osteocytes plasma membrane and the bone, there is the periosteocytic space which contains extracellular fluid. The periosteocytic space provides a large surface area for ion exchange and, by sensing shear-generated forces applied across this space, osteocytes are also thought to play a central role in bone's ability to respond to mechanical strain (Noble and Reeve 2000).

### **Normal bone turnover**

Bone turnover occurs throughout life by a process known as remodelling. This process replaces old bone with new bone in order to allow: the repair of microdamage to the skeleton; the bone to adapt to the mechanical strains it is subjected to; and the participation of bone in calcium homeostasis (Parfitt 2002). This occurs throughout the skeleton at around  $10^6$  discrete foci called the basic multicellular unit (BMU). The remodelling process begins with the activation and contraction of the bone lining cells. Osteoclasts are then recruited from precursors in the bone marrow and the circulation and bind to the exposed bone tissue. The osteoclasts secrete hydrogen ions and proteolytic enzymes in order to excavate a resorption cavity over a period of 2-4 weeks after which they disappear by apoptosis. The boundary of the resorption cavity is marked by a sclerotic border called the cement line. Osteoblasts then line the resorption cavity and secrete osteoid, which subsequently undergoes primary mineralization to form bone

during a process which lasts 4-6 months. Then over a period of several years secondary mineralization occurs to increase the degree of mineralization from 60% to 90-95% of maximum (Davison et al 2006). This process is summarised in figure 1.3.1.

Figure 1.3.1: The basic multicellular unit (Riggs and Parfitt 2005).



It has been estimated that around 30% of BMUs form at sites of microdamage while the remaining 70% are thought to occur in regions of high strain, in response to other undetermined signals and/or, to some degree, random chance (Burr 2002). The rate at which bone remodelling occurs varies with the type of bone and the skeletal site. In general, cortical sites remodel slowly with around 2% of the bone in the radius and 5% of the bone in the femoral neck being remodelled annually (Noble and Reeve 2000). Trabecular bone remodels 10 times faster with around 30% being remodelled annually although the rate can be as high as 50% at certain sites such as the ilium. The rate of

trabecular remodelling is thought to be related to the degree of surrounding red or yellow bone marrow with sites with red bone marrow remodelling quicker due to a more abundant supply of osteoclasts (Noble and Reeve 2000). The differences in bone turnover rate between cortical/trabecular bone and at sites of red/yellow bone marrow may explain the results found in chapter 7 and are discussed again later in this thesis.

### **Constituents of bone strength and the pathogenesis of osteoporosis.**

Bone depends on several intrinsic qualities for its strength. Clearly the amount of bone mass is an important factor but other factors which contribute to overall bone strength include: the material properties of the bone; bone geometry and bone architecture. As stated in the definition, osteoporosis is a disease “characterised by low bone mass and microarchitectural deterioration” resulting in low bone strength and an increased propensity to fracture.

### **Bone mass, bone strength and osteoporosis.**

The amount of bone is an important determinant of bone strength: the more bone tissue the skeleton has, the stronger it is and the greater resistance it has to fracture. In clinical practice BMD is used as an indirect measure of bone mass and overall, in ex-vivo studies, BMD accounts for around 60-70% of bone strength (Granhed et al 1989). Bone mass increases throughout the early years of life until peak adult bone mass (PABM) is achieved during the 3<sup>rd</sup> decade of life (Teegarden et al 1995). Bone mass then remains

stable until around the time of the menopause. At this time there is a period of rapid bone loss over several years followed by a more gradual, but persistent, loss of bone with ageing. Postmenopausal osteoporosis can result from either the failure to achieve an adequate PABM premenopause and/or the excessive loss of bone postmenopause.

The PABM is the starting point from which menopausal bone loss commences and as such women with low PABM are at risk of developing osteoporosis. It has recently been proposed the bone mass tracks throughout life such that a woman with above average bone mass at age 30 will remain above average at age 70 (Cooper et al 2006). PABM reflects various factors which affect the skeleton from in-utero to young adulthood with puberty being particularly important as around 25% of bone mass is gained around the time of peak height velocity (Bachrach 2001). Genetic factors play a key role and the heritability of BMD at the spine and hip has been estimated to lie between 70 and 85%, with values of 50–60% for wrist BMD (Ralston 2002). There are many potential genes being studied which are thought to interact and contribute to PABM including the genes encoding for the vitamin D receptor, oestrogen receptor, type 1 collagen and insulin like growth factor 1 (Bachrach 2001). Habitual and environmental factors occurring during childhood and adolescence also influence the achievement of expected PABM. Such factors include calcium intake, smoking, alcohol consumption and exercise (Javaid and Cooper 2002). Amenorrhoea due to anorexia or excessive exercise and a variety of medications and illnesses can also impair PABM. Even factors effecting the foetus while in-utero, such as maternal smoking, energy intake, weight and vitamin D status, are associated with reduced neonatal and childhood BMD which potentially may track

throughout life leading to a reduced peak adult bone mass and potentially lower bone mass in old age (Cooper et al 2006).

Oestrogen is important for maintaining a healthy skeleton and at the menopause there is a marked reduction in oestrogen levels. The loss of oestrogen is thought to up-regulate the formation of osteoclasts and osteoblasts in the bone marrow leading to a significant increase in the rate of bone remodelling (Manolagas 2000). Furthermore, the loss of oestrogen results in prolongation of the life of osteoclasts and shortening of the life of osteoblasts (Manolagas 2000). As a result of this there is failure of the bone formation phase to completely replace all the bone removed during the resorption phase (negative remodelling imbalance) which, coupled with the large increase in the rate of remodelling, results in the rapid loss of bone mass at both trabecular and cortical sites. An early menopause is associated with an increased risk of developing osteoporosis as it leads to a shorter period of stable PABM and an earlier onset of bone loss and therefore greater bone loss over time. After the initial rapid menopausal bone loss, oestrogen also plays a key role in the rate of continued bone loss as postmenopausal women with low residual oestrogen levels (<5pg/ml) suffer a more rapid decline in BMD than women with higher levels (>10pg/ml) (Stone et al 1998). Furthermore, low residual oestrogen levels (<5pg/ml) have been demonstrated to be associated with an increased risk of hip and vertebral fracture which persisted even after adjustment for calcaneal BMD (Cummings et al 1998).

Other factors are associated with an increased bone loss. Low weight and weight loss after the age of 50 have both been associated with lower bone mass and a higher rate of postmenopausal bone loss (Bauer et al 1993). Weight is thought to effect bone mass in 2 ways. Firstly, after the menopause, adipose-derived oestrogen is the primary determinant of circulating oestrogen levels. Secondly, body weight is an important determinant of the degree of mechanical loading the skeleton is exposed to during daily life. Smoking has consistently been demonstrated to be associated with increased bone loss, possibly though interfering with intestinal calcium absorption due to suppression of the PTH-calcitriol endocrine axis (Need et al 2002). Excessive alcohol and reduced physical activity have also been associated with bone loss although less consistently (Bauer et al 1993, Hannan et al 2000). Deficiency in calcium and vitamin D becomes increasingly common with increasing age and this leads to secondary hyperparathyroidism which maintains serum calcium levels at the expense of increased bone resorption, thus further exacerbating postmenopausal bone loss. In addition to these environmental factors, genetic factors may also play a role in postmenopausal bone loss although the evidence for this at present is conflicting (Ralston 2002).

#### Bone architecture, bone strength and osteoporosis.

In postmenopausal osteoporosis, in addition to the loss of bone mass, there is also deterioration in the architecture of both the cortical and trabecular bone leading to a further reduction in bone strength. Cortical bone contributes greatly to bone strength,

particularly at sites such as the radius and hip. There are 3 main determinants of cortical strength: cortical diameter, cortical thickness and cortical porosity.

With aging, bone is formed on the periosteal surface, which leads to an increase in cortical diameter. This should increase bone strength as the bending strength of bone is proportional to the fourth power of its distance from the neutral axis. However, bone is simultaneously removed from the endocortical surface and this occurs at a greater rate than the periosteal bone formation leading to thinning of the cortex with age (Kaptoge et al 2003). By the ninth decade of life cortical thickness has reduced by 42% (Bousson et al 2001). The overall effect on bone strength depends on the relationship between the increasing cortical diameter and reducing cortical thickness. This can be expressed as the buckling ratio (radius/cortical thickness) and, when the ratio exceeds 10, bone strength is lost due to increased propensity to buckling. In women over 65 the mean cortical buckling ratio at the hip is around 12 and this increases further with age (Kaptoge et al 2003). Therefore, the overall effects of the cortical changes with age result in a reduction cortical strength.

Cortical porosity also contributes to bone strength. After the menopause there is a great increase in bone remodelling which, in the cortex, occurs as deep cutting cones, which remove old bone. Increased porosity of the cortex results in large reduction in bone strength and higher cortical porosity has been reported in patients who suffer fractures of the femoral neck (Jordan et al 2000). The overall degree of cortical porosity depends on both the number of pores and their size. With age in women it has been demonstrated that

pore size and number both increase up to aged 60 (Bousson et al 2001). After age 60 the pore size continues to increase although pore number reduces. This is due to pores coalescing and overall cortical porosity continues to increase with age resulting in further reductions in cortical strength.

Trabecular bone is also an important determinant of bone strength, particularly at predominantly trabecular skeletal sites such as the vertebrae. The trabecular bone forms a honeycomb within the cortical shell. The strength of trabecular bone is related to the number of trabeculae and their thickness with the strength of any given trabecula being proportional to the square of its radius. The orientation of the trabeculae is also important as trabeculae best resist strain inline with their orientation. Finally, there is a high degree of connectivity between the trabeculae which further contributes to trabecular strength. Consider the spine where the forces generated by supporting the upper body are predominantly in the vertical plain. Numerous, thick vertical trabeculae are required to support this loading however the horizontal trabeculae connect and support the vertical trabeculae thus increasing their strength further. The strength of a given section of vertical trabecula is inversely proportional to the square of the distance between horizontal supporting trabeculae.

After the menopause, bone loss is greater for trabecular bone than cortical bone, most likely due to the higher rates of bone turnover in trabecular bone. There is a reduction in trabecular bone volume due to both a reduction in trabecular thickness and number leading to reduced bone strength (van der Linden et al 2001). However, in



postmenopausal osteoporosis there seems to be a preferential loss of horizontal trabeculae leading to a reduction in interconnectivity (Thompson et al 2002). Finite element analysis modelling predicts that this results in a greater loss of bone strength than losing an equal amount of bone tissue from all trabeculae. Silver and Gibson (1997) demonstrated that bone strength was reduced by 70% when horizontal trabeculae were removed to give a 10% reduction in bone volume compared to a 20% reduction in bone strength when an equivalent bone volume was removed in a more uniform manner.

The increase in bone resorption after the menopause not only leads to a structural deterioration of the trabecular bone but also directly reduces trabecular strength as the resorption cavities act as “stress risers”. A stress riser is an area of an object at which stress tends to be concentrated due to a particular shape or consistency of the material.

The stress transmitted through a trabecula is increased in the bone adjacent to a resorption cavity creating a weak area in the trabecula (van der Linden et al 2001).

Although the amount of bone removed by a resorption cavity is small, its effect on bone strength is amplified by the stress riser effect. Using finite element modelling van der Linden et al (2001) demonstrated that removing 20% of the bone volume in the form of resorption cavities reduced trabecular strength by 50%. Removing the same amount of bone by uniform trabecular thinning resulted in only a 30% reduction in strength.

### Other factors affecting bone strength.

It is worth discussing the material properties of bone as these also contribute to bone strength although the role they play in the pathogenesis of osteoporosis is less certain. Bone is highly mineralised, with the mean degree of mineralization of bone (MDMB) predominantly reflecting the duration of secondary mineralization and thus being inversely related to the rate of bone turnover (Boivin and Meunier 2002). In osteomalacia MDMB is very low and the bone is weak. Conversely over-suppressed or adynamic bone turnover leads to very high degrees of mineralization, which may make the bone brittle and weak (Turner 2002). In most postmenopausal women mineralization is in-between these extremes and the optimum level of mineralization is not known. It has been observed that bone from osteoporotic women has a lower MDMB than controls (Roschger et al 2001). This is likely to reflect increased bone turnover and it is uncertain whether this lower MDMB itself reduces bone strength.

Finally, in addition to the mineral content of bone, the organic component (i.e. type 1 collagen) also has a role in determining bone strength. This is best demonstrated in osteogenesis imperfecta where a single point mutation in the collagen molecule leads to a marked reduction in bone strength. Collagen increases the amount of energy a bone can absorb before it fractures and may have a role in preventing the propagation of micro-cracks. The strength of type 1 collagen comes from its covalent cross-links. It has been demonstrated that patients with osteoporosis have a reduction in the number of collagen cross-links compared to age matched controls (Oxlund et al 1996). This suggests the

quality of the osteoporotic bone collagen is reduced and this may also contribute to reduced bone strength.

**Chapter 2:**

**The treatment of Osteoporosis.**

## **Chapter 2.1:**

### **Antiresorptive therapies.**

Until recently, antiresorptive therapies were the only treatment available for osteoporosis and, in the form of bisphosphonates, they remain the mainstay of treatment. There are several different classes of antiresorptive therapy including HRT, bisphosphonates, SERMs and calcitonin. These have different mechanisms of action however overall antiresorptives have 2 main effects on bone tissue. Firstly they reduce the rate of bone turnover, as measured by the activation frequency. Secondly they improve the balance between bone resorption and formation at the level of the BMU as measured by the erosion depth of the resorption cavity and the wall thickness of the osteoid respectively (Chavassieux et al 1997).

#### **Mechanism of fracture reduction.**

Antiresorptives are effective in increasing bone strength and reducing the incidence of fractures. They achieve this without causing large increases in the absolute amount of actual bone tissue through several effects, which reverse or prevent the pathogenic changes of osteoporosis mentioned in chapter 1.3.

Firstly, antiresorptives reduce or prevent the age related loss of bone mass and the deterioration in microarchitecture which characterises postmenopausal osteoporosis. It has been demonstrated that placebo treated women suffer reductions in trabecular

volume, number and connectivity which does not occur in bisphosphonate treated women (Borah et al 2006, Dufresne et al 2003). Therefore, antiresorptive treated women have a smaller decline in bone strength with age. Untreated women suffer ongoing reductions in bone strength which will in part contribute to the higher incidence of fracture observed in the placebo arm of the various fracture intervention trials using antiresorptives.

By reducing bone turnover, antiresorptives reduce the number and depth of erosion cavities (Eriksen et al 2005). The amount of bone gained by this contraction of the remodelling space is relatively small however it results in a significant increase in bone strength as these erosion cavities act as “stress risers” (van der Linden et al 2001). Stress risers result in a marked reduction in bone strength, which is reversed with antiresorptive therapy (Riggs and Parfitt 2005).

By reducing the frequency with which bone undergoes replacement, antiresorptives permit longer periods of secondary mineralization. After primary mineralization of the osteoid, secondary mineralization increases the MDMB from 50-60% to 90-95% of the maximum mineralization (Davidson et al 2006). Treatment with antiresorptives has been demonstrated to increase the MDMB (Boivin et al 2000, Roschger et al 2001). Increased mineralization increases the structural rigidity of bone, which will lead to an increase in bone strength as long as the bone is not over mineralised (Turner 2002). This increase in mineralization is thought to account for most of the increase in BMD seen with antiresorptives and may contribute towards their anti-fracture efficacy (Bovin et al 2000).

Finally, aging is associated with an increase in the porosity of the cortical bone and a reduction in cortical thickness both of which are associated with a reduction in bone strength. Antiresorptives have been demonstrated to reduce cortical porosity, which will also contribute to their anti-fracture efficacy (Roschger et al 2001). Furthermore, antiresorptives have been demonstrated to prevent age related cortical thinning (Hylstrup et al 2001, Dufresne et al 2003) possibly due to a reduction in endocortical bone resorption.

## **Chapter 2.1.1:**

### **Hormone replacement therapy.**

In the 1980-90s hormone replacement therapy (HRT) with oestrogen was the mainstay for the prevention and treatment of postmenopausal osteoporosis. HRT is the original antiresorptive as it reduces the excessive bone turnover and remodelling imbalance which occurs as a result of postmenopausal oestrogen deficiency. This is demonstrated with markers of bone resorption which are increased in peri and postmenopausal women but reduced to the level of pre-menopausal women by HRT (Lewis et al 2000). Oestrogen receptors are also found in a variety of other organs including breast, uterus, vascular endothelium and brain. It was originally hoped that HRT would have overall health benefits for postmenopausal women with a reduction in menopausal symptoms, hyperlipidemia, cardiovascular disease and dementia. The benefits on cardiovascular disease were particularly encouraging as it is the leading cause of death in postmenopausal women and numerous observational studies had suggested that HRT caused a 40% reduction in the risk of developing coronary heart disease (Grady et al 1992).

The publication of a large randomised controlled trial, the Women Health Initiative (WHI) study, in 2002 however failed to confirm these health benefits (Rossouw et al 2002). Not only did the WHI study confirm the known risk of breast cancer, it demonstrated a 29% increase in cardiovascular disease along with increases in stroke and



venous thrombosis. It is therefore somewhat ironic that the WHI study also provided the best evidence to date that HRT has beneficial effects in preventing bone loss and fractures.

The WHI study was considered by many to be the final word on HRT as it was a very large rigorously conducted randomised controlled trial with important clinical endpoints, which therefore provided a “gold standard” evidence base on which to assess the effects of HRT. However, there are limitations to the WHI study. Randomised controlled trials only provide data on the population and intervention studied. Therefore the WHI study only applies to women in their mid 60s, more than 10 years after the menopause, who take oral conjugated equine oestrogen (CEE) at a dose of 0.625mg per day. The results cannot be extrapolated to women in their late 40s and early 50s, which is the group of women most likely to need HRT for menopausal symptoms. This is especially important with regards to the cardiovascular risks where the age commencing HRT may be an important determinant of the effects of HRT on cardiovascular events. Furthermore, it is emerging that HRT at doses lower than those used in the WHI study have positive effects on bone resorption and the adverse outcomes of the WHI study cannot be extrapolated to these low dose regimes. Both of these points are discussed in more detail below. Finally, the WHI studies only followed women for a mean of 5-7 years. As such the benefits in terms of cardiovascular risk, which could be expected to increase with time (Harman 2006), may be underestimated by the WHI study. This may explain the increase in cardiovascular events which contradicts the findings reported in the observational studies which had longer follow up periods (Grady et al 1992).

The WHI study altered the public opinion of HRT and it has been demonstrated that since the WHI study HRT use has declined (Main and Robinson 2008). This may in part be due to the risks of HRT often being expressed as increases in relative risk e.g. “29% increase in cardiovascular events”. While this would understandably be concerning to a woman contemplating HRT it is important to put this in the context of the magnitude of absolute risk which is actually very small, an extra 7 cardiovascular events per 10000 person-years. Furthermore, the negative risks are often considered in isolation, which distorts the perception of HRT. For example the 26% increased risk of breast cancer, still only an extra 8 cases per 10000 person-years, is often quoted without mentioning that overall cancer rates were not increased due to a reduction in the incidence of colorectal cancer (6 less per 10,000 person-years).

Overall it appears that HRT is judged harshly by ignoring the low absolute risks, concentrating on the negatives effects of treatment and by the over extrapolation of the WHI study to different groups of women and HRT preparations. However, despite this it is still felt that the health risks outweigh the benefits. In the UK the Medicines and Healthcare products Regulatory Agency (MHRA) has issued guidance recommending that HRT is only used at the minimum effective dose for the shortest duration of time for the relief of menopausal symptoms and that HRT is not a first line treatment option for osteoporosis. Although the WHI study and MHRA recommendation suggest that HRT is

no longer an appropriate treatment for osteoporosis this may not be the case as there are still many issues with HRT which are unresolved.

**HRT, fractures and bone.**

Even prior to the WHI study many studies suggested that HRT reduced the risk of hip fractures by about 25% (Grady et al 1992). The WHI study confirmed that all types of fracture were significantly reduced by both oestrogen only HRT (Jackson et al 2006) and combined oestrogen and progestogen HRT (Cauley et al 2003). Unlike all other studies of osteoporosis therapy, the WHI study successfully demonstrated fracture reduction in a population which had not been selected on the basis of BMD. BMD also increased progressively with both oestrogen only and combined HRT. The BMD and fracture outcomes of the WHI study are summarised in table 2.1.1.1.

Table 2.1.1.1: The effects of HRT on BMD and fractures.

	<b>Oestrogen only HRT</b>	<b>Combined HRT</b>
<b>Baseline age (yrs)</b>	63.6	63.2
<b>Baseline t-score: spine</b>	-1.19	-1.30
<b>BMD increase year 3: spine</b>	6.0%	6.10%
<b>BMD increase year 6: spine</b>	7.1%	7.50%
<b>Hip fracture:</b>		
Relative risk reduction	35%	33%
# prevented per 10000 person-years	7	5
<b>Clinical vertebral fracture:</b>		
Relative risk reduction	36%	35%
# prevented per 10000 person-years	7	6
<b>Forearm fracture:</b>		
Relative risk reduction	42%	29%
# prevented per 10000 person-years	24	18
<b>Total fracture:</b>		
Relative risk reduction	29%	24%
# prevented per 10000 person-years	53	47

# = fracture

Since the WHI study, HRT is only recommended for short term use around the time of the menopause. With short term HRT BMD will increase during treatment however upon discontinuation of the HRT bone loss will occur. Various rates of bone loss after stopping HRT have been reported but there appears to be a period of rapid bone loss, similar to early postmenopausal bone loss, followed by persistent but slower normal age related bone loss (Greenspan et al 2002, Greendale et al 2002, Sornay-Rendu et al 2003). It is currently uncertain whether this period of rapid bone loss eliminates all the bone mass gained during the treatment period.

*Research topic: Will the short-term use of HRT, as recommended by the MHRA, result in long term benefits in terms of BMD? This is studied in chapter 5 of this thesis.*

One of the limitations of the WHI study is that it studied only one dose of HRT, 0.625mg CEE with or without progestogens. In more recent years there has been much interest in the use of low dose HRT, 0.3mg CEE or equivalent, which it is hoped may provide a treatment for menopausal symptoms and bone loss without the risks associated with conventional dose HRT. Low dose HRT has been reported to reduce menopausal symptoms by 65% (Ettinger 2007).

There have been many studies looking at the BMD effects of low dose oestrogen, mainly using either 0.3mg CEE or 1 mg of oestradiol (E2), with varying progestogen regimes for women with a uterus. Most of these studies are of relatively short duration, ranging from

2-4 years, and direct comparison is somewhat difficult due to differences in treatment regime, sample size and patient age. However, increases in BMD of 1.3-5% at the spine and up to 3% at the hip over 2-3 years have been reported (van der Weijer et al 2007). The BMD response to low dose HRT is less than the BMD response achieved in the WHI study and evidence from bone markers suggest that the antiresorptive effects of HRT is dose dependant (Ettinger 2007). As such the benefits of low dose HRT in terms of fracture prevention is uncertain and cannot be extrapolated from the WHI study. However, neither can the risk of vascular disease and breast cancer observed in the WHI study be applied to low dose HRT regimes. Furthermore, very low dose oestrogen may be given to women with a uterus without progestogens potentially providing protective effects on the bone without the risks associated with progestogens. The potential for low dose HRT to provide long term prevention of postmenopausal bone loss requires further research.

### **HRT and breast cancer.**

Breast cancer is probably the most feared complication of HRT even though the average 50 year old woman is ten times more likely to die from coronary heart disease. A 50 year old woman has a 10% lifetime risk of developing breast cancer and a 3% risk of dying from breast cancer compared to a 30% risk of dying from coronary heart disease (Grady et al 1992, Collins et al 2007). The type of HRT is important with regards to breast cancer. Progestogens are given with oestrogen to women with a uterus. Progestogens reduce the mitotic rate of the endometrial cells, which prevents an increase in the risk of

endometrial cancer due to unopposed oestrogen therapy. However, progestogens increase the mitotic activity of breast tissue, possibly leading to the increased risk of breast cancer. Consistent with this, the PEPI study demonstrated that breast tissue density on mammography was increased in women taking combined HRT compared to oestrogen only HRT (Greendale et al 1999).

Early observational studies revealed mixed results for both oestrogen only HRT and combined HRT (Grady et al 1992). An early randomised controlled trial, designed to assess the effects of HRT on secondary cardiovascular disease prevention (HERS study), demonstrated a non-significant 30% increase in breast cancer incidence in women treated with combined HRT (Hulley et al 1998). It is likely that this study was too small (n=2763) and of insufficient duration (mean 4.1 years) to detect a significant increase in breast cancer. The increased risk of breast cancer associated with combined HRT was confirmed by both a very large observational study, the Million Women study (MWS), and the WHI study. The MWS demonstrated that current users of combined HRT had a 2 fold increased risk of developing breast cancer, that the risk increased with duration of HRT use and that the risk had reduced to baseline within 5 years of discontinuation (Beral et al 2003). The WHI study demonstrated a 26% increase in breast cancer incidence, an extra 8 cases per 10000 person-years, in those women taking combined HRT that separated from the placebo group after 4 years (Rossouw et al 2002).

Oestrogen only HRT appears to have less of an association with breast cancer, if at all. The MWS study demonstrated a significantly increased risk of breast cancer with

oestrogen only HRT although the relative risk was smaller than with combined HRT (RR 1.3 versus 2.0 respectively). The WHI study however did not support the findings of the MWS as there was a trend towards a lower incidence of breast cancer in women taking oestrogen only HRT compared to placebo (23% reduction,  $p=0.06$ ) (Anderson et al 2004).

### **HRT and coronary heart disease (CHD).**

For women at age 50, the lifetime risk of dying from coronary heart disease is 30% (Grady et al 1992, Collins et al 2007). Around the time of the menopause there are unfavourable metabolic changes in lipid and carbohydrate metabolism and the incidence of coronary events increases markedly (Collins et al 2007). Numerous studies have demonstrated that oestrogen has favourable effects on factors associated with cardiovascular disease including increased HDL cholesterol, reduced LDL cholesterol, vasodilatation of the coronary arteries, inhibition of platelet aggregation, reduced fasting insulin levels and reductions in key inflammatory factors (Collins et al 2007, Harman 2006). These effects provide a mechanism by which oestrogen may reduce the progression of atherosclerosis and this has been demonstrated by a study assessing carotid artery wall thickness (Hodis et al 2001). Progestogens may negate some of these positive benefits by reducing vasodilatation and increasing insulin resistance which may lead to atherosclerotic plaque progression (Collins et al 2007, Harman 2006).

The majority of the early observational HRT studies suggested that HRT use was associated with an improvement in risk factors for coronary heart disease and a 40% reduction in coronary events (Grady et al 1992). There was concern that these observational studies were subject to “Healthy user” bias by which women who used HRT were more likely to lead healthier life styles and that this may account for the reduction in coronary events. The HERS study was the first large randomised controlled trial to look at the cardiovascular effects of combined HRT on women with existing coronary heart disease (Hulley et al 1998). Overall there was no difference between HRT and placebo in terms of coronary events. However, compared to placebo, women randomised to HRT experienced more coronary events in the first year and fewer in years 4 and 5. The WHI study demonstrated a significant 29% increase in coronary events, an extra 7 per 10000 person-years, in women receiving combined HRT and no significantly increased risk in women on oestrogen only HRT (Anderson et al 2004, Rossouw et al 2002).

In the WHI study the risk of coronary heart disease increased soon after initiation of HRT. However, HRT is usually prescribed during the early menopausal period for the relief of climacteric symptoms. At this time most women have a low absolute risk for cardiovascular disease and as such any increase in relative risk would lead to only a small increase in absolute risk. Furthermore, the “timing hypothesis” suggests that HRT started at the time of, or soon after, the menopause may lead to a reduction in cardiovascular events due to the inhibition of atherosclerotic plaque formation and progression (Harman 2006). When HRT is started late after the menopause (mean age in the WHI study was



63) women may already have mature atherosclerotic plaques which become at increased risk of causing cardiovascular events due to the increased thrombotic tendency associated with HRT. Evidence supporting the timing hypothesis includes a recent study which reported that coronary artery calcification (a marker of atherosclerotic plaque burden) was reduced in women aged 50-59 who took oestrogen only HRT during the WHI study (Manson et al 2007). Further evidence comes from a reanalysis of the WHI study which demonstrated that women who started HRT within 10 years of the menopause had a lower risk of coronary heart disease than women who started HRT more than 20 years after the menopause (Rossouw 2007). This appears to be the case for both oestrogen only HRT (HR 0.48 and 1.12 respectively, significance of trend:  $p=0.15$ ) and combined HRT (HR 0.88 and 1.66 respectively, significance of trend:  $p=0.05$ ).

The timing hypothesis could explain why the observational HRT studies, where HRT was started for menopausal symptoms, demonstrated a reduction in cardiovascular events. Similarly, it could explain the HERS study findings of increased early coronary events and reduced late coronary events. As such HRT started around the time of the menopause may be safe, or even protective, in terms of cardiovascular disease and allow the treatment of menopausal symptoms and the prevention of postmenopausal bone loss.

### **Other associations with HRT.**

The WHI study demonstrated an increased risk of stroke in women taking either combined HRT (41% increase) or oestrogen only HRT (39% increase). Again the

absolute risk of stroke in women during the early menopausal period is usually low and as such any increase in relative risk would lead to only a small increase in absolute risk. The incidence of colorectal cancer was reduced by combined HRT (37% reduction) and unchanged by oestrogen only HRT. Combined HRT doubled the risk of both deep vein thrombosis (DVT) and pulmonary embolism (PE). Oestrogen only HRT increased the risk of DVT by 47% although there was no significant increase in PE.

### **HRT implications for osteoporosis prevention and treatment.**

The WHI study demonstrates that HRT is not the best treatment option for elderly women with osteoporosis due to the cardiovascular risks and the availability of other effective treatments for osteoporosis. However, other treatments for osteoporosis are poorly studied in younger women. For women with menopausal symptoms, an early menopause or osteoporosis in the early menopausal period HRT may prove to be safe and effective in the prevention and treatment of osteoporosis. The type of HRT requires consideration as there are less risks associated with oestrogen only HRT. Furthermore, consideration needs to be given to the dose of HRT and the route of administration. Low dose HRT appears to be beneficial in terms of menopausal symptoms and bone protection and may not have the risks associated with conventional dose HRT. Transdermal oestrogen does not appear to have the same thrombotic effects as oral oestrogen (Scarabin et al 2003) and progestogens can be given topically via inter-uterine systems such as the Mirena coil. Clearly HRT is not suitable for all women as some women may already have significant

risk factors for, or a history of, breast cancer or cardiovascular disease. However, for low risk young women with osteoporosis HRT may be a good initial treatment option.

## **Chapter 2.1.2:**

### **Bisphosphonates.**

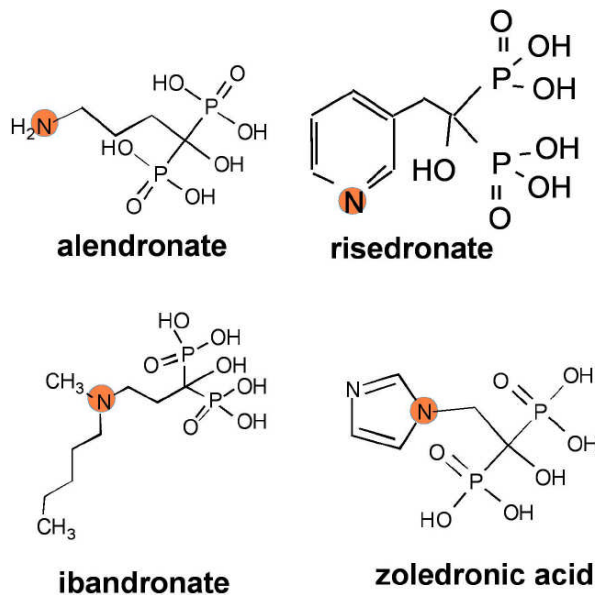
Bisphosphonates are currently considered by many to be first line agents for the treatment of osteoporosis. By inhibiting the function of osteoclasts they are potent suppressors of bone turnover. They have been used in various forms since the 1970s for the treatment of many bone diseases including Paget's disease, myeloma, bone metastases and osteoporosis. The first bisphosphonate used for osteoporosis was etidronate (Didronel). Etidronate is now infrequently used for osteoporosis due to concerns that continuous etidronate therapy may induce osteomalacia and lack of evidence for non-vertebral fracture reduction (Cranney et al 2001). More potent nitrogen containing bisphosphonates are now used for osteoporosis and are the focus of this chapter.

#### **Structure and function.**

Bisphosphonates are metabolically stable analogs of pyrophosphate. They consist of a carbon atom bound to 2 phosphate groups known as the P-C-P backbone. The phosphate groups act as a "bone hook" by binding strongly to hydroxyapatite, which accounts for the high affinity of bisphosphonates for bone. The molecule also has 2 side chains – R1 and R2. The R1 side chain is a hydroxyl group in all bisphosphonates and this further enhances binding to hydroxyapatite (tridentate binding). The R2 group is specific to each bisphosphonate although all modern bisphosphonates contain a nitrogen based group at

this side chain. The molecular structure of modern bisphosphonates is demonstrated in figure 2.1.2.1.

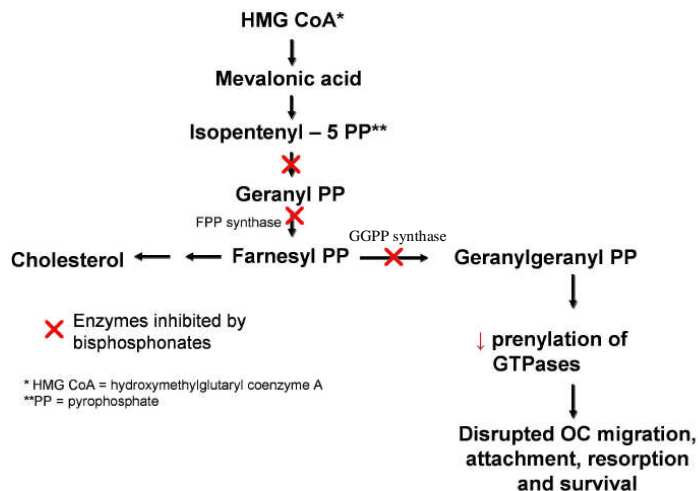
Figure 2.1.2.1: Molecular structure of bisphosphonates



The bioavailability of oral bisphosphonates is poor. Only around 1-2% of an oral dose of bisphosphonate is absorbed in the gut. Approximately 50% of the absorbed bisphosphonate is retained in the bone with the remainder being rapidly cleared from the plasma by the kidneys within 10 hours of administration (Miller 2005). The bisphosphonates bind predominantly to the exposed hydroxyapatite at areas of active bone resorption (Sato et al 1991). During bone resorption, the bisphosphonate is released from the hydroxyapatite and taken up into the osteoclast. Within the osteoclast bisphosphonates inhibit farnesyl pyrophosphate synthase (FPS) and, to a lesser extent, geranylgeranyl diphosphate synthase (GGPPS) which are key enzymes in the mevalonic acid pathway for cholesterol metabolism (Russell 2007). This inhibits the prenylation of GTPases which are vital for the regulation of osteoclast morphology, cytoskeletal

arrangement, membrane ruffling, migration and ultimately cell survival. The mechanism of action of bisphosphonates is demonstrated in figure 2.1.2.2.

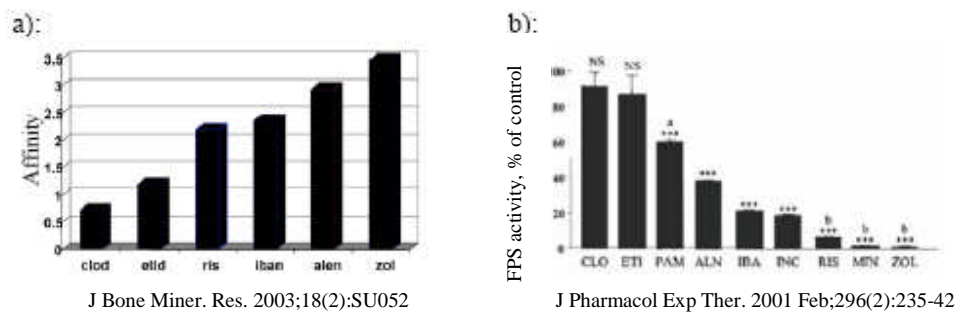
Figure 2.1.2.2: Enzyme inhibition by bisphosphonates.



The different structures of the R2 side chain accounts for the differences between bisphosphonates in terms of bone binding affinity and potency. Individual bisphosphonates have different in-vitro binding affinities for hydroxyapatite as demonstrated in figure 2.1.2.3a. Bisphosphonates with higher binding affinities are retained longer in the bone, are less likely to be released from the hydroxyapatite by the osteoclasts and have higher rates of reattachment to the bone after release from osteoclasts (Russell 2007). The binding affinity is therefore likely to account for the differences in persistence of action of bisphosphonates after discontinuation, which is discussed later in this chapter. Furthermore, binding affinity may effect how well bisphosphonates diffuse through the bone and thus their distribution. The potency of inhibition of FPS in-vitro also differs between bisphosphonates as demonstrated in figure

2.1.2.3b. The in-vivo effects of bisphosphonates on bone resorption is a complex interaction between their binding affinity and potency of FPS suppression which is not fully understood (Russell 2007).

Figure 2.1.2.3: Differences in bisphosphonate binding affinity for hydroxyapatite (a) and potency if inhibition of FPS (b).



### The effect of bisphosphonates on BMD and fractures.

There are 4 nitrogen containing bisphosphonates currently licensed for the treatment of postmenopausal osteoporosis: alendronate, risedronate, ibandronate and zoledronate.

These drugs have been well studied by good quality randomised controlled trials and are proven to effectively suppress bone turnover, increase BMD and, most importantly, prevent fractures. The main clinical outcomes from the fracture prevention trials for these bisphosphonates are illustrated in table 2.1.2.1.

Table 2.1.2.1.1. The effect of bisphosphonates on BMD and fractures from the main phase 3 randomised controlled trials. (Black et al 1996, Cummings (b) et al 1998, Reginster et al 2000, Harris et al 1999, McClung et al 2001, Chestnut et al 2004, Black et al 2007)

	Alendronate		Risedronate		Ibandronate BONE <sup>†</sup>	Zoledronate HORIZON
	FIT1	FIT2	VERT-MN	VERT-NA		
<b>Number of women</b>	207	4432	1226	2458	1964	7765
<b>Age</b>	55-81	55-80	PM, <85	PM, <85	55-80	65-89
<b>Inclusion criteria<sup>††</sup></b>	T-1.6 + #	T-1.6	>2#	T-2 + 1# or 2#	T-2.0 + #	T-2.5 or -1.5 + #
<b>Duration</b>	3 years	4 years	3 years	3 years	3 years	3 years
<b>Dose</b>	5 or 10mg/d	5 or 10mg/d	2.5 or 5 mg/d	2.5 or 5 mg/d	2.5mg/d	5mg/year
<b>Δ BMD spine<sup>†††</sup></b>	6.2%*	6.8%*	5.9%*	4.3%*	5.2%*	6.71%*
<b>Δ BMD hip (nof)<sup>†††</sup></b>	4.1%*	4.6%*	3.1%*	2.8%*	3.7%*	5.06%*
<b>vertebral #: RRR</b>	47%*	44%	49%*	41%*	52%*	70%*
<b>ARR</b>	7.0%	1.7%	10.9%	5.0%	4.9%	7.6%
<b>non-vertebral #:RRR</b>	ns	ns	33%*	39%*	ns	25%*
<b>ARR</b>	51%*	1.1%	5.1%	3.2%	1.8%	2.7%
<b>hip #: RRR</b>	1.1%	ns	ns	ns	30%*	41%*
<b>ARR</b>	1.1%	ns	1.1%	1.1%	1.1%	1.1%

<sup>†</sup> only daily ibandronate is included. <sup>††</sup> # = vertebral fracture <sup>†††</sup> = compared to placebo  
RRR = Relative risk reduction, ARR = Absolute risk reduction, nof = neck of femur, RF = risk factor, PM = postmenopausal  
\* - statistically significant, ns = not significant.



With the exception of intravenous (iv) zoledronate, all the fracture prevention trials were performed using daily oral therapy. Bisphosphonates have strict administration requirements due to their poor absorption, which makes daily therapy inconvenient. However, the prolonged bone retention of bisphosphonates after an oral dose allows intermittent therapy. Studies have demonstrated that weekly alendronate (Rizzoli et al 2002), weekly risedronate (Harris et al 2004) and monthly ibandronate (Reginster et al 2006) provide a BMD and bone turnover marker (BTM) response equivalent to that achieved with daily therapy. As such bisphosphonates are now mostly prescribed as weekly/monthly therapy. It has been demonstrated that women prefer intermittent therapy and that this improves persistence with bisphosphonates (Bartl et al 2006).

### **Differences in the antiresorptive effects of bisphosphonates.**

It is becoming apparent that bisphosphonates may have individual characteristics in terms of antiresorptive properties, onset of fracture reduction and persistence of effect after discontinuation. The antiresorptive properties of bisphosphonates can be compared directly in head to head studies using BMD and BTMs. The FACT trial compared weekly alendronate to weekly risedronate and demonstrated that alendronate is a more potent antiresorptive. Compared to risedronate, 2 years of alendronate therapy resulted in a significantly greater suppression of BTMs (CTX -73% vs. -53%, BSAP -40 vs. -29%, P1NP -62% vs. -46%) and a significantly greater increase in BMD at the spine (5.2 vs. 3.4%) and hip (2.8 vs. 1.0%) (Bonnick et al 2006). A recent, non-inferiority study

(MOTION) demonstrated that monthly ibandronate therapy was comparable to weekly alendronate in terms of BMD gain at the spine (5.1% and 5.8% respectively) and hip (2.9% and 3.0% respectively) after 1 year of treatment (Miller et al 2007). In a separate study, 150mg of ibandronate per month reduced serum CTX by 68% which is similar to the decreases observed with alendronate although this was not a head to head study (Reginster et al 2006).

### **Differences in onset of fracture reduction.**

Comparison between bisphosphonates in terms of fracture reduction is difficult as the populations studied in the major fracture prevention trials were too different to allow direct comparison. A head to head randomised controlled trial to assess for differences in fracture reduction would require far too large a population to be feasible however this has recently been investigated by a large observational study. The REAL study is an observational cohort study using computerised records of health service utilization in the US. It compared the incidence of clinical fractures during the first year of therapy with either weekly risedronate (n = 12,215) or alendronate (n = 21,615) (Silverman et al 2007). In this study, compared to women prescribed alendronate, there were significantly fewer non-vertebral and hip fractures at both 6 and 12 months in women who took risedronate. This suggests that in the first 12 months of therapy risedronate is more effective which may be due to a quicker onset of fracture reduction. This is important as 20% of women who suffer a vertebral fracture will fracture again within 1 year (Lindsay et al 2001). Other studies investigating the speed of onset of fracture reduction

demonstrate that with risedronate reductions in both clinical vertebral and non-vertebral fractures are observed 6 months after treatment initiation (Roux et al 2004, Harrington et al 2004). In contrast, after the initiation of alendronate, vertebral fractures are reduced by 12 months, hip fractures by 18 months and non-vertebral fractures by 24 months (Black et al 2000). These studies are post-hoc analyses of the FIT and VERT trials, which had different selection criteria and had very different sample sizes. This makes it difficult to be certain that the differences observed are genuine however it would explain the greater reduction in fractures achieved with risedronate during the first year of therapy in the REAL study.

#### **Differences in offset of the clinical efficacy of bisphosphonates after discontinuation.**

After the discontinuation of therapy bisphosphonates remain in the bone for a prolonged period of time, the duration of which is thought to be related to the affinity of the bisphosphonate for hydroxyapatite. High affinity bisphosphonates, such as alendronate, bind more avidly to the bone, have lower rates of uptake by osteoclasts and have higher reattachment rates after release from the osteoclast (Russell 2007). After discontinuation, the amount of bisphosphonate in the bone reduces slowly at a rate governed by its affinity. However the duration of suppression of bone resorption may also depend to some extent on the potency of the bisphosphonate. The greater the potency of the bisphosphonate for inhibiting FPS, the longer it will be able to continue to inhibit bone resorption as the residual amount of bisphosphonate declines.

Zoledronate, which has both the highest affinity and potency, is able to suppress bone turnover for 12 months after a single iv infusion (Black et al 2007). Risedronate is also highly potent but has a lower affinity for hydroxyapatite and as such after discontinuation bone resorption rapidly returns to normal. This has been demonstrated in an extension to the VERT-NA trial in which 12 months after the discontinuation of risedronate BSAP and NTX were no longer different from those women who had not taken risedronate at all. (Watts et al 2004). Alendronate has a high affinity and 2 studies have demonstrated that even 5 years after discontinuation there is still suppression of bone turnover, as assessed by BTMs, and an overall gain in BMD (Bone et al 2004, Black et al 2006). The prolonged suppression of bone turnover after the discontinuation of bisphosphonates, especially alendronate, may have consequences if a woman is switched to a different class of osteoporosis therapy. This is discussed further in chapters 2.2 and 2.3 and is investigated in chapters 6 and 7.

The effect of this prolonged suppression of bone turnover on fractures however is more mixed. The FLEX trial demonstrated that, compared to women who continued therapy, 5 years after the discontinuation of alendronate there was a significant increase in clinical vertebral fractures and a non-significant trend towards an increase in all vertebral fractures (Black et al 2006). However, there was no increase in the risk of non-vertebral fractures. It is important to note that women with very low BMD ( $T < -3.5$ ) and those who lost BMD during the first 5 years of treatment were not entered into the FLEX trial. However, the FLEX trial is the best evidence we have regarding the offset of clinical efficacy of alendronate. It suggests that in clinical practice it is safe to allow low risk

osteoporotic women to have a treatment holiday from alendronate for up to 5 years. For women at high risk of fracture it may be more appropriate to either continue life long treatment or to limit treatment holidays to a shorter period of time.

### **Chapter 2.1.3:**

#### **Other antiresorptives.**

Although bisphosphonates are the most frequently prescribed antiresorptive, there are 2 other classes of these drugs: selective oestrogen receptor modulators (SERMs) and calcitonin. While these treatments are not the focus of any of the studies included in this thesis they are mentioned in some of the discussions. Therefore, they are briefly reviewed in this chapter to provide basic background information.

#### **Selective oestrogen receptor modulators (SERM).**

To date the only SERM in clinical practice is raloxifene. Raloxifene is a non-steroid compound which binds to the oestrogen receptor. It has oestrogen agonist effects in some tissues while having oestrogen antagonist effects in others. In the bone raloxifene is an oestrogen receptor agonist and thus reduces bone resorption. Compared to bisphosphonates, raloxifene is a less potent antiresorptive, which is reflected in the BTM and BMD response. The MORE trial demonstrates that the licensed dose of 60mg/day reduces osteocalcin (formation marker) by 18% and serum CTX (resorption marker) by 26% compared to placebo (Ettinger et al 1999). BMD increased significantly more than placebo at the spine (2.6%) and femoral neck (2.1%) over 3 years although the BMD response is less than that achieved with bisphosphonates. Raloxifene reduced vertebral fractures by 30% but did not significantly reduce the incidence of non-vertebral fractures. Unlike bisphosphonates, raloxifene does not bind to the bone so it has a rapid offset of

action with reductions in BMD being observed within 1 year of discontinuation (Neele et al 2002).

As raloxifene stimulates the oestrogen receptor it is important to consider some of the health issues around HRT. Raloxifene has anti-oestrogen effects on breast tissue and blocks oestrogen induced DNA transcription. Two large randomised controlled trials have demonstrated that long term raloxifene reduces the risk of invasive oestrogen receptor positive breast cancer by 55-76% with no significant effect on oestrogen receptor negative breast cancer (Barrett-connor et al 2006, Martino et al 2004).

Raloxifene has no effect on the incidence of gynaecological cancers although uterine polyps are more frequent (Martino et al 2005). Raloxifene does not cause an increased risk of coronary events, even in women at high risk of CHD (Barrett-connor et al 2006). In osteoporotic women in general raloxifene does not increase the risk of stroke (Martino et al 2005) however a 49% increase in risk of fatal stroke has been reported in women with an increased risk of CHD (Barrett-connor et al 2006). Raloxifene causes a 40-70% increase in the risk of DVT and PE (Martino et al 2005, Barrett-connor et al 2006). Other adverse effects of raloxifene include hot flushes, oedema and leg cramps.

### **Calcitonin.**

Physiological calcitonin is released from the C-cells in the thyroid gland. Calcitonin reduces bone resorption by decreasing osteoclast formation and attachment. For osteoporosis salmon calcitonin is usually used via either a subcutaneous injection or a

nasal spray. It is a weak antiresorptive. The PROOF study demonstrated that the licensed dose of 200 iu/day of nasal calcitonin resulted in only a 1.0% increase in BMD and a 12% reduction in serum CTX compared to placebo (Chestnut et al 2000). The PROOF study demonstrated a 33% reduction in vertebral fractures with 200 iu/day but no significant non-vertebral fracture reduction. Calcitonin is a well tolerated drug with the only common side effect being an increased incidence of nasal symptoms. One advantage of calcitonin is that it appears to have analgesic benefits. It has been demonstrated in randomised controlled trials that calcitonin significantly reduces pain and the number of days of bed rest required after an acute vertebral fracture compared to placebo (Lyritis and Trovas 2002). However, the only rescue analgesia permitted in the trial was paracetamol. Whether such a benefit would have been observed if stronger conventional analgesics had been permitted is unknown.



## **Chapter 2.2:**

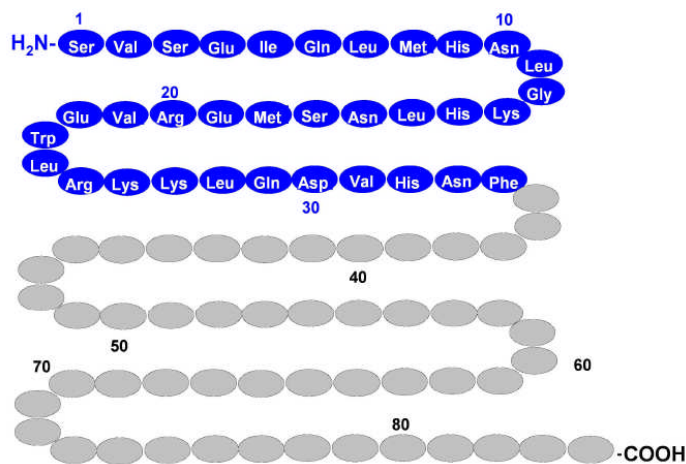
### **Anabolic therapy.**

Anabolic therapies are an exciting and important development in the treatment of osteoporosis. Unlike antiresorptives, which preserve and strengthen existing bone, anabolic therapy leads to new bone formation. This leads to an increase in bone mass and improvements in bone microarchitecture thus reversing the pathological changes characteristic of osteoporosis. Historically, the first anabolic drug used for the treatment of osteoporosis was fluoride. Fluoride is incorporated into the hydroxyapatite crystal leading to an increase in osteoblast cell attachment, proliferation and differentiation (Qu and Wei 2006), which stimulates bone formation leading to increases in trabecular bone volume and connectivity (Eriksen et al 1981, Vesterby et al 1991). However, it was also observed that fluoride lead to incomplete mineralisation of the osteoid with woven bone formation (Eriksen et al 1981) and biomechanical testing of bone biopsies demonstrated a reduction in bone strength (Sogaard et al 1994). Finally, in 2000 a large meta-analysis demonstrated that treatment with fluoride did not reduce vertebral fractures and non-vertebral fracture incidence actually increased after 4 years of therapy (Haugenauer et al 2000).

With fluoride no longer considered as an effective treatment for osteoporosis the only licensed anabolic therapy to date is recombinant human parathyroid hormone (PTH). Endogenous PTH is an 84 amino acid protein. The N-terminal is responsible for the actions of PTH and only the first 34 amino acids are required for receptor activation and

biological effect. Studies investigating the anabolic actions of PTH date back almost 30 years (Reeve et al 1980) and there are currently 2 forms of PTH licensed for osteoporosis: teriparatide, comprising of the first 34 amino acids of PTH (PTH 1-34); and full length PTH (PTH1-84) (Figure 2.2.1).

Figure 2.2.1: The structure of PTH and teriparatide (PTH 1-34).



### Cellular effects of PTH.

The physiological role of PTH is to maintain adequate serum calcium levels. In response to hypocalcaemia, PTH increases serum calcium levels by reducing the renal excretion of calcium and increasing the formation of 1,25 dihydroxyvitamin D, which leads to increased calcium absorption from the intestine. However, most relevant to osteoporosis is PTH's effect on bone where osteoclast mediated bone resorption is increased in order to release calcium into the circulation. It is therefore somewhat counter-intuitive that PTH therapy can lead to bone formation.

The effect of PTH on bone depends on its mode of administration. Continuous infusion, which maintains a persistently elevated serum PTH level, as seen in primary hyperparathyroidism, stimulates osteoclast mediated bone resorption. However, when given as daily subcutaneous injections the PTH concentration peaks at approximately 4-5 times the upper limit of normal after 30 minutes and returns to basal level within 3 hours. These brief peaks in serum PTH result in bone formation rather than resorption.

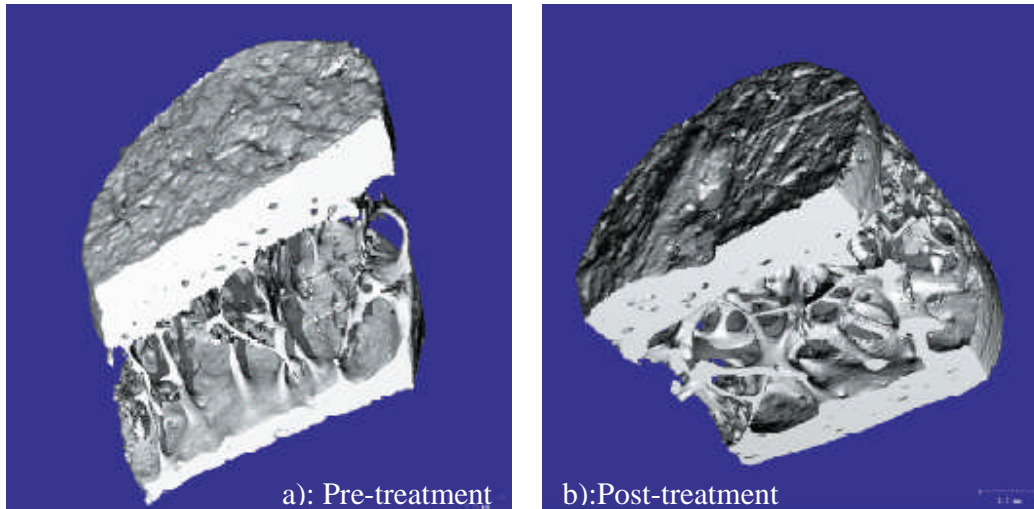
The effects of PTH are induced by the binding of the N-terminal of PTH to the PTH receptor on the surface of the osteoblast. The effect of PTH on osteoclasts is indirect as the osteoclast does not have a PTH receptor. Within the osteoblast, activation of the PTH receptor results in the rapid (within minutes) activation of several intracellular pathways, including the cyclic AMP-dependant protein kinase A and the calcium-dependant protein kinase C signalling pathways, which ultimately regulate gene expression and osteoblast function (Canalis et al 2007). The alterations in osteoblast gene expression depend on the exposure to PTH. In one study, continuous PTH exposure resulted in the activation of 195 genes while intermittent PTH activated 41 genes (Onyia et al 2005). The exact mechanism for PTH's anabolic effects is unknown but ultimately intermittent PTH therapy increases osteoblast differentiation and survival leading to an increase in osteoblast number and bone formation (Canalis et al 2007). Furthermore, in response to PTH the osteoblasts also regulate the activity of the osteoclasts via alterations in the RANKL/OPG pathway (Ma et al 2001).

### **The effects on intermittent PTH on bone structure.**

Intermittent PTH therapy results in the formation of both trabecular and cortical bone. Bone biopsy studies using 2D histomorphometry and 3D microCT demonstrate that daily teriparatide increases the volume of trabecular bone. Other improvements in microarchitecture include increased connectivity between the trabeculae and changing of the trabeculae from a rod-like structure to a more plate-like structure (Jiang et al 2003). Teriparatide also improves cortical bone with increases in cortical thickness associated with an overall increase in the diameter of the bone (periosteal circumference) (Jiang et al 2003, Zanchetta et al 2003). At the hip, these cortical changes have been shown to improve bone geometric strength as demonstrated by an increase in the bending strength and a decrease in the buckling ratio (Uusi-Rasi et al 2005). The changes in bone structure are illustrated in figure 2.2.2.

Teriparatide reverses the postmenopausal decline in bone mass and the deterioration in microarchitecture which characterises osteoporosis although there is one exception – cortical porosity is increased (Jiang et al 2003). An increase in cortical porosity would, to some extent, counter the beneficial effects, which the other structural changes have on cortical strength. However, the effect of the increase in cortical porosity is limited as it predominantly occurs at the endocortical bone surface, which contributes less to overall cortical strength than the periosteal bone surface (Jiang et al 2003).

Figure 2.2.2: The effects of 20µg/day of teriparatide for 21 months on trabecular and cortical bone structures at the iliac crest as measured using microCT (Jiang et al 2007).

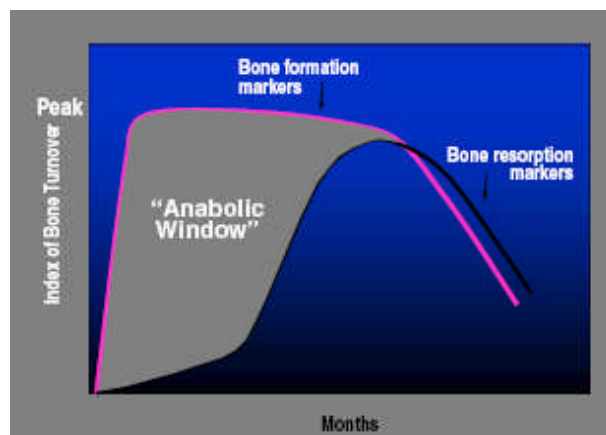


**The clinical effects of intermittent PTH on BTM's, BMD and fractures.**

Compared to antiresorptives, PTH has the opposite effect on bone turnover with increases of bone formation and resorption markers. Bone formation markers demonstrate a significant increase 1 month after the initiation of PTH therapy, peak at 6 months, plateau for a time before gradually declining back towards baseline (Chen et al 2005, Ettinger et al 2004, Greenspan 2007). Bone resorption markers increase at a slower rate and peak later. Therefore there is a time period when bone formation is believed to greatly exceed bone resorption and PTH is thought to have the majority of its anabolic effects – this period is known as the “anabolic window” (figure 2.2.3) (Girotra et al 2006). This concept is supported by evidence from bone histomorphometry, which demonstrates that

bone formation indices are increased after 1 month of teriparatide but not after 18 months of treatment (Jiang et al 2003).

Figure 2.2.3: The different profiles of bone formation and resorption markers in response to PTH therapy and the anabolic window (Girotra et al 2006).



The original fracture prevention trial was prematurely terminated by the sponsor after a mean of 18 months because of a reported increase in the incidence of osteosarcoma in rats treated with long term teriparatide (Neer et al 2001). The risk of osteosarcoma has never been demonstrated in humans however because of the increased incidence in rats, and the lack of long term human data, PTH therapy is usually limited to 18 months. This may not actually be a disadvantage as the “anabolic window” suggests that it is the early period of treatment, which may be most important in terms of gains in bone mass.

The main fracture prevention trials with PTH demonstrated that after 18 months of therapy BMD had increased at the spine by 6.9% (full length PTH) and 8.7%

(teriparatide) compared to placebo (Greenspan 2007, Neer et al 2001). After 18 months femoral neck BMD had increased by 2.5% (full length PTH) and 3.5% (teriparatide) compared to placebo. During the first 6 months of treatment with PTH it has been observed that BMD at the hip declines slightly (Greenspan 2007). This occurs as the hip is a predominantly cortical site and there is an increase in cortical porosity. Furthermore, even though new bone is being formed it will take 4-6 months to complete primary mineralization and thus have maximum effect on BMD. This was demonstrated by Black et al (2003) who used quantitative CT to investigate the effects of 12 months of therapy with full length PTH. In this study cortical BMD at the hip was reduced even though cortical volume was increased suggesting new bone formation. In the same study, trabecular BMD at the spine increased by 25.5% in response to full length PTH reflecting the effects of PTH therapy on trabecular bone.

As with any therapy for osteoporosis, ultimately it is vital that intermittent PTH reduces the incidence of fractures. The main fracture prevention trial with teriparatide demonstrated that after a mean of 18 months of therapy with 20µg/day vertebral fractures were reduced by 65% (9% absolute risk reduction (ARR)), all non-vertebral fractures were reduced by 35% (4% ARR) and non-vertebral fragility fractures were reduced by 53% (3% ARR) (Neer et al 2001). The study was not powered to look for site specific fracture reduction (i.e. hip). Furthermore, follow up studies have demonstrated that teriparatide therapy provides long term reductions in vertebral fracture incidence. During an 18 month follow up period women who had received teriparatide during the fracture

prevention trial had a 41% (7.7%ARR) reduction in the incidence of new vertebral fractures compared to women who received placebo during the trial (Lindsay et al 2004).

Full length PTH also reduces vertebral fractures by 58% (2% ARR) at the dose of 100µg/day (Greenspan et al 2007). However, in this study full length PTH did not demonstrate significant non-vertebral fracture reduction, which is likely to be due to the women having a lower baseline fracture risk. This is illustrated by the 5.9% non-vertebral fracture rate in the placebo group which is lower than the 9.7% reported in the placebo arm of the teriparatide study (Neer et al 2001).

### **Interactions between anabolic and antiresorptive therapies.**

#### **1): Antiresorptives after PTH.**

PTH is usually prescribed for 18 months. Therefore it is important to consider how to treat women after the completion of PTH therapy. PTH therapy results in bone formation however once therapy is discontinued, postmenopausal bone loss resumes. This is illustrated by the observation that BMD at the spine declines after the discontinuation of both teriparatide (Lindsay et al 2004) and full length PTH (Black et al 2005).

Antiresorptives would be expected to reduce bone loss and protect the bone mass gained during PTH therapy. Furthermore, antiresorptives would cause contraction of the remodelling space and allow prolonged secondary mineralization of the newly formed bone. This is supported by evidence that BMD increases further when bisphosphonates



are commenced after PTH therapy (Lindsay et al 2004, Black et al 2005, Prince et al 2005). Cosman et al (2001) also reported that BMD was maintained in women who took HRT after teriparatide therapy although in this study there was no control group which did not receive HRT for comparison. If raloxifene is commenced after teriparatide there is a significant reduction in BMD at the spine however there is a greater reduction if no therapy is commenced (Adami et al 2007). None of these studies had sufficient power to detect a significant reduction in vertebral and non-vertebral fracture incidence if antiresorptive therapy was commenced after PTH. Despite the lack of fracture data, it is recommended that bisphosphonates are prescribed to women completing PTH therapy.

## 2): Antiresorptives combined with PTH.

The observation that bone resorption markers increase with PTH therapy has led to interest into combining PTH and antiresorptive therapy. It was hoped that this approach would increase the amount of bone mass gained by inhibiting bone loss while allowing new bone formation. Early studies were encouraging with reports that HRT combined with teriparatide resulted in fewer vertebral fractures and better BMD gains than HRT alone (Lindsay et al 1997, Cosman et al 2001). However in these studies HRT was unable to prevent the increase in bone resorption markers and the overall changes in resorption markers were similar to those reported with teriparatide therapy alone. Furthermore, it is not known whether HRT-teriparatide combination therapy results in a greater, similar or smaller BMD response than teriparatide monotherapy as there was no such group included in these studies for comparison.

2 studies were performed looking at the combination of alendronate and PTH therapy. Finkelstein et al (2003) reported that, compared to teriparatide monotherapy, the combination of teriparatide and alendronate in men resulted in smaller gains in BMD after 30 months. In a 1 year study of postmenopausal women, Black et al (2003) reported that alendronate and full length PTH combined did not result in a significantly greater increase in BMD at the spine or neck of femur than full length PTH alone. As both treatments were started simultaneously in these studies it is uncertain to what degree the increase in BMD observed was due to new bone formation and how much was due to the antiresorptive effects of alendronate. The bone formation marker response was severely suppressed by combination therapy in both of these studies suggesting that alendronate was suppressing the anabolic effects of PTH. Therefore a large proportion of the BMD increase may reflect the actions of alendronate. In these studies quantitative CT demonstrated that, compared to PTH monotherapy, combination therapy significantly inhibited the increase in trabecular bone density at the spine and the increase in cortical volume at the hip. These observations suggest that alendronate impairs the ability of PTH therapy to stimulate new bone formation.

Interestingly, the SERM raloxifene does appear to be able to suppress the bone resorption response to PTH therapy without inhibiting the bone formation response. In one study of postmenopausal women combining raloxifene with teriparatide delayed the increase in bone resorption markers and resulted in a significantly lower level at 6 months compared to teriparatide monotherapy (Deal et al 2005). The changes in bone formation markers

were identical between the 2 groups. BMD at 6 months increased to a greater extent in the combination group although the difference was only significant at the hip. It therefore appears that raloxifene, by selectively reducing the bone resorption response, may be able to increase the size of the “anabolic window” leading to increased amounts of new bone formation although a longer term study would be needed to properly assess the BMD benefits. The differences between combination PTH therapy with alendronate and raloxifene may be due to differences in the mode of action or antiresorptive potency.

### 3): Antiresorptive therapy before PTH.

As PTH therapy is expensive, in the UK it is only prescribed to women who have had an inadequate response to antiresorptive therapy. Bisphosphonates are the most commonly prescribed antiresorptive. After discontinuation bisphosphonates remain detectable in the body for many months (Russell 2007) and alendronate has been demonstrated to suppress bone turnover for up to 5 years after discontinuation (Black et al 2006). As already discussed, concurrent bisphosphonate therapy blunts the anabolic effects of PTH. There is therefore concern that the residual effects of prior bisphosphonate therapy may cause long term bone suppression leading to a blunting of the effects of PTH. To date there is only one study looking at this. Ettinger et al (2004) studied postmenopausal women who had previously been treated with either alendronate or raloxifene for a mean of 29 months. Women with prior raloxifene exposure achieved the expected BTM and BMD response. In contrast, prior alendronate use led to a general reduction in the BTM

response and a significant reduction in the BMD gain at the spine and hip. This suggests that prior bisphosphonate use may blunt the anabolic effects of PTH.

*Research topic: In the UK, the National Institute for Health and Clinical Excellence restricts the prescribing of teriparatide to women who have had previous bisphosphonate therapy. The study by Ettinger et al (2004) suggests that this policy will blunt the response achieved in clinical practice to teriparatide. This is investigated in chapter 6 of this thesis.*

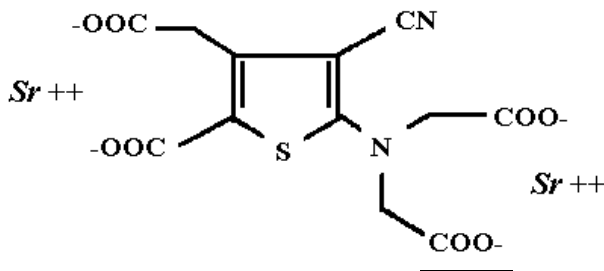
## **Chapter 2.3:**

### **Strontium Ranelate.**

Strontium ranelate is the first of a new class of osteoporosis therapy, the dual action bone agent (DABA). Strontium was originally discovered in 1808 by Sir Humphry Davy in the village of Strontian in Scotland from which its name is derived. Strontium is a bone seeking element which belongs to the same chemical family as calcium. To the general public it is commonly thought of as the radioactive isotope strontium 90, which was produced by nuclear weapons testing and the Chernobyl disaster and is associated with bone cancer and leukaemia. Fortunately, natural strontium 38 is nonradioactive and nontoxic. Strontium ranelate is comprised of 2 strontium atoms, the bone active component, bound to ranelic acid, which increases its bioavailability (figure 2.3.1). Strontium makes up 34% of the molecular weight of strontium ranelate so the licensed dose of 2g/day delivers 680mg of strontium to the intestine of which 25% is absorbed. Strontium ranelate has unique effects on bone although its exact effects and mechanisms of action are still being determined. Unlike antiresorptive and anabolic therapies, strontium ranelate appears to have little effect on the overall rate of bone turnover as measured by the activation frequency (Arlot 2005). Instead it seems to predominantly affect the remodelling balance at the level of the BMU by uncoupling bone formation and resorption. By increasing bone formation while reducing bone resorption strontium ranelate is thought to cause a positive remodelling balance and an overall gain in bone mass with each remodelling cycle. In theory this suggests that strontium ranelate has

anabolic properties although this will be questioned by the results of chapter 7 in this thesis.

Figure 2.3.1 Chemical structure of strontium ranelate.



### Cellular mechanisms of strontium ranelate.

How strontium ranelate affects bone remodelling is uncertain. Strontium ranelate increases osteoblast proliferation and differentiation (Bonnelye et al 2007) which is likely to be important in strontium ranelate's effects on bone formation. This is in part due to strontium's ability to activate the calcium sensing receptor (CSR) on the osteoblasts although other pathways are also likely to be involved as osteoblast replication can still be induced by strontium in the absence of the CSR (Chattopadhyay et al 2007, Bonnelye et al 2007). Another potential mechanism of action for strontium is through the induction of cyclooxygenase 2 in osteoblasts, which leads to increased prostaglandin E2 synthesis (Choudhary et al 2007). Prostaglandin E2 has autocrine effects on the osteoblast leading to increased differentiation and has been demonstrated to increase bone formation (Choudhary et al 2007).

Strontium ranelate has also been demonstrated to inhibit osteoclast differentiation, increase osteoclast apoptosis and inhibit osteoclast mediated bone resorption by disrupting the ruffle border between the osteoclast and the bone (Bonnelye et al 2007). The mechanism by which osteoclasts are inhibited by strontium is again uncertain although recent data suggests the RANKL/OPG pathway is involved. It has been demonstrated that strontium ranelate can down regulate RANKL expression on osteoblasts while increasing osteoblast OPG expression (Breenan et al 2007). Therefore, the RANKL/OPG ratio is reduced resulting in decreased activation of RANK on osteoclasts which in turn leads to reduced osteoclastogenesis and bone resorption.

#### **The effects on strontium ranelate on bone remodelling.**

These cellular effects provide a mechanism by which strontium ranelate may increase bone formation and reduce resorption. Evidence supporting this was originally provided by animal studies. In ovariectomized rat models of postmenopausal osteoporosis, strontium ranelate was demonstrated to reduce histomorphometric measures of bone resorption (osteoclast surface and osteoclast number) while maintaining elevated bone formation indices (bone formation rate and osteoblast surface) (Marie et al 1993). Similar histomorphometric effects have been reported in monkeys (Buehler et al 2001) further supporting the “dual action” of strontium ranelate.

More recently the histomorphometry findings from animal studies have been confirmed using human bone biopsies. Arlot et al (2005) demonstrated that strontium ranelate

increased osteoblast surface and mineral apposition rate (bone formation indices) associated with a trend towards a reduction in eroded surfaces, osteoclast surface and osteoclast number (resorption indices). The same study demonstrated no change in activation frequency (rate of bone turnover) or impairment of mineralization.

### **The effects on strontium ranelate on bone structure.**

By increasing bone formation and reducing bone resorption, strontium ranelate should cause an overall increase in bone mass and improvements in microarchitecture. In rats 2 years treatment with strontium ranelate has been demonstrated to increase bone volume, trabecular thickness, trabecular number and cortical area (Ammann et al 2004).

Furthermore, no increase in cortical porosity was evident (Ammann et al 2004). In this study compression testing demonstrated that the mechanical properties of the bone were improved leading to an overall increase in bone strength with strontium ranelate therapy.

These findings have again been confirmed with human bone biopsies. Jiang et al (2006) used microCT to demonstrate that, compared to placebo, women treated with strontium ranelate had an increased trabecular number (+14%), a reduced trabecular separation (-16%) and an increased cortical thickness (+18%). The trabecular structural model index also improved suggesting a shift from rod-like trabeculae to a more plate-like pattern. In contrast to PTH therapy there was no increase in cortical porosity. This suggests that, compared to no treatment, strontium ranelate reverses the postmenopausal microarchitectural deterioration discussed in chapter 1.3, thus leading to an increase in



bone strength. However, there were no baseline biopsies in either group for comparison and therefore this does not prove that strontium has anabolic properties. Similar differences in microarchitecture could arise from a purely antiresorptive effect by preventing the deterioration in microarchitecture which would occur in placebo treated group.

To prove strontium ranelate has anabolic properties biopsies before and after treatment would be required. To date there is only one small report on paired bone biopsies in postmenopausal women. Busse et al (2007) demonstrated that, compared to baseline, 12 months treatment with strontium ranelate resulted in an increase in markers of active bone formation (osteoid volume and osteoid surface) as well as an increase in structural indices (bone volume, trabecular interconnectivity and trabecular thickness). This suggests that strontium ranelate does increase bone formation, which leads to an increase in the amount of bone and improved microarchitecture. Therefore strontium may indeed have anabolic effects in postmenopausal women although evidence from chapter 7 in this thesis will cast some doubt on this.

### **The effects of strontium ranelate on BTM's.**

Much of the data suggesting that strontium ranelate has a dual mode of action is derived from animal and in-vitro studies. It is therefore important that evidence from BTMs in postmenopausal women also supports strontium ranelate's dual effects. The first study to show this was the phase 2 dose ranging study (STRATOS) (Meunier et al 2002). Even in

this small study, 2g/day of strontium ranelate for 2 years increased BSAP (formation marker) by 11% while reducing urinary NTX (resorption marker) by 10%. Subsequently a large phase 3 study (SOTI) confirmed strontium ranelate's differential effects on formation and resorption markers. In this study strontium ranelate again increase BSAP by 8% and reduced serum CTX (resorption marker) by 12% (Meunier et al 2004). Therefore the BTM response to strontium ranelate supports the preclinical data and suggests that in postmenopausal women strontium ranelate does increase bone formation while reducing bone resorption.

#### **The clinical effects of strontium ranelate on BMD.**

Strontium ranelate induces large increases in BMD as measured by DXA. The phase 3 clinical studies demonstrated that after 3 years of treatment BMD had increased by 14% at the spine and 8% at the hip compared to placebo (Meunier et al 2004, Reginster 2005). These BMD increases are far greater than those observed with 3 years treatment with antiresorptives. Unfortunately a large part of this increase in BMD is an artefact rather than a true increase in bone mass. Strontium has a higher mass than calcium (atomic number 38 and 20 respectively) which leads to a greater attenuation of x-rays. DXA scanners calculate BMD by measuring the attenuation of x-rays as they pass through bone. As such, the incorporation of strontium into bone results in a greater x-ray attenuation, which is incorrectly interpreted as an increase in calcium content, artificially increasing BMD. It has been estimated that approximately 50% of the measured BMD is an artefact and, after correction for this, the increase in "true" BMD at the spine from

baseline in the SOTI study was estimated at 6.8% (Meunier et al 2004). This adjustment was based on the bone strontium content (BSC) of a small number of women (n=14), who had an iliac crest bone biopsy as part of the SOTI study, and the ratio of BSC in the spine compared to the iliac crest of female cynomolgus monkeys (ratio = 0.61). However, other animal models give different spine to pelvis BSC ratios and it is surprising that the ratio is not closer to, or greater than, 1.0 given that the spine has a higher rate of bone turnover and therefore could be expected to have a higher BSC (Blake et al 2007). If a ratio of 1.0 is used for the adjustment calculation then the percentage increase in “true” BMD from baseline in the SOTI study changes from 6.8% to around 3% (Blake and Fogelman 2005). Until data from humans is available any attempts at correction are potentially flawed and therefore unreliable.

If this artefact accounts for a proportion, but not all, of the BMD response to strontium ranelate, the remaining portion must reflect the effects of strontium ranelate on the bone. If strontium does have anabolic properties then the increasing bone mass and improvements in microarchitecture will lead to an increase in BMD. Likewise if strontium has significant antiresorptive properties then part of the increase in BMD observed may be due to contraction of the remodelling space and prolonged secondary mineralization. The majority of the BMD increase due to bisphosphonates occurs in the first few years of treatment with a plateauing of the BMD response at the hip and a slower rate of increase at the spine after 3 years of treatment (Black et al 2006, Bone et al 2004). In contrast long term data from the SOTI study demonstrates that BMD continues to rise in a uniform manner over 5 years at both the spine and hip (Blake et al 2007). This

suggests that either strontium continues to be incorporated into the skeleton over 5 years or there is continued increases in bone mass or a combination of both. Data from bone biopsies demonstrate that BSC does not increase further after 2 years of treatment with 2g/day of strontium ranelate (Boivin et al 2006). The number of biopsies studied was small but if this is the case then it suggests that the increase in BMD observed beyond 2 years is due to an actual increase in bone mass.

Although the BMD artefact prevents direct comparison between strontium ranelate and other osteoporosis therapies it does make BMD a very useful way to monitor the response to treatment. The increase in BMD with strontium ranelate exceeds the least significant change of a DXA scanner within 6-12 months, which is earlier than many other osteoporosis treatments (Blake et al 2007). This allows an earlier follow up DXA scan to assess the treatment response, thus enabling early reassurance to both the physician and the woman that the treatment is clinically effective. If no improvement is apparent enquires should be made regarding compliance and whether the woman is taking the strontium ranelate in the correct manner. A lack of a BMD response in a woman who is taking strontium ranelate regularly and correctly for 1-2 years would be unusual and therefore should prompt consideration of medical conditions associated with malabsorption (e.g. coeliac disease) or ongoing bone loss.

### **The clinical effects of strontium ranelate on fractures.**

The phase 3 studies confirmed that the effects of Strontium ranelate on bone leads to a reduction in the incidence of osteoporotic fracture. Vertebral fracture reduction was investigated by the SOTI study (Meunier et al 2004), which included 1649 postmenopausal women with a prevalent vertebral fracture who received strontium ranelate or placebo for 3 years. The risk of a new vertebral fracture was 49% lower (ARR 5.8%) in the strontium ranelate group after 1 year and 41% lower (ARR 11.9%) after 3 years. Clinical vertebral fractures were reduced by 38% (ARR 6.1%) over 3 years.

Non-vertebral fracture reduction was assessed in the TROPOS study. Reginster et al (2005) investigated 5091 postmenopausal women with osteoporosis at the femoral neck who were either aged over 74 or over 70 if they also had an additional risk factor for fracture. After 3 years there was a significant 16% reduction (ARR 1.7%) in all non-vertebral fractures and a 19% reduction (ARR 1.7%) in the risk of suffering a major non-vertebral fracture. Hip fractures were reduced by 15% in the population as a whole but this was not significant as the study was not powered to investigate hip fractures. In a subset of high risk women (over 75,  $T < -3.0$ ) there was a significant 36% reduction (ARR 2.1%) in the incidence of hip fractures. The TROPOS study also confirmed the reductions in vertebral fracture observed in the SOTI study. 3640 women in TROPOS underwent yearly spinal x-rays and in these women vertebral fractures were reduced by 45% over the first year and 39% over 3 years (ARR 6.3%). This study also demonstrated that strontium ranelate significantly reduced the incidence of vertebral fractures in

women with or without prevalent vertebral fractures at baseline (32% and 45% RRR respectively).

Both the SOTI study and the TROPOS study have been continued for 5 years although in the last year of the SOTI study women in the strontium group were randomly assigned to either continuing strontium ranelate or to switch to placebo. These studies confirm that strontium ranelate continues to reduce fractures beyond 3 years. The TROPOS study demonstrated that, after 5 years, strontium ranelate reduced vertebral fractures by 24% (ARR 4.1%) and non-vertebral by 15% (ARR 2.3%) (Reginster et al 2007). Again in the high risk subgroup over the 5 years hip fractures were reduced by 43%. Years 4-5 of the SOTI study also demonstrated a 33% (ARR 9.4%) reduction in vertebral fractures over 4 years (Blake et al 2007).

### **Strontium ranelate in women over 80.**

Of all the treatments for osteoporosis, strontium ranelate has the best evidence for fracture reduction in the over 80s. This is a particularly important group of women as it is the fastest growing population age group and contributes to over 30% of all fractures and 60% of all hip fractures (Seeman et al 2006). Both the SOTI and TROPOS studies had no upper age limit on recruitment and therefore 1556 women over 80 were recruited.

Seeman et al (2006) performed a pooled analysis of these older women and found that strontium ranelate significantly reduced the incidence of vertebral fractures by 59%

(ARR 4.8%) at 1 year and 32% (ARR 7.4%) at 3 years. Non-vertebral fractures were also significantly reduced by 41% (ARR 1.6%) at 1 year and 31% (ARR 5.5%) at 3 years.

Other therapies are poorly studied in women over 80. The FIT trials (alendronate) and MORE trial (raloxifene) excluded women over 80. The VERT-NA and VERT-MN trials (risedronate) only included 180 and 137 women respectively over 80. The HIP study (risedronate) specifically included women over 80 with at least one risk factor for fracture or low BMD at the hip. However, the HIP study failed to demonstrate a significant reduction in hip or non-vertebral fractures. A subsequent pooled analysis of all women over 80 with osteoporosis at the hip who had participated in the VERT and HIP studies demonstrated that there was again no significant reduction in non-vertebral fractures although vertebral fractures were reduced (Boonen et al 2004). The HORIZON trial (zoledronate) included women up to 89 years of age but provided no data specifically for women over 80. The teriparatide fracture prevention trial was reanalysed to assess the effects of teriparatide on women over 75 although the number of women was small and only 48 were over 80 (Boonen et al 2006). This study suggested that increasing age did not reduce the efficacy of teriparatide and vertebral fractures were significantly reduced in those women over 75. However, the number of women was too small so show a significant reduction in non-vertebral fractures.

The reason why strontium ranelate reduces non-vertebral fractures in women over 80 while risedronate, the only other treatment specifically studied in this age group, fails to do so is uncertain. It was suggested that risedronate's failure to reduce non-vertebral

fractures was due to non-skeletal risk factors, such as falling, which increase with age (Boonen et al 2004). However, similar factors were likely to exist in those women over 80 in the strontium ranelate studies. This suggests that these factors are not solely responsible for the lack of efficacy of risedronate unless strontium ranelate somehow addresses these factors. One explanation maybe that by age 80 bone mass and microarchitecture have deteriorated to such a degree that simply reducing the rate of bone resorption is inadequate to sufficiently reduce the risk of non-vertebral fractures. In this case strontium ranelate, which is thought to have anabolic properties, may improve bone mass and microarchitecture leading to a reduction in non-vertebral fractures.

#### **Interactions with other osteoporotic therapies.**

There is very little data regarding the interactions of strontium ranelate with other therapies for osteoporosis. When strontium ranelate is discontinued BMD declines as strontium is released from the bone and/or bone mass is lost (Ortolani and Diaz-curiel 2007). Bisphosphonates after strontium ranelate may theoretically reduce or prevent this decline in BMD but there are no studies assessing this yet. Combining strontium ranelate with bisphosphonates may increase its antiresorptive effects but may also blunt its anabolic actions, as occurs with teriparatide, but again this has not been studied.

The effect of prior bisphosphonate therapy on the subsequent response to strontium ranelate is a particularly important interaction to consider, as in the UK bisphosphonates are usually prescribed as first line therapy. If strontium ranelate does have anabolic



properties then prior bisphosphonate use may blunt these effects as has been reported with teriparatide (Ettinger et al 2004). Furthermore, the prolonged suppression of bone turnover by prior bisphosphonate therapy may reduce the uptake of strontium into the bone as strontium is predominantly deposited in newly formed bone (Boivin et al 2006, Boivin et al 2007).

*Research Topic: The long term suppression of bone turnover by prior bisphosphonate therapy could be expected to reduce the BMD response to strontium ranelate due to blunting of the possible anabolic actions of strontium and/or the reduced uptake of strontium into the bone. This is investigated in chapter 7.*

## **Chapter 2.4:**

### **Percutaneous vertebroplasty for painful vertebral fractures.**

As discussed in chapter 1.2, vertebral fractures are the commonest osteoporotic fracture and are associated with significant morbidity. The pain associated with an acute vertebral fracture can vary from a mild transient pain for which no medical help is sought to debilitating back pain requiring hospitalisation. In most women the back pain settles with conservative treatment over a period of weeks to months but a significant number of women are left with persistent, chronic pain (Heini 2005, Nevitt et al 2000). This chronic pain can arise due to persistent instability associated with micromotion of the vertebra causing pain during spinal loading and movement (Heini 2005). This is illustrated in figure 2.4.1. Other causes of chronic pain after a vertebral fracture include radiculopathy due to foraminal narrowing and, with sufficient kyphosis, impingement of the ribs on the iliac crests. Increased kyphosis also results in spinal imbalance leading to increased mechanical strain on the facet joints and paraspinal ligaments/muscles. Traditionally, the treatment of painful vertebral fractures was based on bed rest, potent analgesia and, if necessary, external bracing.

Vertebroplasty was first used for painful vertebral lesions by Galibert and Deramond in France in the mid-1980s for the treatment of vertebral haemangiomas. Soon after, vertebroplasty was applied as a minimally invasive technique for the treatment of other painful vertebral lesions or fractures. This technique involves the insertion of cement into the vertebral lesion/fracture in order to stabilise and strengthen the vertebra. Although

indications for vertebroplasty include haemangiomas, spinal metastases and multiple myeloma, this chapter of the thesis will concentrate on its use for the treatment of osteoporotic vertebral fractures. Vertebroplasty is currently a relatively new treatment option and at present the majority of women who suffer painful osteoporotic vertebral fractures do not undergo a vertebroplasty. This is in part due to limitations in the availability of vertebroplasty services which are often only available at larger bone centres. There are also issues regarding patient selection and the timing of the vertebroplasty relative to the occurrence of the fracture, which further limit the number of women deemed eligible for vertebroplasty. These are discussed in more detail below.

Figure 2.4.1. A severe wedge fracture of T11 on erect x-ray (a) with a degree of spontaneous correction on lying down for MRI (b) suggesting instability of the fracture. (Heini 2005).



### **Vertebroplasty: patient selection and assessment.**

As vertebroplasty is not without risks, careful patient selection is required to target patients who will benefit from the procedure. Vertebroplasty is performed for pain relief so should only be offered to patients with painful vertebral fractures. The location of the pain should be in the midline of the spine over the site of the fracture and there is usually tenderness on palpation/percussion of the affected vertebra. Other causes of back pain, such as spondylosis and radiculopathy, which would not be expected to respond to vertebroplasty, should be considered. Full medical history and examination should be performed to look for other potential causes of the vertebral fracture, neurological deficit and medical conditions, which may complicate vertebroplasty.

Potential contraindications for vertebroplasty include overlying infection, uncorrectable coagulopathy, fractures associated with neurological deficit, and significant respiratory disease. Vertebral plana fractures are technically more difficult to vertebroplasty. A fracture of the posterior wall of the vertebra or retropulsed bone fragments also needs to be looked for on imaging as this would increase the risk of spinal cord compression when the cement is injected.

Imaging of the spine is vital prior to vertebroplasty. Imaging allows assessment of the location and extent of vertebral collapse and identifies other pathological causes for fracture, such as malignancy. It also permits assessment of the pedicles, the extent of cortical disruption and whether there is complicating spine or nerve root compression.

Finally, imaging can assess whether the fracture is acute or “active”. Plain x-rays are usually performed to confirm the presence of a vertebral fracture and provide basic information on the number and severity of fractures. Comparison with previous x-rays can help gauge the age of the fracture. However, more accurate imaging is usually required.

An MRI scan is usually the imaging modality of choice. This allows accurate assessment of the fracture and the whole spine anatomy including assessing for spinal cord and nerve root involvement. MRI also helps distinguish acute/active fractures from chronic stable fractures. Acute or “active” fractures are indicated by the presence of bone oedema, which is demonstrated as a decreased signal in T1 images and an increase in signal in short-tau inversion recovery (STIR) sequence (Figure 2.4.2). This is particularly useful in patients with multiple vertebral fractures of varying age in order to determine which fracture(s) is most likely to be responsible for the pain. Although bone oedema is often sought to identify acute fractures, the absence of bone oedema is not an absolute contraindication to vertebroplasty. Brown et al (2005) demonstrated that 100% of patients with bone oedema on MRI (n=30) reported an improvement in pain after vertebroplasty. However, an improvement in pain was still reported in 80% of patients (n=15) undergoing vertebroplasty for severe focal fracture pain with no corresponding bone oedema. Even though the response rate was almost significantly lower ( $p=0.07$ ) for those with no bone oedema, this study demonstrates that vertebroplasty is still capable of reducing pain in the majority of patients with non active fractures. This is in agreement with the observation that studies which selected patients for vertebroplasty on the basis of

bone oedema (Diamond et al 2006, Kobayashi et al 2005) yielded comparable results to those which included patients regardless of MRI findings (Do et al 2005, Evans et al 2003, Anselmetti et al 2007).



Figure 2.4.2: a T2 weighted sagittal STIR MRI scan demonstrating high signal in the L3 vertebrae indicating bone oedema (Anselmetti et al 2007)

In patients unable to undergo an MRI, a CT scan can be performed to assess the vertebral architecture however CT poorly differentiates acute and chronic fractures. In these cases an isotope bone scan can be performed on which acute fractures demonstrate an increased uptake of radioisotope. Maynard et al (2000) demonstrated that 93% of patients with an increased uptake on a bone scan reported an improvement in pain after a vertebroplasty. Unfortunately, the lack of a control group in this study means it is not known if patients with fractures which do not have increased uptake on bone scan respond more poorly to vertebroplasty.

### **Vertebroplasty: when to perform.**

There is no agreement on the optimum time at which to perform a vertebroplasty. When performed acutely (days – weeks) after a vertebral fracture, vertebroplasty is highly effective at rapidly reducing pain and permitting an early return to activity. Diamond et al (2006) reported the only large study (n=126), which included a control group and assessed the efficacy of vertebroplasty in the acute setting (range 1-6 weeks). Those who underwent an acute vertebroplasty had a 60% reduction in pain and a 29% improvement in physical function after 24 hours compared to no improvement in the control group. However, by 6 weeks there was no significant difference in terms of physical function and only a small benefit for the vertebroplasty group in terms of pain reduction (-75% vs. -65%, p=0.002). By 6 months the pain had reduced by the same amount in each group (85% vs. 80%, p=0.36). This is because most painful fractures will improve with time and suggests that vertebroplasty should not be used routinely for all acute vertebral fractures. Instead a period of months of conservative treatment should be allowed before considering vertebroplasty. The possible exception to this is severely painful fractures which require hospitalisation and bed rest despite adequate analgesia. In these patients an acute vertebroplasty may aid mobilisation and avoid the complications associated with prolonged bed rest. Acute vertebroplasty has been demonstrated to reduce mean hospital stay from 17.5 to 10.4 days (Diamond et al 2006).

In most cases vertebroplasty is performed at least a few months after the acute fracture in patients whose pain persists despite analgesia. However, there is no evidence to support

an upper time limit from fracture to vertebroplasty. Evans et al (2003) reported outcomes of vertebroplasty depending on the age of the fracture. This study demonstrated that pain, ambulation and ability to perform activities of daily living improved equally in patients with acute (< 3 months) and chronic (>1 year) fractures. Brown et al (2005) also reported a high rate (80%) of symptomatic improvement in patients undergoing vertebroplasty more than 1 year after the fracture occurred. Therefore it appears that while vertebroplasty should not be routinely offered for acute fractures, women with ongoing pain from a vertebral fracture should not be excluded from vertebroplasty on the basis of chronicity.

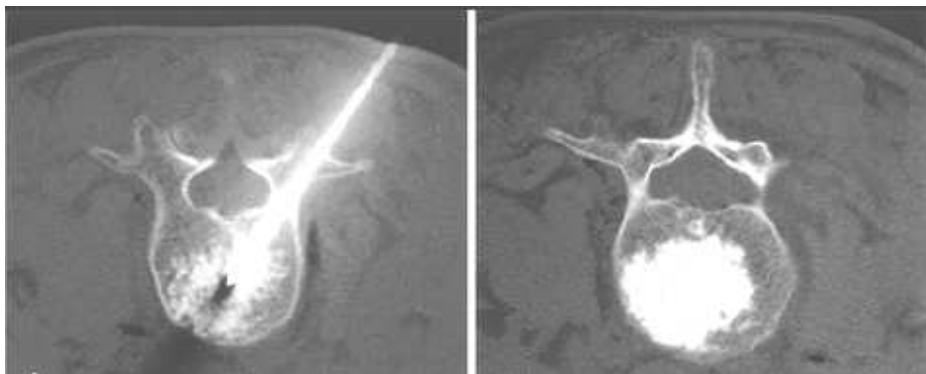
### **Vertebroplasty: the procedure.**

The patient is positioned prone on a radiolucent table. In most cases local anaesthetic is used in combination with intravenous sedation although general anaesthetic is used in some cases. The relevant area of skin is sterilised and patients often receive antibiotic prophylaxis. Radiographic guidance is used, usually in the form of C-arm fluoroscopy although CT guidance can be used. A small paramedian skin incision is made over the appropriate pedicle and an 11 gauge bone biopsy needle is advanced into the vertebral body via a transpedicular (Figure 2.4.3a) or peripedicular route. The transpedicular route is most commonly used as this maximises the distance between the entry point of the needle and the site of cement injection thus reducing the risk of cement leakage back through the entry point. A unilateral vertebroplasty usually provides adequate filling of the whole vertebral body although a bilateral approach can be used if a uniform



distribution of cement is not achieved with a unilateral approach. Once the needle is in the vertebral body it is advanced into the anterior third of the vertebra. At this point some operators chose to inject contrast medium in order to ensure there is no leakage either into the venous system or out of the vertebral body via defects in the cortex. Once the needle is in the correct position, bone cement is injected under fluoroscopic guidance until the cement reaches the posterior third of the vertebra. Typically 2-3ml of cement is required for thoracic vertebrae and 3-5mls for lumbar vertebrae (Figure 2.4.3b). The cement sets within minutes of injection and patients are able to mobilise once they have recovered from the sedation. Although patients are often kept in overnight after a vertebroplasty it is possible to perform vertebroplasty as a day case procedure.

Figure 2.4.3: a): An 11 gauge bone biopsy needle is advanced down the right pedicle into the vertebral body under CT guidance. b): cement in-situ after vertebroplasty (Kobayashi et al 2005).



## Cement types

Polymethylmethacrylate (PMMA) has been used as bone cement for orthopaedic procedures for decades. PMMA is used in the vast majority of vertebroplasty reports in the literature. For vertebroplasty PMMA is often modified to improve its performance. To increase its visibility on x-ray compounds containing tungsten or barium are added. Extra monomer can also be added to extend its working time. In the early days of vertebroplasty this mixing was originally performed by the operator at the time of the procedure. More recently specifically designed pre-mixed PMMA is now available for vertebroplasty.

In recent years there has been interest in developing other, non-PMMA, cements for vertebroplasty with improved performance. Cortoss™ (Orthovita, Malvern, Pa) is a modified bisphenol-a-glycidyl dimethacrylate (bis-GMA) resin, which has been specifically developed for vertebroplasty. Cortoss is inherently radiopaque making it easier to visualise on fluoroscopy and it is easier to handle as it requires no premixing or modification and hardens in 5-8minutes. It is less exothermic during polymerisation than PMMA (63 °C vs. 84°C) reducing the risk of thermal damage to the bone. Cortoss has a modulus of elasticity, which is close to that of bone and binds more strongly to bone than PMMA which is often separated from the bone by a layer of fibrous tissue (Erbe et al 2001). There is very little clinical data on Cortoss vertebroplasty in general. Whether the potential advantages of Cortoss result in a better clinical outcome is not known as there are no head to head studies comparing PMMA and Cortoss.

*Research Topic: At our centre all vertebroplasties are performed using Cortoss cement.*

*In chapter 8 of this thesis the clinical outcomes of our Cortoss vertebroplasty service are studied and compared to the reported outcomes from PMMA vertebroplasty.*

### **The clinical benefits of vertebroplasty.**

There are many reports of vertebroplasty in the literature. Comparing the results is difficult as the studies are a mix of small and large retrospective or prospective observational studies, which are almost invariably uncontrolled. Furthermore some studies include a variety of vertebral lesions while others are restricted to osteoporotic fractures, which seem to achieve better pain relief with vertebroplasty than malignant lesions (Martin et al 1999, Barr et al 2000). The duration of the lesion undergoing vertebroplasty varies from days to years in different studies while some, but not all, studies only performed a vertebroplasty after an MRI had confirmed an “active” fracture. Almost all the studies to date involve PMMA cement although some studies used specific makes of PMMA while others either added extra compounds to improve the cement’s performance or do not specify the type of PMMA. The results from the largest vertebroplasty reports to date are summarised in table 2.4.1.

Despite the differences between the studies, on the whole, the majority of patients (76-100%) reported an improvement in pain post vertebroplasty. The visual analogue scales (VAS), a validated measurement of pain, demonstrated dramatic reductions in the mean

level of pain after a vertebroplasty. Most patients were able to reduce their analgesia requirements post procedure while many discontinued analgesia altogether.

Improvements in quality of life (measured by SF36), physical function (Barthel index) and mobility have also been reported (Table 2.4.1). However, it is important to remember that most studies lack a control group and Diamond et al (2006) demonstrated that vertebroplasty resulted in no benefit over conservative management 6 months after an acute fracture. Whether or not vertebroplasty has benefits over conservative management in non-acute persistently painful vertebral fractures remains to be proven.

#### **The potential complications of vertebroplasty.**

Vertebroplasty is largely a safe procedure. The complications encountered in the large vertebroplasty studies are summarised in table 2.4.2. The commonest complication is leakage of the cement into the surrounding tissue, disc space or vein. This has been reported in up to 75% of vertebroplasties although it is usually asymptomatic and of no clinical relevance. In some cases the cement leakage can embolise to the lungs or cause compression of the spinal cord or nerve roots although this is rare. Up to 4 % of patients have been reported to have transient nerve root symptoms despite no evidence of cement compressing the nerve root on CT. Rib fractures occur in 1-2% of patients, probably a consequence of lying patients with osteoporosis prone for the procedure. Haematomas have also been reported in around 1% of cases.

**Table 2.4.1. Details and outcomes from the largest published vertebroplasty studies.**

Author	Anelmetti (2007)	Pitton (2007)	Diamond (2006)	Do (2005)	Kobayashi (2005)	Evans (2003)
study type	retrospective	prospective	prospective, control	prospective	prospective	retrospective
n (patients)	283	191	88	167	205	245
Age (mean±sd)	73.8 ± 9.9	70.7 ± 9.7	76.8 ± 8.7	74.6 ± 12.2	77.9 ± 8.5	76 ± 9
n (vertebroplasties)	749	317	133	207	250	563
% osteoporotic #	74.50%	100%	100%	100%	100%	100%
% Malignancy	23.30%	0%	0%	0%	0%	0%
% other lesion	2.20%	0%	0%	0%	0%	0%
Duration of lesion	3-12 weeks	na	1-6 weeks	<4 months	1-225 days	<2weeks - >1year
vertebral MRI status	mixed	all active	all active	na	all active	not checked
Guidence	fluroscopy	CT	fluroscopy	fluroscopy	CT	fluroscopy
Cement used	Osteopal (PMMA)	PMMA	PMMA	PMMA mix	Simple P (PMMA)	PMMA
Cement vol (mean)	4.1ml	4.8ml	1-6ml	na	3.9ml	na
Pain, %pts improved	86%	95.7%	na	na	96.4%	na
Pain, VAS (pre→post)	8→1*	7.8→na	4→1*	8.7→2.8*	7.2→2.1*	8.9→3.4*
Analgesia	62% stopped*	95.7% reduced	24% stopped*	score 2.9→1.6*	"none increased"	"substantial ↓"
function/disability	na	na	Barthel: ↑36%	SF36 9/10↑	56→0% immobile	↑mobility (3/5 → 2/5)

\* = p<0.05, stated in paper

**Table 2.4.2. Complications observed with vertebroplasty**

Author	Anelmetti (2007)	Pitton (2007)	Diamond (2006)	Do (2005)	Kobayashi (2005)	Evans (2003)
asympt leak	na	55.6%	na	na	75.6%	na
PE	0	na	0	0	0	0
transient/radiculopathy	3.9%	na	0	0	0	0.8%
neurological injury	0	na	0	0	0	0
other	0.4% haematoma	na	2.3% rib# 1.2% haematoma	nil	0.5% ↑ pain 0.5% haematoma	2.9% rib# 1.2% ↑ pain

### **Kyphoplasty.**

Kyphoplasty is a more recently developed technique for the treatment of painful vertebral fractures. This technique is similar to vertebroplasty however a balloon is inflated within the vertebra before the cement is injected. The balloon reduces the fracture prior to fixation. This procedure has several potential advantages over vertebroplasty as it reduces the kyphotic angle of the spine as well as stabilising the fracture. This may lead to better pain relief in patients with a significant kyphosis as it will correct the mechanical factors discussed above which contribute to the chronic pain associated with vertebral fractures. Whether this leads to significantly better clinical outcomes compared to vertebroplasty is yet to be proven and the role of kyphoplasty remains to be established. However, kyphoplasty is not studied in this thesis so it is only mentioned briefly here for completion.

**Chapter 3:**

**Methods of assessing treatment response.**

### **Chapter 3:**

#### **Methods of assessing treatment response.**

Osteoporosis is a chronic disease, which requires long term treatment. After initiating therapy it is important to monitor the treatment response as, unless a fracture occurs, osteoporosis is a silent disease in which therapy provides no symptomatic relief. Monitoring treatment with surrogate markers, such as BMD and BTMs, provides reassurance that the treatment is working and acts as a means of reinforcing the need for adherence to long term therapy. Treatment monitoring also enables the detection of poor responders to treatment. Potential causes for a poor treatment response are poor compliance, incorrect treatment administration, malabsorption of the drug, and other conditions affecting bone metabolism. Treatment monitoring during research studies provides insight into the effects of certain drugs on bone. In clinical trials monitoring surrogate markers also provides a means of assessing and comparing the efficacy of different treatments with smaller numbers of subjects than would be required if fracture incidence was used as the primary endpoint. However, it is important to remember that surrogate markers are a poor substitute for hard clinical outcomes such as fractures. This is best illustrated with fluoride, which causes large increases in BMD but does not reduce the incidence of fractures. There are several potential tools for monitoring treatment however in clinical practice, and in the studies in this thesis, axial BMD and BTMs are used predominantly and are therefore discussed in detail in this chapter.



### **Treatment monitoring and the least significant change.**

Whether using BMD or BTMs to monitor an individual patient it is important to understand the concept of the least significant change (LSC). Whenever a measure is repeated the change observed depends on 2 factors: the true change in the measure (e.g. the treatment effect) and the repeatability of the measure (test-retest precision). Various factors can affect the precision of a measurement including device errors, operator variability, differences in patient positioning (BMD), time of day (BTMs) and fasting (BTMs). The precision error is expressed as the coefficient of variation (CV). For BMD the CV ranges from 0.9-1.9% at the spine and 0.9-2.5% at the hip (Delmas 2000). The CV for BTMs varies from around 4-14% depending on the population studied and the exact marker used.

The LSC is defined as the least amount of change between 2 measurements over time that must be exceeded before one can be 95% confident that a true change in the measure has occurred. The LSC is usually calculated as  $2.77 \times CV$  (Sheperd and Lu 2007) although other definitions have been proposed (Delmas 2000). For example, an individual must have an increase in BMD of more than 2.5- 5.2% at the spine in order to be confident that they have had a true increase in BMD in response to therapy.

While the LSC is important for monitoring individual patients, the LSC is less important for clinical trials where the treatment response from a group of women is averaged. This effectively cancels out the effect of the precision error meaning that a small increase in

the measure can be considered significant even if it is less than the LSC. The difference between treatment monitoring in clinical trials and individual patients can be illustrated with raloxifene. The MORE trial demonstrated that raloxifene induced a modest 2.6% increase in BMD at the spine over 3 years (Ettinger et al 1999). However, if an individual woman achieved a 2.6% increase in BMD then one could not be entirely confident that her BMD had truly increased as it barely exceeds the most optimistic LSC for spinal BMD.

### **Using bone mineral density to monitor therapy.**

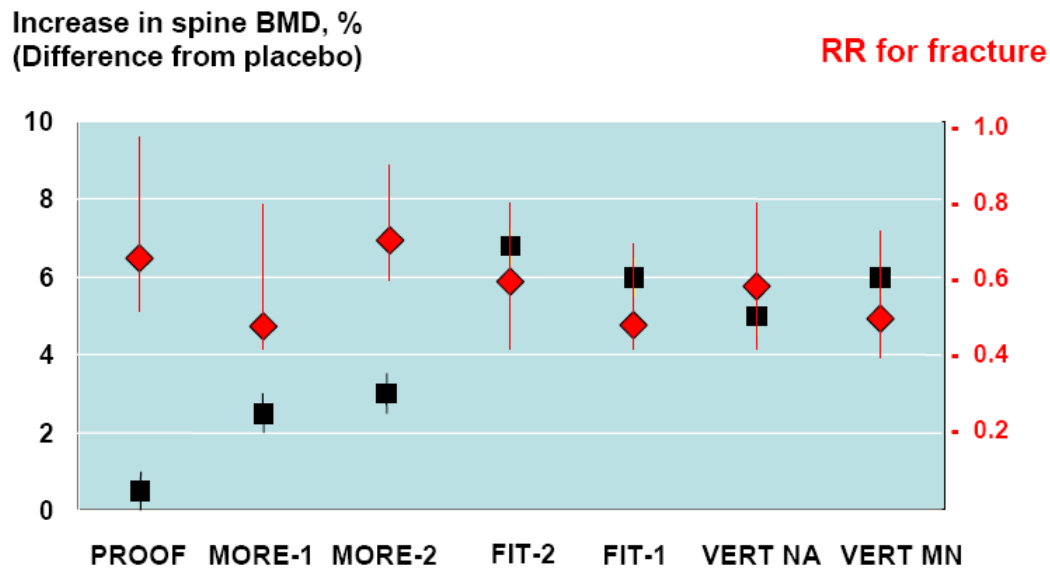
BMD is a logical means of monitoring the treatment response. The spine is usually the preferred site as the lumbar vertebrae demonstrate the quickest and greatest response to therapy due to the high proportion of trabecular bone. Low BMD defines osteoporosis and, whether treated with antiresorptives, anabolic agents or strontium ranelate, BMD increases to varying degrees demonstrating a beneficial response to therapy which is easily understood by physicians and patients alike. Furthermore, the majority of women undergo a DXA prior to starting therapy and therefore have a baseline BMD measurement for comparison. However, BMD increases slowly with treatment and depending on the therapy used a period of 12-24 months between DXA scans is required for BMD to increase by more than the LSC. Furthermore, the increase observed in BMD represents different changes in the bone tissue with different therapies. Degenerative changes and vertebral fractures can also falsely elevate spinal BMD. Finally, the increase in BMD with treatment only accounts for a small proportion of the observed reduction in

fracture risk. Therefore, although BMD is used as a surrogate marker of treatment efficacy in clinical trials, the use of BMD as a means of monitoring individual patients has limitations.

### **Bone mineral density changes and the reduction in fracture risk with treatment.**

The extent to which increases in BMD correlate with reductions in fracture risk is controversial. All antiresorptives reduce the risk of vertebral fracture by 30-50% even though bisphosphonates, raloxifene, calcitonin and HRT all result in different increases in BMD (Figure 3.1). Changes in BMD only explain 4-28% of the vertebral fracture reduction observed with antiresorptive therapy suggesting that a large proportion of the increase in bone strength with antiresorptives is due to factors, which have little effect on BMD (Eastell et al 2003). The likely explanation for this large discrepancy between fracture reduction and BMD change is the effect of antiresorptives on the erosion cavities. By reducing the number and depth of these cavities antiresorptives greatly increase bone strength by reducing the “stress riser” effect, as discussed in chapter 1.3, however the effect of this on BMD is minimal as the absolute amount of bone gained is small. Instead the increase in BMD is more likely to reflect the increased MDMB due to prolonged secondary mineralisation, which has less certain effects on bone strength.

Figure 3.1: Data from the principal antiresorptive fracture prevention trials demonstrating consistent reductions in vertebral fracture risk despite variable effects on BMD.



Overall, there does appear to be a relationship between change in BMD with antiresorptive therapy and reduction in fracture risk. Meta-analyses of antiresorptive trials demonstrate that greater increases in BMD are associated with greater reductions in vertebral (Wasnich and Miller 2000, Cummings et al 2002) and non-vertebral fracture risk (Hochberg et al 2002). However, the magnitude of the reduction in risk that is attributable to change in BMD is uncertain. Cummings et al (2002) reported that increases in spine BMD explained only 16% of the reduction in vertebral fracture risk compared to over 50% reported by Wasnich and Miller (2000). Chapurlat et al (2005) reported that women who complied with alendronate and yet had a 0 to 4% decline in BMD still obtained a reduction in vertebral fracture risk that was equal to those women who gained BMD with treatment. Only those women who lost more than 4% of their spine BMD despite complying with alendronate did not achieve a significant reduction in

vertebral fracture risk. The 4% cut off in this study was equivalent to the LSC suggesting that effective fracture reduction is achieved with alendronate even if there is no significant change in BMD. Wasnich and Miller (2000) and Cummings et al (2002) also reported reductions in vertebral fracture risk in women who did not experience an increase in BMD although this was not found to be the case with non-vertebral fractures by Hochberg et al (2002). It is generally agreed that with antiresorptive therapy BMD should not reduce by more than the LSC. Therefore the aim of monitoring antiresorptive therapy with BMD is to ensure BMD remains stable or increases.

With strontium ranelate BMD provides a convenient means of monitoring therapy as BMD increases greatly with treatment resulting in a change of more than the LSC after only 6-12 months. Changes in BMD correlate well with vertebral fracture reduction as each percentage increase in BMD at the hip is associated with a 2-3% reduction in the absolute risk of vertebral fracture (Bruyere et al 2007). In this study the change in BMD after three years explained around 75% of the reduction in vertebral fracture risk observed with treatment. Furthermore, a non-significant trend was found between the incidence of new non-vertebral fractures and the 3 year change in femoral neck BMD ( $P = 0.09$ ) and total hip BMD ( $P = 0.07$ ). In a subgroup analysis of 465 women aged over 74 years with a hip T score  $< -2.4$  Bruyere et al (2007) found that, after 3 years treatment, for each percentage increase in hip BMD the risk of hip fracture was decreased by 7% ( $p = 0.04$ ).

BMD changes with teriparatide are also associated with vertebral fracture reduction although the magnitude is smaller. Chen et al (2006) reported that changes in spine BMD accounted for 30-41% of the reduction in vertebral fracture risk. There is no data on the association between BMD changes with teriparatide and non-vertebral fracture reduction.

### **Bone turnover markers (BTMs).**

BTMs are products of bone turnover, which are either released from the activated bone cells or from the breakdown or formation of type 1 collagen. Monitoring for changes in BTMs provides an indirect in-vivo assessment of alterations in bone turnover in response to therapy. There are 2 groups of BTMs. Bone formation markers are all measured in the serum and include bone specific alkaline phosphatase (BSAP), osteocalcin, procollagen, type 1 amino terminal propeptide (P1NP) and procollagen type 1 carboxy terminal propeptide (P1CP). Bone resorption markers are mostly products of collagen degradation, which are measured in the serum or urine. They include hydroxyproline, pyridinoline, deoxypyridinoline (DPD), carboxy-terminal crosslinking telopeptide of type 1 collagen (CTX), amino-terminal crosslinking telopeptide of type 1 collagen (NTX). BSAP, P1NP and CTX are the markers used in this thesis so they are discussed in detail.

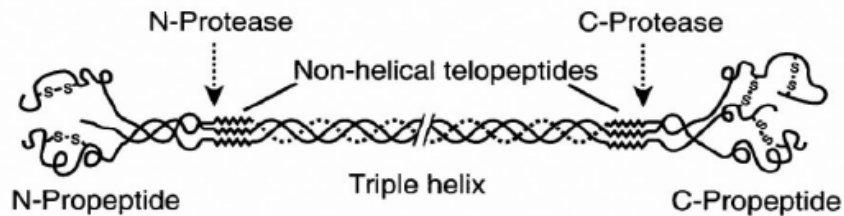
Alkaline phosphatase (AP) is produced by various tissues, including bone, liver, intestine, kidney and placenta. Using techniques such as heat denaturation or electrophoresis it is possible to identify and quantify the bone isoform of AP although there is up to 20% cross-reactivity with liver AP making interpretation difficult in patients with liver

disease. BSAP is a membrane bound enzyme expressed on the cell membrane of activated osteoblasts, which is produced during bone formation. The precise function of BSAP is not known although it is thought to be involved in osteoid formation and mineralization (Seibel 2005). Serum BSAP can be measured by a variety of techniques but for the studies contained in this thesis enzyme-linked immunosorbent assay (ELISA) was used (Metra BAP, Quidel Corp, CA, USA). Using this method the normal range for postmenopausal women is 14.2-42.7U/L with a CV of 8%.

P1NP is produced during the synthesis of type 1 collagen which makes up 90% of the organic matrix of bone. Osteoblasts synthesize procollagen which is secreted into the extracellular space where propeptidases cleave the terminal extension propeptides from the amino and carboxy terminals of the procollagen molecule to produce the type 1 collagen molecule. The cleaved propeptides are released into the circulation as P1NP and P1CP which are subsequently removed by the liver. This is illustrated in figure 3.2.

Although other tissues such as skin, fibrocartilage and tendons also contain type 1 collagen, P1NP is thought to provide a quantitative measure of type 1 collagen formation in bone, as these other tissues are metabolically much less active than bone (Seibel 2005). For the studies contained in this thesis electrochemiluminescence immunoassay was used to measure P1NP (total P1NP, Roche diagnostics, IN, USA). P1NP undergoes rapid thermodegradation in the blood from a trimeric to a monomeric structure. This technique uses a monoclonal antibody to detect both fractions of P1NP and the normal range for postmenopausal women is 30-78 µg/L with a CV of 4.5%.

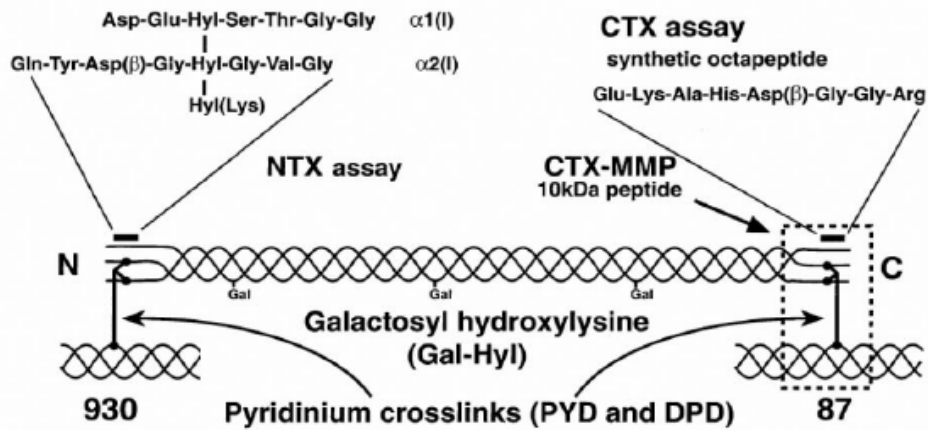
Figure 3.2: An illustration of the procollagen molecule demonstrating the terminal extension propeptides prior to cleavage by propeptidases (Seibel 2005).



During the breakdown of type 1 collagen crosslinked telopeptides are released from the carboxy (CTX) and amino (NTX) terminals of the collagen molecules. These molecules can be detected in the serum or urine by a variety of methods and provide a measure of bone resorption. For the studies contained in this thesis electrochemiluminescence immunoassay was used to measure CTX in the serum ( $\beta$ -crosslaps, Roche diagnostics, IN, USA). This method is specific for crosslinked isomerised telopeptides which include a specific octapeptide containing beta-asparic acid (Asp( $\beta$ )) (figure 3.3). Asparic acid converts from its  $\alpha$  form to its  $\beta$  form as bone ages thus the telopeptides identified using this technique are specific for the degradation of the type 1 collagen dominant in bone. This technique uses monoclonal antibodies, which recognise collagen telopeptides which contain this octapeptide regardless of the nature of the crosslink. Using this method the normal range for postmenopausal women is 0.10-1.01  $\mu\text{g/l}$  with a CV of 7.6%.



Figure 3.3: An illustration of the type 1 collagen molecule demonstrating the carboxy and amino terminal telopeptides



**Using bone turnover markers to monitoring therapy.**

BTMs have two major advantages over BMD for monitoring therapy. Firstly there are significant and detectable changes in BTMs within 3-6 months of treatment initiation compared to BMD where 1-2 years are required for an increase greater than the LSC (Delmas et al 2000). This allows a more rapid detection of poor responders and thus rapid intervention to improve response. Secondly BMD measures changes in bone mass and mineral density and therefore increases whether treatment is with an antiresorptive, an anabolic agent or strontium ranelate. While this is useful to assess the treatment response in clinical practice it provides the researcher with little information about the actual effect the drug has on bone turnover. BTMs provide an in-vivo method of assessing the effect of treatment on the rate of bone turnover as well as the relative changes in bone formation and resorption (Meunier et al 2004).

BTMs require careful consideration when used to monitor an individual patient's treatment response. It is useful, if not essential, to have a pre-treatment level of the BTM to which a follow up measurement can be compared. It is also important to understand the mechanism of action of the prescribed therapy in order to interpret the BTM changes correctly. With bisphosphonates a reduction in BTM, which is greater than the LSC demonstrates that bone resorption is being inhibited and treatment is having an effect on bone turnover. The opposite is true of PTH therapy where an increase in BTMs of more than the LSC suggests that bone is being formed and treatment effective. In general it is preferable to measure an antiresorptive therapy with bone resorption markers (CTX) while PTH therapy is best monitored with bone formation markers (P1NP) as these show the earliest response to the respective therapy (Bonnick et al 2006, Girotra et al 2006). This however is not essential as usually bone formation and resorption are coupled leading to similar overall changes in both formation and resorption markers with therapy (Seibel 2005).

With strontium ranelate, raloxifene and calcitonin the mean change in BTMs observed is less than the LSC making it difficult to meaningfully assess an individual patient's treatment response with BTMs (Delmas 2000). However, BTMs are useful in clinical trials of these therapies in order to assess the effects of these drugs on bone turnover (Meunier et al 2004).

When using repeated BTM measurements to monitor therapy it is important to consider, and where possible control for, several factors which influence the level of BTMs leading

to an increase in CV. Careful handling of the samples with rapid transfer to the laboratory for storage is necessary as BTMs are sensitive to thermodegradation and photolysis (Delmas et al 2000). Furthermore, it is important to standardise the timing of sample collection as BTMs demonstrate significant diurnal variation with high levels in the early hours of the morning and low values during the afternoon/evening. Diurnal variation for most markers is around 15-30% although diurnal variability is high for CTX (up to 66%) and low for P1NP (6%) (Seibel 2005). Some BTMs, including serum CTX, are affected by food intake therefore necessitating fasting blood samples while P1NP is not affected by diet (Seibel 2005). Vigorous exercise can induce a short term increase in BTMs and as such should be avoided prior to BTM measurement. BTMs are also affected by other bone diseases such as Paget's disease and malignancy. Most importantly for osteoporosis, fractures are associated with an increase in BTMs, which may persist for 6 to 12 months (Veitch et al 2006). Therefore BTMs are not reliable in women with a recent fracture and a sudden unexpected increase in BTMs may reflect a subclinical vertebral fracture.

#### Do baseline bone turnover markers predict the response to treatment?

As BTMs reflect the rate of bone turnover it can be hypothesised that the level of pre-treatment BTMs can be used to predict treatment response. The most logical case for this is with antiresorptives. Women with high baseline bone turnover are likely to have a greater remodelling space and therefore gain more bone mass when the remodelling space is filled. This is consistent with reports that women with high BTMs have a greater BMD response to calcitonin, HRT and bisphosphonates (Delmas 2000). Similar findings

have been reported with anabolic agents. Chen et al (2005) demonstrated a significant positive correlation between baseline P1NP or NTX and the change in lumbar spine BMD at 18 months ( $r=0.41$  and  $0.40$  respectively,  $p<0.05$ ). Therefore baseline BTM level does appear to be associated with the BMD response to these therapies.

Although baseline BTMs are associated with the BMD response to treatment, the association with vertebral fracture risk reduction is less clear. With risedronate Seibel et al (2004) reported that women with a high pre-treatment level of bone resorption, as assessed by urinary deoxypyridinoline (DPD), experienced a similar reduction in risk of vertebral fracture compared to those with a low baseline DPD after 1 (RR 0.28 vs. 0.33) and 3 years (RR=0.52 vs. 0.54). However those women with high baseline DPD had a greater incidence of vertebral fracture than those with low DPD. Therefore high baseline DPD resulted in a greater reduction in absolute risk of fracture despite the similar reduction in relative risk. This effect was more pronounced after the first year (absolute risk reduction 7.1% vs. 4%) than after 3 years (absolute risk reduction 8.3% vs. 7.1%). Eastell et al (2003) also studied risedronate and reported that the relationship between baseline CTX or NTX level and vertebral fracture incidence was not significant after correcting for BMD. More recently Bauer et al (2006) have reported that with alendronate there was no significant association between baseline P1NP and relative risk of vertebral fracture.

In contrast to the data for vertebral fractures, Bauer et al (2006) reported that women in the highest tertile of baseline P1NP experience a significantly greater reduction in non-

vertebral fracture risk with alendronate therapy than women in the lowest tertile (RR 0.54 vs. 0.88 respectively,  $p=0.03$ ). A similar trend for non-vertebral fractures was also observed with BSAP although it was not significant (RR 0.61 vs. 0.83 respectively,  $p=0.17$ ).

For anabolic therapy, Delmas et al (2006) reported that the reduction in the relative risk of vertebral fracture achieved with teriparatide was independent of baseline BTM level. However, again a greater reduction in absolute risk was observed in those with high pre-treatment bone turnover. Overall it is currently uncertain whether baseline bone turnover should influence either the choice of treatment or the subsequent response to therapy.

#### Short term changes in BTMs as a means of monitoring treatment efficacy.

As BTM changes occur soon after the initiation of therapy, there has been much interest in whether short term changes in BTMs can predict the long term efficacy of therapy.

With antiresorptives a greater reduction in BTMs suggests a greater closure of the remodelling space and therefore a better response to therapy. This is consistent with reports that women with the greatest reduction in BTMs in response to HRT or bisphosphonates experience the greatest gain in BMD after 2 years (Delmas 2000).

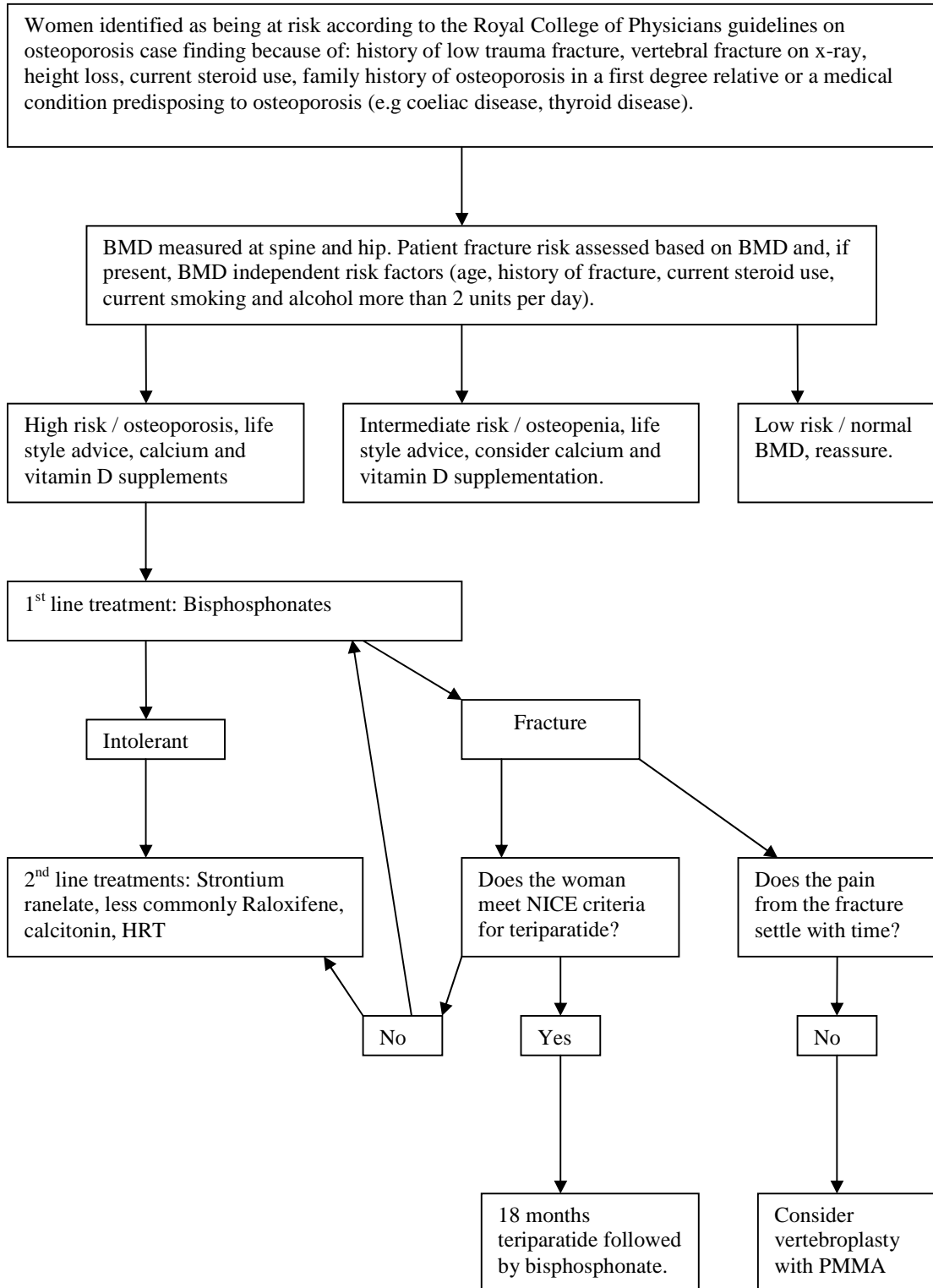
Likewise with anabolic agents a greater increase in BTMs suggests more bone formation and better treatment efficacy. Chen et al (2005) reported significant positive correlations between the change in PICP at 1 month / PINP at 3 months and the change in spine BMD at 18 months ( $r=0.65$  and  $0.61$  respectively;  $p < 0.05$ ). Given the relationship between

BTM and BMD changes it is possible to define a minimum change in BTM which predicts that an individual woman will have a significant increase in her BMD. For antiresorptives using cut-offs of a 40-55% reduction in serum CTX or a 30-40% reduction in BSAP predicts a significant (>3%) increase in BMD with 90% specificity (Delmas 2000). For teriparatide if a woman has an increase in P1NP at 3 months of 17.2ng/ml or more then she has a 88% probability of achieving a >3% increase in spinal BMD at 18 months (Chen et al 2005).

As well as predicting the BMD response, it is also important that short term BTM changes are associated with a significant reduction in fracture risk with therapy. Eastell et al (2003) reported a significant non-linear relationship between 3-6 month change in CTX and the incidence of vertebral and non-vertebral fractures over 1 and 3 years. Up to a point, the greater the percentage reduction in CTX at 3-6 months the lower the risk of incident fracture. However, reducing CTX by more than 55-60% from baseline did not result in further reduction in fracture incidence. Similar findings were also reported with alendronate by Bauer et al (2004). In this study those alendronate treated women who achieved the greatest percentage reduction in BSAP at 1 year had the lowest risk of fracture. For each standard deviation reduction in BSAP the incidence of spine, non-vertebral and hip fracture was reduced by 26%, 11% and 39% respectively. In contrast to Eastell et al (2003) the relationship was linear with no plateauing of effect. Change in P1NP and serum CTX was also associated with reductions in vertebral fracture incidence although the trend was not significant for non-vertebral or hip fracture (Bauer et al 2004). Therefore it does appear that for bisphosphonates short term changes in BTMs can be

used to assess the anti-fracture efficacy of therapy although the optimum level of suppression has not yet been determined. There is no data to date regarding the relationship between BTM changes and fracture incidence for anabolic agents.

## Introduction summary, the treatment of postmenopausal osteoporosis.





**Chapter 4:**

**Routine versus targeted vertebral fracture assessment**

**for the detection of vertebral fractures**

## **Introduction.**

Vertebral fractures are the commonest osteoporotic fractures and are often considered the hallmark of osteoporosis. As discussed in chapter 1.2, vertebral fractures predict future vertebral, non-vertebral and hip fractures independent of BMD (Lindsey et al 2001, Ismail et al 2001) making the knowledge of vertebral fracture status important when assessing fracture risk. Two thirds of women with vertebral fractures are unaware of them (Melton et al 1993) and in these women their future fracture risk will be substantially underestimated which may lead to the inappropriate withholding of treatment.

The only way to detect these asymptomatic vertebral fractures is radiologically. Modern DXA scanners are able to perform a Vertebral Fracture Assessment (VFA) of the spine which can detect vertebral fractures with a high degree of sensitivity and specificity (Rea et al 2000b, Binkley et al 2005, Chapurlat et al 2006). Compared to spinal x-rays, VFA has the advantages of being less expensive, having a lower radiation dose and being performed at the same time as DXA (Rea et al 2000). This makes VFA a potential screening tool which can be performed on women attending for DXA.

This study compares two different VFA screening strategies used at our centre: screening all women (routine VFA screening) and screening only those women with reasons to suspect a prevalent vertebral fracture (targeted VFA screening). We hypothesize that attempting to target VFA results in large numbers of women with fractures being excluded from the screening program. We also examine the merits of routinely screening

women depending on their BMD and the potential for routine screening to influence treatment decisions.

## **Methods.**

### Subjects.

Since 2001 all patients attending for bone densitometry at the Centre for Metabolic Bone Disease in Hull have had spine and hip BMD measured using a Lunar Prodigy bone densitometer (GE Lunar, Madison, WI) which has VFA capability. Vertebral fracture screening using VFA was initially targeted only at women with reasons to suspect a possible fracture. Indications for a targeted VFA were reported height loss (>2.5cm, 1 inch), Dowager hump, suspected fracture on anterior-posterior spine DXA and known vertebral fracture. In August 2005 our Centre changed to a routine screening program under which all women who attended for DXA underwent VFA if they were over 65 and physically able to do so. The BMD and VFA results along with basic patient details, including age, sex, gender and menopause age, are routinely recorded on the Prodigy's database at the time of attendance. Using this database we identified all women over the age of 65 at the time of their first DXA scan. Depending on the screening policy at the time of attendance, women were identified as either the targeted screening group (pre-August 2005) or the routine screening group (post-August 2005).

### Vertebral Fracture Assessment.

Our Centre has 3 Lunar Prodigy bone densitometers with VFA capability. The scanners are subject to a rigorous quality assurance procedure which includes weekly scanning of a purpose designed phantom for VFA (Steel et al 1999). The scans are performed and analysed by qualified, experienced bone densitometrists following standardised protocols.

Women initially undergo a standard anterior-posterior DXA assessment of the spine and femur in the supine position. If a VFA is to be performed then the woman is repositioned into the left lateral decubitus position. The scanner is then passed over the whole of the spine in order to obtain a view of the spine in the sagittal plane. A single energy x-ray display is used for analysis of the VFA. Initially, T4-L4 are assessed by the densitometrist for fractures using the semi-quantitative method described by Genant et al (1993). Any vertebrae which are considered to be fractured subsequently undergo a six point quantitative assessment using the Prodigy computer software to measure the posterior, middle and anterior vertebral height. Fractures are graded as mild (grade 1), moderate (grade 2) or severe (grade 3) if there is a 20-25%, 25-40% or greater than 40% reduction in vertebral height respectively. VFA has been demonstrated to correlate well with spinal x-ray for grade 2 and 3 fractures (Rea et al 2000, Rea et al 2000b, Binkley et al 2005) as such these fractures are identified. 50% of mild fractures detected by VFA are normal on x-ray (Binkley et al 2005) and therefore, grade 1 fractures are not identified. The VFA and DXA scans are then validated by a clinical scientist specialised in bone densitometry before the data is finally entered into the database. A final report to the

women's general practitioner is issued by an osteoporosis consultant who may also review the VFA qualitatively but this report is not recorded on the database.

### Analysis.

Basic population demographics were determined for the targeted screening group and the routine screening group and then were compared using 2 sample t-test (with the appropriate assumption of variance) or the Mann-Whitney U test depending on the distribution of the data. Chi-square was used for categorical data. The routine screening group was used to determine the prevalence, type and site of vertebral fractures in our local population. Using this prevalence data, the number of women with vertebral fractures that remained undetected by targeted screening was estimated.

The routine and targeted screening groups were then divided by hip BMD at the neck of femur (NOF) into normal, osteopenic or osteoporotic. Hip BMD was used to define BMD category as this avoids the artefactual increase in spine BMD due to vertebral fracture and is the recommended site for the diagnosis of osteoporosis (Kanis and Gluer 2000). Using this data we determined the number of osteopenic women in whom the knowledge of vertebral fracture status may influence the treatment decision. Finally, the number of women with vertebral fractures that remained undetected by targeted screening for each category of BMD was estimated. Statistical analysis was performed using SPSS for Windows (version 14.0 SPSS, Inc., Chicago, IL). The data collection and analysis was

performed as part of a service review at our centre and therefore ethic approval was not required although permission was obtained from the local audit committee.

## **Results.**

### **Subjects.**

A total of 8564 women over the age of 65 when attending for their first DXA were identified. 6388 attended during the period of targeted VFA while 2176 women attended during the routine screening period. The routine screening group were slightly, but significantly, older (mean age 74.3 vs.72.5 years). The routine screening group also had a slightly older menopause age, lower hip BMD and higher spine BMD. Although these differences were statistically significant, the absolute differences between the groups for these characteristics were all less than 2.5%. Subject demographics are demonstrated in table 4.1.

### **Routine VFA screening for the detection of vertebral fractures.**

Of the 2176 women attending during the period of routine screening, 2098 (96.4%) women underwent VFA. Grade 2 and 3 vertebral fractures were identified in a total of 420 women (19.3% of the population, 20.0% of VFAs) of whom 185 (44.0%) had 2 or more vertebral fractures (Table 4.2). Routine screening detected a total of 755 grade 2 and 3 vertebral fractures. Wedge and biconcave fractures were more frequent than

compression fractures. Table 4.3 demonstrates the frequency of each type of vertebral fracture. Vertebral fractures were commonest around T7 to T9 and the thoracolumbar junction, T11-L1. Figure 4.1 shows the frequency of fracture at each vertebral level.

Table 4.1: Demographics of women over 65 attending for a DXA scan.

	<b>Targeted VFA</b>	<b>Routine VFA</b>	<b>Difference</b>	<b>test used</b>	<b>equal variance</b>	<b>p value</b>
<b>Age (yrs)</b>	72.5 (5.9)	74.3 (6.1)	1.8 (2.5%)	u	na	<0.001
<b>Caucasian (%)</b>	99.4	99.5	0.1 (0.1%)	chi	na	0.34
<b>Menopause age (yrs)</b>	46.9 (5.9)	47.6 (6.0)	0.7 (1.5%)	t	y	<0.001
<b>Weight (kg)</b>	65.0 (12.8)	65.6 (14.0)	0.6 (0.9%)	t	n	0.073
<b>NOF BMD (g/cm<sup>2</sup>)</b>	0.784 (0.1)	0.776 (0.1)	-0.008 (1.0%)	t	y	0.017
<b>Spine BMD (g/cm<sup>2</sup>)</b>	1.021 (0.2)	1.035 (0.2)	0.014 (1.4%)	t	y	0.006

Numbers represent mean (sd) or %. NOF = neck of femur

t = 2 sample t test, Chi= chi squared, u = Mann Whitney U test, na = not applicable

Table 4.2): The number of vertebral fractures detected in women undergoing routine

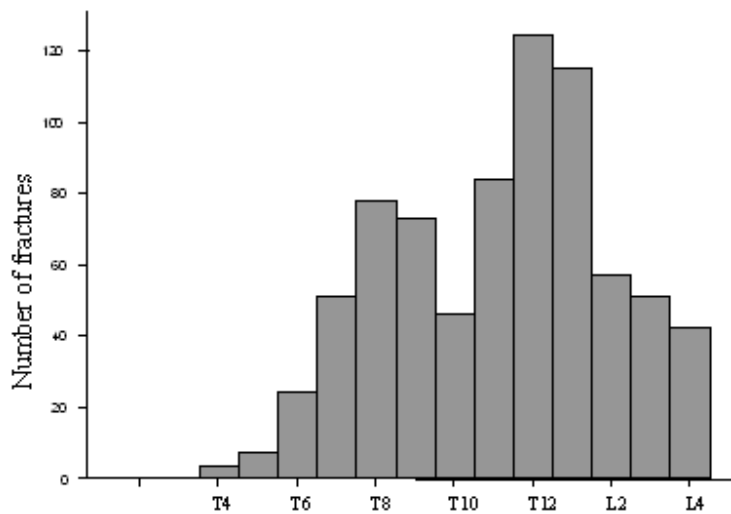
VFA.

<b>Number of Fractures</b>	<b>Number of women</b>	<b>%</b>
<b>0</b>	1756	80.7
<b>1</b>	235	10.8
<b>2</b>	103	4.7
<b>3</b>	42	1.9
<b>4</b>	24	1.1
<b>5</b>	11	0.5
<b>6</b>	2	0.1
<b>7</b>	1	0.0
<b>9</b>	2	0.1
<b>Total</b>	2176	100

Table 4.3): Type and severity of vertebral fractures detected in women undergoing routine VFA

	Moderate		Severe		Overall %
	n	%	n	%	
<b>Wedge</b>	110	14.6	191	25.3	39.9
<b>Biconcave</b>	142	18.8	222	29.4	48.2
<b>Compression</b>	51	6.8	39	5.2	11.9
<b>Total</b>	303	40.1	452	59.9	

Figure 4.1: Number of fractures detected at each vertebral level in women undergoing routine VFA.





### Targeted VFA screening for the detection of vertebral fractures.

Of the 6388 women in the targeted group, a total of 332 (5.2%) underwent VFA resulting in the detection of 122 women with grade 2 or 3 vertebral fractures. Targeted screening resulted in a higher detection rate per VFA performed (36.7%) although only 1.9% of the total population attending for DXA had vertebral fractures detected. If it is assumed that the overall vertebral fracture prevalence rate was similar between the 2 groups then 1277 women in the targeted group would have been expected to have one or more prevalent vertebral fractures on VFA. Only 122 (9.6%) of these women with fractures were detected by targeted screening leaving undetected vertebral fractures in an estimated 1,155 women, 18.1% of the population attending for DXA.

### Vertebral fracture detection by category of BMD

In the targeted and routine VFA groups similar proportions of women were in the 3 categories of hip BMD: normal (29.7 vs. 28.7%,  $p=0.37$ ), osteopenia (55.1 vs. 55.6%,  $p=0.70$ ) and osteoporosis (15.2 vs. 16.6%,  $p=0.10$ ). In the routine screening group, 300 of the 420 (71.4%) women with prevalent vertebral fractures did not have BMD compatible with osteoporosis. The majority of fractures occurred in women with osteopenia (236/420, 56.2%). In the routine screening group the prevalence of vertebral fractures was 10.3% in those women with normal BMD, 19.9% in osteopenic women and 33.2% in those with osteoporosis (Table 4.4). For the 420 women with fractures detected on VFA a history of known vertebral fracture was obtained from 8/64 (12.5%) of women with

normal BMD, 53/236 (22.5%) of osteopenic women and 34/120 (28.3%) of osteoporotic women. In total only 95 out of the 420 (22.6%) women with a vertebral fracture were aware of the fracture prior to VFA.

**Table 4.4: Prevalence of vertebral fractures detected by VFA in each category of BMD.**

	BMD category <sup>a</sup> (%)	VFA at 1st visit		Fracture on VFA		No. of fractures on VFA	
		n	%	n	%	mean	range
<b>Targeted</b>	<b>Normal (29.7%)</b>	74	3.90	24	1.27	1.67	1 to 5
	<b>Osteopenia (55.1%)</b>	184	5.22	60	1.70	1.55	1 to 6
	<b>Osteoporosis (15.2%)</b>	74	7.64	38	3.92	2.32	1 to 7
	<b>Total</b>	332		122		221	
<b>Routine</b>	<b>Normal (28.7%)</b>	597	95.67	64	10.26	1.34	1 to 4
	<b>Osteopenia (55.6%)</b>	1159	97.48	236	19.85	1.75	1 to 7
	<b>Osteoporosis (16.6%)</b>	341	94.20	120	33.15	2.13	1 to 9
	<b>Total</b>	2097 <sup>b</sup>		420		755	

<sup>a</sup> BMD category relates to BMD at NOF. Spine BMD is used in cases with no data for NOF BMD (n=207).

<sup>b</sup> 1 woman was unable to lie supine for axial BMD although a VFA was obtained.

In the targeted screening group vertebral fractures were detected in 1.3%, 1.7% and 3.9% of the normal, osteopenic and osteoporotic women respectively. If it is again assumed that the actual prevalence of vertebral fracture was similar between the two groups, then targeted screening underestimated vertebral fracture prevalence in each BMD category. The proportion of women with undiagnosed vertebral fractures increased with decreasing BMD: 9% of women with normal BMD, 18% with osteopenia and 29% with osteoporosis (Table 4.5).

Table 4.5: Estimated number of women with undiagnosed vertebral fractures despite undergoing targeted VFA.

<b>BMD category</b>	<b>Estimated* number of women with #</b>	<b>Women with # detected</b>	<b>No. of women with undiagnosed #</b>	<b>% of women with undiagnosed #</b>
<b>Normal, n=1897</b>	195	24	171	9
<b>Osteopenia, n=3522</b>	699	60	639	18
<b>Osteoporosis, n=969</b>	321	38	283	29

\* Estimate derived from the prevalence of vertebral fractures in the routine screening group.

## **Discussion**

We report the actual application of VFA as a screening tool for the detection of vertebral fractures in women over 65 referred for bone densitometry. To our knowledge, this is the largest study of routine population screening with VFA and there are no previous studies comparing routine and targeted screening methods. Vertebral fractures are common and knowledge of vertebral fracture status provides important information for assessing fracture risk (Ismail et al 2001). However, despite their high prevalence and clinical relevance only one third of women with vertebral fractures are aware of them (Melton et al 1993). This suggests that there is a need for screening for vertebral fractures. Although thoracic and lumbar spine x-rays are the gold standard for vertebral fracture detection, VFA provides a more practical screening tool as it is available at the point of service for women attending for DXA. Furthermore it has a lower cost and the radiation dose of

VFA (<0.02 millisieverts (mSv)) is a fraction of the radiation dose of conventional spine radiographs (2-3 mSv) (Rea et al 2000).

When used routinely, over 95% of women were willing and physically able to undergo VFA at our centre demonstrating that the procedure was acceptable for most women. Overall, routine screening of all women over 65 identified one woman with grade 2 or 3 vertebral fractures for every 5 VFAs (20%) performed and almost half of these women had multiple fractures. The majority of fractures detected by routine screening occurred in the mid thoracic region and thoracolumbar junction which is consistent with previous reports using both x-ray (Genant et al 1993, Genant et al 1996) and VFA (Rea et al 2000, Chapurlat et al 2006). As with previous reports, the majority of fractures detected were wedge or biconcave (Rea et al 1999, Rea et al 2000b) although we found biconcave fractures to be the most common.

As would be expected, when women were divided up by BMD category, the number of women with vertebral fractures detected by routine screening increased as BMD decreased. VFA is performed after axial DXA and as such it would be possible to perform routine VFA screening only in women with certain categories of BMD. Adopting a policy of routine VFA screening for women over 65 only if they have osteoporosis on their axial DXA would require VFA to be performed in only 16% of women and would increase the rate of vertebral fracture detection to 1 in 3 women screened. Routine VFA in this BMD category would also allow the identification of women with the highest risk of future fracture i.e. both osteoporosis and prevalent

vertebral fractures. However, adopting this policy would miss the majority of women with vertebral fractures as 71% of the women with vertebral fractures detected by routine screening did not have BMD compatible with osteoporosis. This confirms the findings of 2 smaller studies in which 60-70% of women with vertebral fractures did not have osteoporosis (Greenspan et al 2001, Schousboe et al 2002). Furthermore, knowledge of vertebral fracture status in osteoporotic women is less likely to alter the patient's management as, over the age of 65, the majority of these women would receive treatment anyway.

Vertebral fractures may have more significant therapeutic implications in women without osteoporosis. Osteopenic women would not normally be considered for bone protective treatment based on BMD alone. The presence of a vertebral fracture would increase the risk of subsequent fracture making treatment appropriate. We found that 20% (1 in 5) of osteopenic women had vertebral fractures detected by VFA. A similar 14-20% fracture prevalence in osteopenic women has been reported although direct comparison is difficult as these studies included grade 1 fractures and women less than 65 years of age (Greenspan et al 2001, Schousboe et al 2002). Only 22.5% of osteopenic women with a fracture on VFA gave a history of known vertebral fracture. Therefore, vertebral fractures were identified for the first time in 15.8% of osteopenic women. This suggests that routine VFA may directly alter the management of around 1 in 6 osteopenic women. It has been demonstrated that antiresorptive therapy is effective at reducing the risk of future fracture in women with osteopenia if they have a vertebral fracture (Kanis et al 2005, Quandt et al 2005) and a recent analysis suggests that this treatment is cost

effective (Schousboe et al 2006). Osteopenic women are most likely to benefit from routine screening with VFA given the high prevalence rate, the therapeutic and clinical implications of a vertebral fracture and the cost effectiveness of treatment.

10% of women in our population with normal BMD had vertebral fractures which is again similar to previous reports (Greenspan et al 2001, Schousboe et al 2002). There is little evidence to suggest that bone protective treatment is of benefit or cost effective in women with normal BMD. As such the clinical relevance of finding vertebral fractures in women with normal BMD is less clear and the case for routine VFA in these women is weaker.

In addition to affecting the initial treatment decision, routine screening may also aid monitoring and future treatment decisions as it provides a pre-treatment image of the spine. This is a reference for the future from which incident fractures occurring despite treatment can be diagnosed. Osteoporotic women have the highest incidence of vertebral fracture (Kanis et al 2005) and as such routine VFA in osteoporotic women will provide valuable baseline information even though it may not effect the initial treatment decision. Incident fractures are especially important in countries like the United Kingdom where anabolic bone agents, such as teriparatide, can only be prescribed to women who have been proven to suffer further fractures despite antiresorptive therapy.

We also report the outcomes of a targeted vertebral fracture screening policy for which only women with reasons to suspect the presence of a fracture undergo a VFA. Adopting

this approach to screening women over 65 greatly reduced the number of VFAs performed as only 5% of the population underwent screening. With a targeted approach 1 in 3 women undergoing VFA had vertebral fractures detected compared to 1 in 5 with routine screening. However, using the targeted approach to screening, only around 10% of women with fractures were detected which confirms our hypothesis. Of all the women referred for DXA during the period of targeted VFA, 18% are estimated to have had vertebral fractures, which remained undetected. The proportion of women with vertebral fractures which remain undetected increased to almost a third in women with osteoporosis. We therefore do not consider our targeted screening policy to have been effective.

The data for the targeted screening group were calculated using the assumption that the vertebral fracture prevalence was the same during the two screening periods. There are 2 potential problems with this assumption. Firstly there were statistically significant differences between the groups in terms of age and BMD, which are risk factors for vertebral fracture. These differences may have arisen due to the non-randomised nature of this study. However, the women were drawn from the same local population, from the same age group, and the difference in these factors were all less than 2.5%, thus unlikely to be of clinical significance or have a major effect on fracture prevalence. Secondly, this study compares 2 different time periods and if there was a secular trend towards an increased vertebral fracture incidence then this would lead to an overestimation of the number of fractures missed by targeted VFA screening. However, the overall period of time studied is only 7 years so any effect due to a secular trend should be small. In order

to test the assumption that the vertebral fracture prevalence was the same during the two screening periods it would have been interesting to apply the criteria for targeted screening to the routine VFA group. If this led to similar numbers of women with fractures being missed then this would confirm that the assumption was valid.

Unfortunately some of the criteria for targeted screening were not on the database so this analysis was not possible.

The women underwent screening as part of normal clinical practice, which, combined with the large number of women involved, means that it was not possible to confirm the VFA findings with spinal x-rays. However, our screening program only identifies grade 2 and 3 fractures. When compared to x-ray, VFA has been reported to have a sensitivity of 80-95% for detecting grade 2 and 3 fractures and a specificity of 82-96% for excluding vertebral fractures (Rea et al 2000b, Binkley et al 2005, Schousboe and Debold 2006). Therefore, we believe that the majority of grade 2 and 3 fractures we detected were identified correctly. Our approach to screening is consistent with a recent position paper by the International Society of Clinical Densitometry which recommends that only grade 2 and 3 fractures should be identified by VFA (Laster et al 2007).

It is well recognised that some vertebrae are uninterpretable on VFA. This can be due to poor image quality, which most frequently occurs above T7, or due to the presence of severe scoliosis or degenerative changes although similar limitations are recognised with x-ray (Laster et al 2007). Previous studies report that around 90-95% of vertebrae are interpretable (Rea et al 2000b, Schousboe and Debold 2006). The majority of



uninterpretable vertebrae occur above T7 (Schousboe et al 2002, Binkley et al 2005) where the prevalence of fracture is low which preserves the negative predictive value of VFA (Chapurlat et al 2006). On our database any fractures which occurred in an uninterpretable vertebra would not have been labelled as fractured which may have reduced the number of fractures we detected. This has less of an impact when categorising women, rather than individual vertebrae, as fracture or non-fracture cases. Women with fractures in uninterpretable vertebrae would still be correctly classified if they also had a fracture in an interpretable vertebra. At our centre, the final report issued by the osteoporosis consultant provides an opportunity to recommend x-rays in women with uninterpretable VFAs although this data is not available on our database.

With our screening program grade 1 fractures are not routinely identified and flagged. Previous studies have demonstrated that around one third of vertebral fractures are grade 1 fractures (Rea et al 1999, Rea et al 2000b) and as such this approach reduces our apparent yield from screening. This is reflected in our 20% vertebral fracture prevalence, which is lower than the 33% prevalence on x-ray reported by Genant et al (1996) who included grade 1 fractures. However, this is compensated for by the increased accuracy of our screening method. Including grade 1 fractures in VFA reduces the sensitivity from 80-95% to 50-70% (Rea et al 2000b, Schousboe and Debold 2006). This is in part because of difficulties in differentiating mild fractures from degenerative vertebral remodelling due to the lower resolution of VFA. The impact of this is minimised by our exclusion of grade 1 fractures. Grade 1 fractures may have less clinical significance. Although there is an increased risk of subsequent fracture in women with grade 1

fractures, the incidence is lower than in women with grade 2 and 3 fractures (Gallagher et al 2005). Furthermore grade 1 fractures are associated with less morbidity (Crans et al 2004). Again, when the VFAs and DXA scans undergo their final report by the osteoporosis consultant, possible grade 1 fractures may be identified and an x-ray recommended but this data is not available.

We report the results of two screening programs actually used as part of normal clinical practice at our centre involving a large number of women referred for routine bone densitometry. Despite these strengths there are certain limitations. We have already discussed the lack of x-ray confirmation of fracture, the differences between the 2 groups and that some fractures may have remained undetected if they occurred in uninterpretable vertebrae or were grade 1. Our results are only applicable to women over the age of 65. VFA screening of men or younger women would be expected to result in a lower yield as the prevalence of vertebral fracture is lower. Furthermore, we only targeted women with reasons to believe that a fracture was actually present. If our targeted screening program had also included women with risk factors for vertebral fracture, such as steroid use or prior non-vertebral fracture, then more women would have undergone VFA and a greater proportion of the women with fractures may have been detected.

Although spinal x-rays remain the gold standard for vertebral fracture detection and differentiation, VFA is a more practical screening tool for the detection of women with grade 2 and 3 fractures. This study demonstrates that routine screening results in the detection of one woman with vertebral fractures for every 5 VFAs performed. The

majority of women with fractures have osteopenia on their axial DXA and in these women the knowledge of their fractures status may directly effect their treatment. As well as potentially effecting the initial treatment decision, routine VFA allows better assessment of fracture risk, provides a baseline record of fracture status and can indicate the need for spinal x-rays in women with possible grade 1 fractures or uninterpretable VFA. This study also demonstrates that targeted screening greatly reduces the number of VFAs performed however this results in only around 10% of women with fractures being selected for screening. For women over 65 who are referred for a DXA scan, routine screening for vertebral fractures with VFA is more effective than targeted screening.

**Chapter 5:**

**The effects of short term Hormone Replacement Therapy on  
long term bone mineral density.**

## **Introduction.**

Previously HRT was the cornerstone of treatment for postmenopausal osteoporosis. However, as discussed in chapter 2.1.1, the WHI study demonstrated an increased risk of breast cancer and cardiovascular events with long term HRT use (Rossouw et al 2002). This resulted in long term HRT no longer being considered an appropriate treatment option for osteoporosis. Bisphosphonates are now first line therapy and it is recommended by the MHRA that HRT is only used in the short term around the time of the menopause for the relief of menopausal symptoms.

Bisphosphonates are effective treatments for osteoporosis but lately concerns have been expressed regarding the efficacy and safety of the long term suppression of bone turnover with bisphosphonates (Ott 2005). If there are concerns about long term bisphosphonate use, how should we treat osteoporotic women in their 50's who potentially require 30-40 years of treatment? HRT does not have the same prolonged effects on bone turnover as bisphosphonates (Greenspan et al 2002) so one option may be to initially use a short course of HRT.

With short term HRT BMD would be expected to increase during treatment but upon discontinuation BMD will be lost. It is not known whether this loss of BMD will reduce BMD to the same level as those women who do not take short term HRT or whether there is an overall benefit compared to no treatment. In this study we test our hypothesis that women who take short term HRT around the time of the menopause will have long term gains in their BMD compared to those who take no treatment.

## **Methods.**

### **Original study participants.**

In the 1990's the Centre for Metabolic Bone Disease at Hull Royal Infirmary commenced a feasibility study to investigate the logistics of population screening for osteoporosis (Purdie et al 1996). All women in the local area aged 50-54 were invited by letter for a BMD assessment by DXA of the spine and hip using a Lunar DPX-L densitometer (GE Lunar, Madison, WI). The only exclusions from screening were terminal illness, weight in excess of 125 Kg and physical inability to comply with the standard DXA scanning technique. At baseline informed consent was obtained and data was collected regarding menopause age, medical conditions, family history, smoking status, fractures and medications.

### **Treatment.**

As this study commenced prior to the WHO definition of osteoporosis, women were deemed "at risk" if their BMD was in the lowest quartile for their age matched population. These women were recommended for treatment with HRT, the bone protective treatment of choice at the time for the early post-menopausal period. The subject's general practitioner made the final choice of HRT preparation from a list of HRT regimes then known to be osteoprotective. Thus, treatment regimes contained either

2mg oestradiol, 0.625mg conjugated equine oestrogen or a 50 µg transdermal patch.

Progestogens were prescribed to women with a uterus.

#### Follow up.

Those women considered at risk, and an equal number of randomly selected women not recommended for treatment, were invited back for repeat assessment 2, 5 and 9 years later. Patients were free to stop or change therapy under the guidance of their GP in between visits. Patients were blinded to the 2 years scan results. As such, those discontinuing HRT early did so due to intolerance rather than BMD changes. At each follow up visit a medical history was taken documenting general health, medications (including HRT) and clinical fractures. A repeat DXA was performed using the same DXA machine as for the baseline visit. All details were recorded on the database at our Centre.

#### Subjects for present analysis.

The present analysis included all women who were followed up for 9 years after the screening program. From the database, we identified all women who could be allocated to one of 3 groups: those who took no HRT; those who took 24 to 48 months of HRT prior to the 5 year visit with no subsequent HRT use (short term HRT group); and those who took at least 8.5 years HRT during the 9 year follow up period (long term HRT group). The duration of treatment chosen for the short term HRT group was selected to

represent patients who had received HRT for enough time to be able to detect a change in BMD (2 years) but less than the time taken for the incidence of breast cancer to differentiate from placebo in the WHI study (Rossouw et al 2002). The only exclusion criteria were the use of bisphosphonates or raloxifene before or during the follow up period and not meeting the above HRT treatment group requirements. Calcium supplementation was permitted.

The primary end point was the difference in BMD after 9 years at the spine (L2-4) and hip (neck of femur (NOF)) in the no HRT group compared to the short term HRT group. The primary analysis was carried out on these 2 groups only as long term HRT is no longer recommended and the aim of the study was to compare short term HRT to no treatment. Secondary end points were change in BMD over 9 years within each group and fracture rates in the no HRT and short term HRT groups.

The local ethics committee approved both the original screening program and the present analysis of the 9 year data. As this study was a reanalysis of an existing database and required no patient contact or access to the medical records the ethics committee deemed that it was not necessary to re-consent the subjects.

#### Statistical analysis.

Baseline characteristics were analysed using a one way analysis of variance (ANOVA) for continuous data and Pearson's  $\chi^2$  test for categorical data. Means within groups were



compared using a paired t-test. A Multivariate General linear model adjusted by covariates (Multivariate ANCOVA) was used to examine the effect of treatment after 9 years follow-up on the dependent variables and to obtain adjusted means; the dependent variables were Spine BMD and NOF BMD measured after 9 years follow-up, covariates were Spine BMD and NOF BMD at baseline. A Fisher exact test was performed to test the association between Fractures and HRT. The significance level chosen was 0.05. The program package used was SPSS for Windows (version 12.5 SPSS, Inc., Chicago, IL).

### **Results.**

1303 women were on the database and had been followed up for 9 years. 125 women were excluded due to bisphosphonate or raloxifene use. Of the remaining 1178 women, a further 591 women were excluded due to HRT use incompatible with the required groups. 587 (49.8%) women could be allocated to one of the 3 groups: 340 no HRT (57.9%); 60 Short term HRT (10.2%); and 187 Long term HRT (31.9%). Baseline characteristics of each group are shown in table 5.1. The mean (sd) duration of HRT use was 34.7 (8.5) months in the Short term HRT group and 107.4 (2.3) months in the Long term HRT group.

Table 5.1: Baseline characteristics.

	<b>No HRT (n = 340)</b>	<b>Short term HRT (n = 60)</b>	<b>Long term HRT (n = 187)</b>	<b>P value</b>
<b>Age (yrs)</b>	52.5 (1.4)	52.5 (1.33)	52.3 (1.4)	0.50
<b>Weight (kg)</b>	67.1 (10.6)	63.5 (9.6)	61.8 (9.8)	<0.001
<b>Menopause age (yrs)</b>	49.3 (4.7)	49.1 (3.6)	47.3 (4.7)	< 0.001
<b>Family history (%)</b>	38 (11.2)	15 (25)	30 (16)	0.06
<b>Current smoking (%)</b>	98 (28.8)	23 (38.3)	69 (36.9)	0.098
<b>Alcohol (u/week)</b>	2.4 (3.5)	2 (3)	2.3 (3.3)	0.72
<b>BMD spine (g/cm<sup>2</sup>)</b>	1.114 (0.16)	1.059 (0.12)	1.002 (0.12)	<0.001
<b>BMD NOF (g/cm<sup>2</sup>)</b>	0.893 (0.11)	0.836 (0.09)	0.820 (0.09)	<0.001

Values are expressed as mean (sd) or n (%).

Within group analysis.

The absolute 9 year change in BMD in each group is shown in table 5.2 and the percentage change from baseline at each visit is shown in figures 5.1 and 5.2. Over the 9 year period those treated with long term HRT sustained a significant increase in BMD at the spine (+8.0%, p<0.001) and hip (+2.4%, p<0.001). Those not taking HRT lost a significant amount of BMD at the spine (-3.5%, p<0.001) and hip (-4.2%, p<0.001). Despite a downward trend, the short term HRT group had no significant change in BMD over the 9 years at the spine (-1.4%, p=0.18) or hip (-1.6%, p= 0.08). There was no significant difference in weight gain between the 3 groups to confound the measurement of BMD (no HRT +3.6kg, Short term HRT +3.8 kg and Long term HRT +3.6kg, p=0.97).

Table 5.2: Absolute change in BMD over 9 years within each treatment group.

	No HRT	Short-term HRT	Long-term HRT		No HRT	Short-term HRT	Long-term HRT
	<i>BMD spine (g/cm<sup>2</sup>)</i>				<i>BMD NOF (g/cm<sup>2</sup>)</i>		
<b>Year 1</b>	1.114	1.059	1.002		0.893	0.836	0.820
<b>Year 9</b>	1.075	1.044	1.084		0.856	0.822	0.840
<b>Mean change</b>	-0.039	-0.015	0.081		-0.037	-0.013	0.020
<b>Percentage change</b>	-3.5%	-1.4%	8.0%		-4.2%	-1.6%	2.4%
<b>p Value</b>	<0.001	0.18	<0.001		<0.001	0.08	<0.001

Figure 5.1: Mean  $\pm$  standard error percentage change from baseline in BMD at the spine over 9 years within each treatment group.

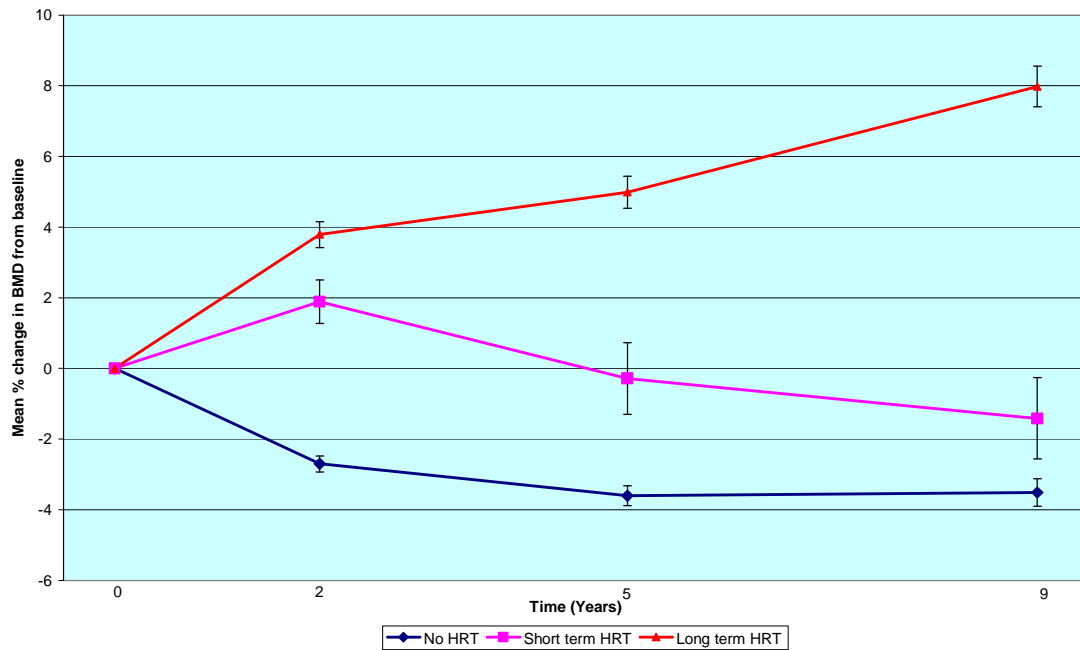
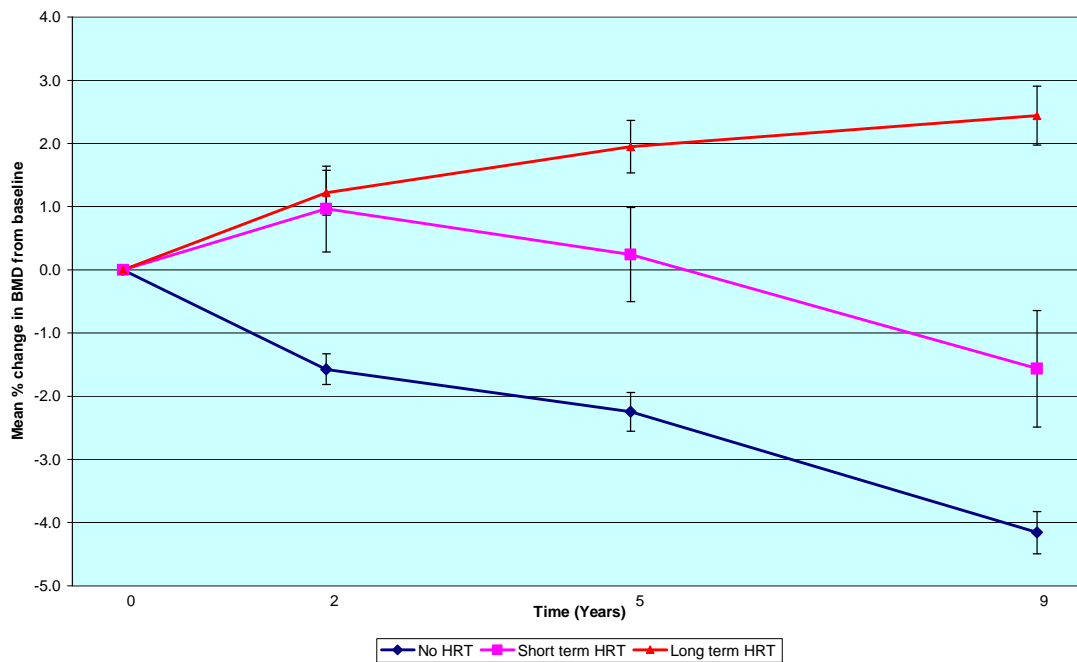


Figure 5.2: Mean  $\pm$  standard error percentage change from baseline in BMD at the neck of femur over 9 years within each treatment group.



Between group analysis.

The BMD in the No HRT group and the Short term HRT group were compared after adjusting for the difference in baseline BMD. At 9 years, those women taking short term HRT had a significantly higher spinal BMD than those taking No HRT (adjusted BMD: 1.091 g/cm<sup>2</sup> vs. 1.068 g/cm<sup>2</sup>, p = 0.048). The hip (NOF) BMD was also significantly higher in the short term HRT group (0.865 g/cm<sup>2</sup> vs. 0.849 g/cm<sup>2</sup>, p=0.042).

### Fractures.

All fracture types were grouped together for analysis as the sample populations were too small to allow specific fractures sites to be compared. In the No HRT group 54 (15.9%) women suffered a total of 64 fractures compared to 6 (10.0%) women suffering a total of 7 fractures in the short term HRT group. Over the 9 year period, the short term HRT group had a reduced risk of fracture compared to the No HRT group although this was not statistically significant (RR = 0.63, p=0.33).

### Discussion.

The WHI study confirmed the bone protective effects of HRT however this was offset by an increase in vascular events and breast cancer (Rossouw et al 2002). The increase in breast cancer did not occur until after 4 years of treatment and hence HRT is still licensed for short term use for the relief of menopausal symptoms. The present study suggests that women who take between 2 and 4 years of HRT in the early postmenopausal period have a prolonged benefit in terms of BMD, as 4 to 5 years after discontinuing HRT they had a higher BMD than the non-users. Furthermore, over 9 years there was no significant loss of BMD in short term HRT users. It therefore appears that our hypothesis was correct. This study also suggested that, compared to non-users of HRT, short term HRT users may have a lower risk of fracture. The study was underpowered to detect a difference in fractures and as such this reduction did not reach significance however the reduction in fracture risk observed does support the findings of an earlier study which demonstrated

that short term HRT reduced the risk of fracture in early postmenopausal women by 52% (Bagger et al 2004).

Short term HRT may have a role to play in the overall treatment strategy for women with low BMD during the early postmenopausal period. Recently concerns have been raised regarding the long term safety and efficacy of bisphosphonates (Ott 2005). The 10 year data for alendronate from the FLEX trial suggests that there are no benefits in continuing treatment beyond 5 years in terms of non-vertebral fractures or morphometric vertebral fractures (Black et al 2006). A smaller 10 year study also demonstrated that stopping alendronate at 5 years resulted in little difference in terms of vertebral fracture compared to continuing alendronate (Bone et al 2004). Of more concern is the possibility of harm due to long term bisphosphonate use. Osteonecrosis of the mandible has been repeatedly reported although predominantly with high dose bisphosphonates used for bone related malignancy (Migliorati et al 2006, Woo et al 2006). A recent paper reported a series of patients with low trauma fractures occurring after long term bisphosphonates who had severely suppressed bone turnover on bone biopsy (Odvina et al 2005). Animal models also demonstrate microdamage accumulation with long term bisphosphonate exposure (Mashiba et al 2001). If there are concerns about long term bisphosphonate use, what treatment should be offered to women with low BMD in their 50s who have, or are at risk of developing, osteoporosis and therefore require a treatment strategy for the next 30-40 years? BMD will continue to decline if treatment is delayed, as in the No HRT group in this study. Raloxifene could be used if the site of concern is the spine but this could exacerbate the menopausal symptoms common in the early postmenopausal period and

has no proven benefits in terms of non-vertebral fractures (Ettinger et al 1999). Our study suggests that short term HRT in the early menopausal period may provide both relief of menopausal symptoms and preservation of BMD, thus allowing bisphosphonate therapy to be delayed.

Only 1 previous study by Bagger et al (2004) has examined the effects of short term HRT in the early menopausal period. As in the present study, those women treated with short term HRT had long term benefits in terms of BMD and this study also demonstrated a significant reduction in the risk of both vertebral and all-fractures. The women in both studies were of similar age and in the early postmenopausal period but there were several differences in the methodology. Bagger et al amalgamated 4 randomized controlled trials in which only otherwise healthy women were recruited and set treatment regimes were used. Our study was an observational one in which the general population was screened, appropriate clinical advice regarding treatment was given and the women were free to change or stop their HRT under their GPs guidance. As such our study is more representative of real clinical practice and suggests that the benefits of short term HRT predicted by Bagger et al still occur when the general population is studied. This is important as recent studies have demonstrated how patient selection for clinical trials can bias the characteristics of study populations (Al-Shahi et al 2005, Junghans et al 2005). Bagger et al also had to use different models of DXA scanner throughout their study, thus requiring the use of a conversion factor, whereas in our study each patient was scanned on the same machine at each visit allowing direct comparison. We also prospectively

followed up the patients at 2,5 and 9 years whereas Bagger et al followed up all patients at one point in time, either 5, 11 or 15 years after the end of their original trial.

The main limitation is that this is not a randomised controlled trial as women were allocated to HRT or no treatment depending on their BMD. Although this mirrors clinical practice, it is possible that this could lead to selection bias which could confound the study in different ways. Potentially, the women with lower BMD, and therefore allocated to HRT, may have already undergone the period of rapid postmenopausal bone loss while those women with higher BMD (no HRT group) may still be in the early stages of rapid bone loss. If this was the case then the no HRT group would be expected to lose more BMD during the follow up period and this could theoretically account for the results of this study. However at baseline the short term HRT and no HRT groups had practically identical age and menopause age which makes this less likely. An alternative way in which selection bias could confound the results is that women with lower BMD at baseline may be “fast losers” of BMD. This is certainly a possibility as, compared to the no HRT group, women in the short term HRT group had a lower weight and a trend towards a higher prevalence of smoking which are factors associated with an increased rate of postmenopausal BMD loss (Ravn et al 1999, Law and Hackshaw 1997). If it is the case that selection bias led to women who were “fast losers” being allocated into the short term HRT group then this study provides a conservative estimate of the benefits of short term HRT as these women should have lost even more BMD than the no HRT group.



There are other limitations to this study. As women were not randomised to each treatment arm there were significant differences between the short term HRT and no HRT groups at baseline in terms of BMD and weight. While the statistical analysis corrected for the differences in BMD, it was not also adjusted for weight which is an oversight although, as discussed above, not correcting for weight would be expected to make our results more conservative. Women over 125kg were excluded and we have no record of what proportion of the population were excluded due to this criteria as this was not entered into the database or reported in the original study (Purdie et al 1996). Finally, despite having a low BMD for their age the women in this study were not osteoporotic by the WHO definition. T-scores at baseline were -0.75 and -1.17 in the no HRT group and short term HRT group respectively. Bagger et al (2004) also looked at women with normal BMD and as such there are no studies assessing the affect of short term HRT on osteoporotic women in the early postmenopausal period.

When considering HRT it is important to balance the benefits of treatment with the risks of vascular disease and breast cancer. The type of HRT required also needs consideration as oestrogen only HRT, recently confirmed to also provide fracture protection (Jackson et al 2006), does not have the increased incidence of coronary heart disease and breast cancer associated with combined HRT (Anderson et al 2004). HRT may not be a suitable treatment option for all patients. However, for women with low BMD in the early menopausal period short term HRT may provide a useful initial treatment option and have lasting benefits.

**Chapter 6:**

**The effect of prior bisphosphonate exposure on the treatment  
response to teriparatide in clinical practice.**

## **Introduction.**

Teriparatide is an effective treatment for osteoporosis which, unlike most other treatments for osteoporosis, is an anabolic bone agent as it stimulates bone formation (Jiang et al 2003). In the UK, the National Institute for Health and Clinical Excellence (NICE) restricts the prescribing of teriparatide to those patients who suffer further fragility fractures despite prolonged treatment with bisphosphonates. However, as discussed in chapter 2.2, bisphosphonates have the opposite effect on bone remodelling which persists after their discontinuation (Bone et al 2004, Black et al 2006) and in theory this may blunt the anabolic effects of teriparatide. This is supported by a previous small study demonstrating a diminished BMD response to teriparatide in patients with prior alendronate exposure (Ettinger et al 2004).

This study reports the results of teriparatide therapy on patients attending our osteoporosis centre. We hypothesize that the prolonged use of bisphosphonates, as required by NICE, will impair the clinical response to by teriparatide as assessed by BMD and BTMs.

## **Method.**

At our centre, patients being considered for teriparatide therapy are initially assessed for secondary causes of metabolic bone disease, which may be responsible for the fracture despite bisphosphonate therapy. The conditions screened for are vitamin D deficiency, hyperparathyroidism, hyperthyroidism, myeloma, coeliac disease and hepatic or renal

disease. If no secondary cause is detected then patients are commenced on teriparatide if they are eligible for treatment under the NICE guidelines. All patients commenced on teriparatide receive supplementation with 1g calcium and 800iu vitamin D.

Once commenced on teriparatide, patients are treated for 18 months and followed up regularly to ensure compliance and allow close monitoring. The treatment response is determined using both bone turnover markers and BMD measurements. The early bone formation response is assessed using P1NP measured pre-treatment and at 3 and 6 months by electrochemiluminescence immunoassay (total P1NP, Roche diagnostics, IN, USA). P1NP is considered to be the best currently available marker of bone formation as it has the lowest analytical variation, lowest degree of biological variation and does not require the patient to be fasted (Seibel 2005). The BMD response is then assessed at the spine and hip pre-treatment and at 12 and 18 months by DXA using a Lunar Prodigy bone densitometer (GE Lunar, Madison, WI).

All patients treated with teriparatide have their details entered into a database at our centre. This database is updated regularly using the patient's medical record and includes data on osteoporosis risk factors, fractures, medical history, medication, biochemical data and BMD measurements. With the permission of Eli Lilly and company, this database includes a small number of patients treated at our centre with teriparatide as part of a phase 4 trial who are therefore bisphosphonate naïve and form the control group for this study.

For this study all patients on the database who had completed at least 12 months treatment with teriparatide were identified. These patients were divided into 2 groups depending on whether they had prior bisphosphonate exposure. The BMD and P1NP response to teriparatide in those women with prior bisphosphonate exposure was compared to the response in the bisphosphonate naïve group and to the published literature.

The data collection and analysis was performed as part of a service review at our centre and therefore ethic approval was not required although permission was obtained from the local audit committee.

#### Statistical analysis.

The distribution of the data was determined using a Kolmogorov-Smirnov test for normality. Baseline characteristic were analysed using a 2 sample T test or Mann Whitney U test depending on the distribution of the data. A Chi-square test was used for categorical data. A repeated measures ANOVA was used to assess the within group change in BMD and P1NP from baseline. A multivariate ANOVA was used to examine the difference in BMD and P1NP between the 2 groups at the different time points. The significance level chosen was 0.05. The program package used was SPSS for Windows (version 14.0 SPSS, Inc., Chicago, IL).

## Results.

### Patients.

A total of 52 postmenopausal women had been treated with teriparatide for more than 1 year. 38 had prior bisphosphonate use, 14 were bisphosphonate naïve. In the prior bisphosphonate group, the mean duration (sd) of bisphosphonate use was 67 (37.6) months and the bisphosphonate was discontinued a mean (sd) of 1 (1.7) month previously. The prior bisphosphonate group had a significantly lower baseline P1NP as expected with recent antiresorptive therapy. The prior bisphosphonate group were required to have suffered a further fragility fracture in order to be eligible for teriparatide and as such there was a higher baseline prevalence of vertebral fractures in this group. Otherwise there were no significant differences between the 2 groups. Prior bisphosphonate usage is described in table 6.1 and full baseline characteristics of the study population are shown in table 6.2

Table 6.1: Bisphosphonate use immediately before teriparatide and ever used in the prior bisphosphonate group.

	<b>Immediately prior: n (%)</b>	<b>Ever Used: n (%)</b>
<b>Alendronate</b>	22 (57.9)	30 (78.9)
<b>Risedronate</b>	8 (21.1)	12 (31.6)
<b>Didronel</b>	3 (7.9)	20 (52.6)
<b>Pamidronate (IV)</b>	5 (13.2)	7 (18.4)

Table 6.2: Baseline characteristics.

	BP naïve n=14	Prior BP n=38	Test used	equal variance	p value
Age starting TP (yrs)	69 (5.8)	72.3 (9.0)	t	y	0.21
Menopause age (yrs)	49.2 (5.7)	46.6 (6.0)	t	y	0.16
BMI (kg/m <sup>2</sup> )	26.1 (4.8)	25.7(4.1)	t	y	0.73
Current Smoking (n)	2 (14.3)	6 (15.8)	chi	na	0.89
Alcohol >14u/w (n)	0 (0)	0 (0)	na	na	na
Vitamin D (nmol/l)	78.8 (27.1)	70.9 (37.8)	t	y	0.66
PTH (pg/ml)	29.8 (13.2)	40.9 (20.8)	t	y	0.23
Vertebral fracture*	1.4 (1.5)	3.9 (2.9)	t	y	<0.001
Non-vertebral fracture*	1.3 (1.1)	1.0 (1.0)	t	n	0.43
BMD spine (g/cm <sup>2</sup> )	0.797 (0.1)	0.782 (0.1)	t	y	0.71
T score	-3.4	-3.5			
BMD NOF (g/cm <sup>2</sup> )	0.719 (0.1)	0.667 (0.1)	t	y	0.08
T score	-2.2	-2.6			
P1NP (ug/l)	49.1 (18.5)	29.5 (15.4)	t	y	0.001

Numbers represent mean (sd) or n (%) BP = bisphosphonate, TP = teriparatide

\* Mean (sd) number of fractures per patient

t = 2 sample t test, chi = chi squared test, na = not applicable

#### P1NP response.

At baseline bisphosphonate naïve patients had a significantly higher pre-treatment P1NP than bisphosphonate treated patients (49.1ug/l and 29.5ug/l respectively, p=0.001). The bisphosphonate naïve patients maintained a higher P1NP at 3 months (108.8 vs. 71.5ug/l, p=0.036) and by 6 months the difference in P1NP had increased further (183.1 vs. 125.6ug/l, p=0.007). P1NP changes in the 2 groups are demonstrated in Figure 6.1.

In the prior bisphosphonate group, P1NP increased significantly from baseline by 42.0ug/l at 3 months and 96.1ug/l at 6 months. The bisphosphonate naïve group also experienced a significant increase in P1NP at both 3 months (59.7ug/l increase) and 6 months (134.0ug/l increase). Table 6.3 demonstrates the P1NP changes from baseline.

The magnitude of the increase from baseline was not significantly different between the groups at 3 (p=0.27) however by 6 months the change from baseline was significantly greater in the bisphosphonate naïve group (p=0.030).

Figure 6.1: Mean  $\pm$  standard error serum P1NP response to teriparatide in women with and without prior bisphosphonate exposure.

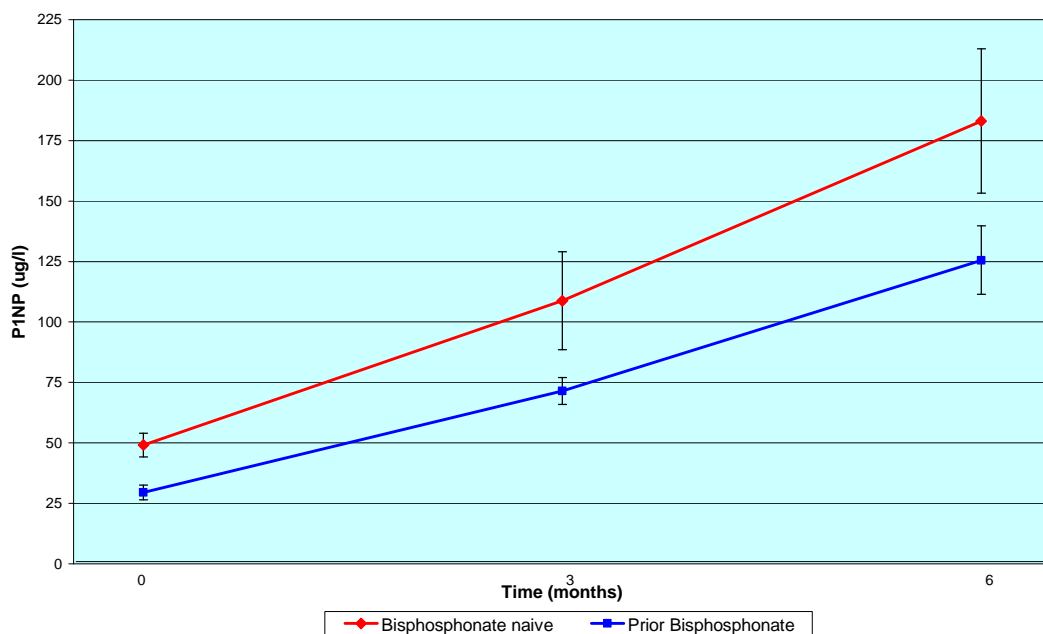


Table 6.3: Mean change in P1NP from baseline at 3 and 6 months within each group.

	P1NP (ug/l)	
	BP naïve	Prior BP
<b>Baseline</b>	49.13	29.51
<b>3 months</b>	108.80	71.48
<b>Δ 0-3 months</b>	59.67	41.97
<b>p value</b>	0.01	<0.001
<b>6 months</b>	183.11	125.61
<b>Δ 0-6 months</b>	133.98 <sup>†</sup>	96.10 <sup>†</sup>
<b>p value</b>	0.001	<0.001

BP = bisphosphonate

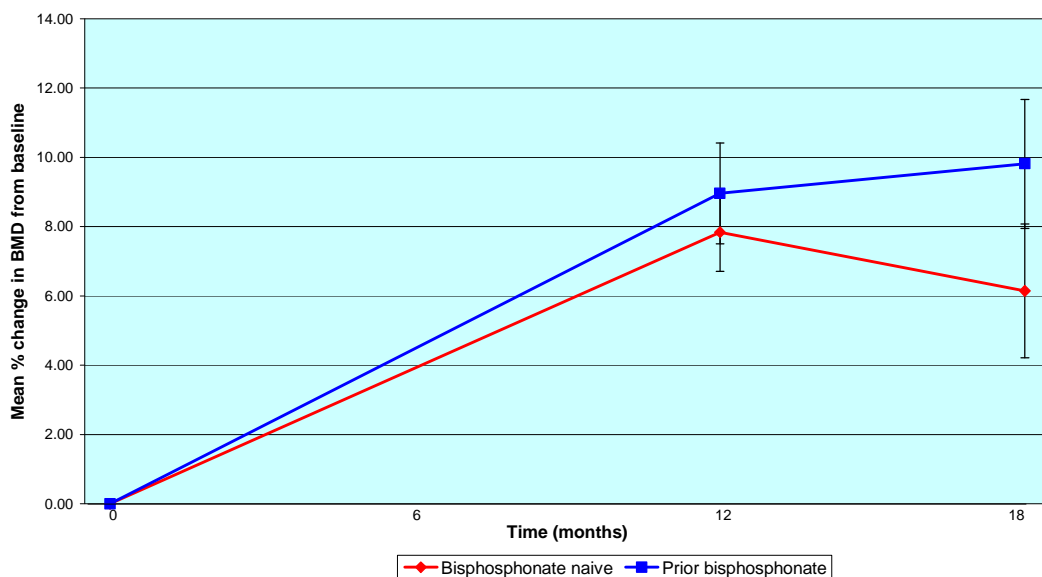
<sup>†</sup> Significant difference between groups (p=0.03)



BMD response.

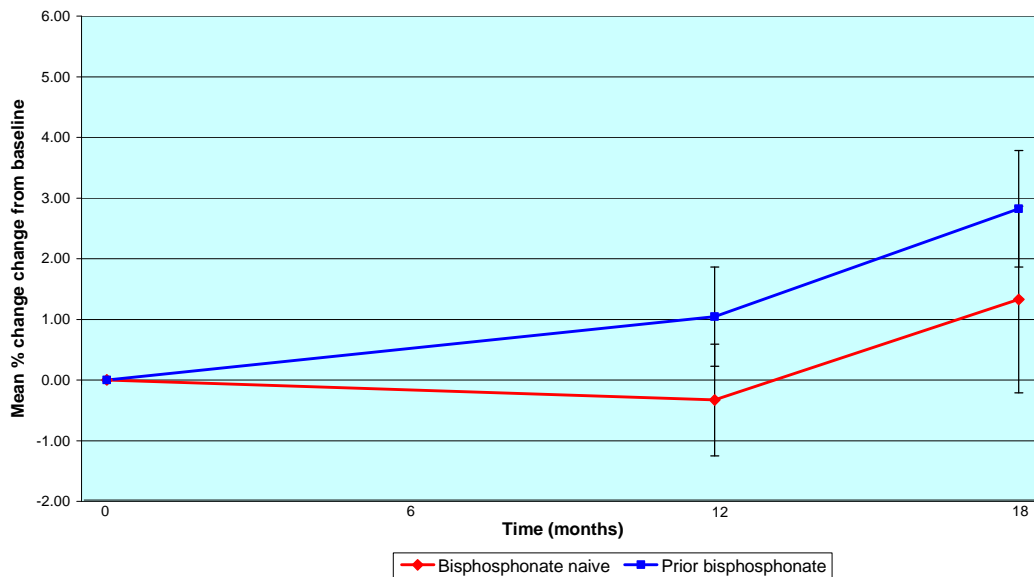
Of the 52 patients, only 33 patients had completed 18 months of therapy to date, 25 with prior bisphosphonate exposure and 8 bisphosphonate naïve patients. Figure 6.2 demonstrates the percentage change in spine BMD from baseline. In both groups the increase in spine BMD after 18 months of teriparatide was significant (prior bisphosphonate:  $p < 0.001$ , bisphosphonate naïve:  $p = 0.006$ ). The change in BMD at the spine was not significantly different between the bisphosphonate treated patients and the bisphosphonate naïve patients at either 12 months (9.0% and 7.8% respectively,  $p = 0.64$ ) or 18 months (9.8% and 6.1% respectively,  $p = 0.43$ ).

Figure 6.2: Mean  $\pm$  standard error percentage change from baseline in BMD at the spine in response to teriparatide in women with and without prior bisphosphonate exposure.



After 18 months of teriparatide there was a significant increase in hip BMD in the prior bisphosphonate group but not the bisphosphonate naïve group ( $p=0.023$  and  $p=0.15$  respectively) (figure 6.3). Patients without prior bisphosphonate exposure had a small reduction in BMD at the hip compared to a small increase seen in bisphosphonate treated patients at 12 months although the difference was not significant ( $-0.3$  vs.  $1.0\%$  respectively,  $p=0.98$ ). The change in BMD at the hip was not significantly different between the groups after 18 months ( $1.3$  vs.  $2.8\%$  respectively,  $p=0.82$ ).

Figure 6.3: Mean  $\pm$  standard error percentage change from baseline in BMD at the neck of femur in response to teriparatide in women with and without prior bisphosphonate exposure



## **Discussion.**

This is the first study to report the effects of prior bisphosphonate therapy on the subsequent response to teriparatide prescribed as part of routine clinical practice. Following the publication of the NICE guidelines, teriparatide is only prescribed in the UK to patients who have had an inadequate response to prolonged treatment with bisphosphonates. However, as discussed in chapter 2.2, there is concern that the response to teriparatide may be blunted by the persistent suppression of bone turnover due to prior bisphosphonate use. In the present study, patients who had previously taken bisphosphonates did not achieve the same serum levels of P1NP as bisphosphonate naïve patients. Although this suggests a degree of blunting of the anabolic effects of teriparatide, bisphosphonate exposure did not prevent a significant increase in P1NP at 3 or 6 months and by 6 months the prior bisphosphonate group had achieved a 4.3 fold increase in P1NP. Despite the lower serum P1NP levels in the prior bisphosphonate group, in the present study there was no evidence of a reduction of the BMD response to teriparatide. At both 12 and 18 months the increase in BMD at both the spine and hip was not significantly different between the 2 groups. Furthermore, the increase from baseline of 9.8% at the spine and 2.8% at the hip achieved in the prior bisphosphonate group at 18 months in this study is practically identical to the increase reported in treatment naïve patients in the main teriparatide fracture prevention trial (Neer et al 2001). This suggests that our hypothesis is wrong and in fact prior bisphosphonates exposure does not reduce the subsequent BMD response to teriparatide.

One previous clinical trial has assessed the response to teriparatide after bisphosphonates. Ettinger et al (2004) compared alendronate pre-treated women to women pre-treated with raloxifene. Compared to the present study, Ettinger et al enrolled more bisphosphonate naïve patients (22 women) but less bisphosphonate treated patients (26 women). The women were similar in terms of age, BMI and BMD but the women in our study had a greater duration of bisphosphonate exposure. As in our study, Ettinger et al demonstrated a smaller increase in P1NP throughout the treatment period in those women with prior alendronate exposure. However, contrary to our findings, those women with prior alendronate use had a smaller increase in BMD than bisphosphonate naive women after 18 months at the spine (4.1% vs. 10.2%) and hip (0.3% vs. 1.8%) suggesting blunting of the response to teriparatide. Interestingly the raloxifene pre-treated women achieved the expected BMD and bone turnover marker response suggesting that raloxifene does not cause prolonged suppression of bone turnover, which may subsequently inhibit the response to teriparatide. This is supported by evidence that BMD declines immediately upon the cessation of raloxifene (Neele et al 2002). This is likely to be due to raloxifene being a weaker antiresorptive and it does not have the high affinity for bone which is responsible for the prolonged duration of action of bisphosphonates (Russell 2007).

Other studies assessing the interaction between alendronate and PTH therapy have demonstrated that the combination of the 2 therapies resulted in a profound reduction in the increase in bone formation markers (Black et al 2003, Finkelstein et al 2003). Black et al (2003) demonstrated a 16% reduction in P1NP at 12 months with combination therapy compared to a 150% increase in those treated with PTH 1-84 alone. In a second

study in men BSAP increased by 80% in response to teriparatide compared to around 10-15% in those treated with combination therapy (Finkelstein et al 2003). Furthermore, in both studies combining bisphosphonates with PTH therapy resulted in a 50% reduction in trabecular bone formation compared to PTH mono-therapy. These studies demonstrate that alendronate is capable of blunting the anabolic effects of teriparatide. However, when teriparatide is given after bisphosphonates, as in the present study, teriparatide seems able to overcome the effects of the bisphosphonates with only a small blunting of the bone marker response and little effect on the BMD response.

Normally when alendronate is discontinued BMD remains stable at the spine and declines slowly at the hip (Bone et al 2004, Black et al 2006). This suggests that the increase in BMD in response to subsequent teriparatide therapy is due to the actions of teriparatide, i.e. new bone formation. The findings of our study therefore suggests that NICE's recommendation that bisphosphonates should be used first line does not have a detrimental effect on the subsequent anabolic actions of teriparatide.

Despite relatively similar baseline characteristics in our study and Ettinger et al's study, these studies demonstrated contrasting effects of prior bisphosphonate therapy on the BMD response to teriparatide. This may be due to differences in study design. Ettinger et al enrolled healthy women into a clinical trial whereas in our study only patients deemed to have failed bisphosphonates were switched over to teriparatide, as is clinical practice in the UK. By using patients deemed to have "failed" bisphosphonates, it may be that the patients in our study were poorly complying with the bisphosphonates and as such

suffered less blunting of the response to teriparatide. This is unlikely to be the case as a significantly lower baseline P1NP was observed in the bisphosphonate users consistent with suppressed bone turnover and compliance with treatment.

Another potential reason for the different BMD response in our study is that Ettinger et al only included women with prior alendronate use whereas in our study the bisphosphonate use was more varied. As discussed in chapter 2.1.2, it appears that different bisphosphonates may have different characteristics in terms of potency and duration of clinically relevant effect after discontinuation (Russell 2007). Other bisphosphonates may have a quicker off-set of action than alendronate which may explain the normal BMD response in our study. However, the majority of women in our study were on alendronate prior to teriparatide. Furthermore, overall 79% of women were on either alendronate or risedronate and these bisphosphonates have been demonstrated to result in an equal BMD response to teriparatide (Boonen et al 2006b).

The main advantage of this study is that the prior bisphosphonate group represents “real world” patients undergoing treatment with teriparatide as per clinical practice in the UK. Our results may therefore be more applicable to the clinical setting than the results of clinical trials as such trials only involve specific subsets of the population and it has been previously demonstrated how this can skew the results (Al-Shahi et al 2005, Junghans et al 2005). Furthermore, all patients were drawn from the same local population, the 2 groups were reasonably comparable and the bisphosphonate group had all had extensive bisphosphonate therapy.

There are limitations to this study. The size of the study population was governed by the number of patients receiving teriparatide at our centre and, due to the NICE guidelines, there were very few patients in the bisphosphonate naive group. As such the study was very much underpowered to detect a difference in BMD with only a 28.4% probability of detecting a significant difference in spine BMD between the 2 groups. The study had even less power at the femoral neck (13.0%) where the overall BMD response in both groups was small and the precision error of DXA is greater (Sheperd et al 2006). There is therefore a risk of a type 2 statistical error with this study and we cannot say for certain that there was no significant blunting in the prior bisphosphonate group. However, against this are the facts that the magnitude of the BMD increase observed in our study is practically identical to the increase reported in bisphosphonate naive women by Neer et al (2001) and more than double the increase reported by Ettinger et al (2004) in women with prior bisphosphonate exposure. Other limitations are that the patients received different bisphosphonates before teriparatide and a larger study would have permitted a comparison of the effects of different bisphosphonates on the subsequent response to teriparatide. Also, like Ettinger et al, our study is too small to assess the effects of prior bisphosphonate use on fracture risk, which is the most important outcome for osteoporosis therapy, and instead we had to rely on BMD as a surrogate marker.

This study demonstrated a significant 4 fold increase in P1NP in response to teriparatide in patients with prior bisphosphonate exposure. Although there was a smaller P1NP response compared to bisphosphonate naive patients, in our clinic population this did not

result in blunting of the gain in BMD. At both the spine and hip those women with prior bisphosphonate use had a BMD response to teriparatide, which was similar to bisphosphonate naïve patients in both this study and the existing literature. In clinical practice the first line use of bisphosphonates does not impede the subsequent response to teriparatide suggesting that NICE is correct to limit teriparatide, the more expensive treatment, to women who fracture despite bisphosphonates.



**Chapter 7:**

**The effect of prior bisphosphonate therapy on the subsequent**

**BMD and bone turnover response to Strontium Ranelate.**

## **Introduction.**

In clinical practice many women with osteoporosis are already receiving bisphosphonate therapy and for newly diagnosed women bisphosphonates are recommended as the first line therapy for osteoporosis (NICE guideline 2005). In the previous chapter we discussed switching from bisphosphonate therapy to teriparatide. Women who develop side effects from bisphosphonates, such as oesophagitis, or have a poor treatment response and yet do not fulfil the NICE guidelines for teriparatide may be considered for switching to strontium ranelate. However there is no evidence regarding the effect of prior bisphosphonate therapy on the subsequent response to strontium ranelate as most women in the SOTI and TROPOS studies were largely treatment naïve and women who had taken bisphosphonates for more than 14 days in the 12 months preceding the study were actively excluded.

There are 2 theoretical reasons why prior bisphosphonate therapy may inhibit the subsequent BMD response to strontium ranelate. Firstly, bisphosphonates continue to inhibit bone turnover, thus reducing new bone formation, even after discontinuation (Bone et al 2004, Black et al 2006). As strontium is predominantly deposited in newly formed bone, prior bisphosphonate exposure may inhibit the uptake of strontium (Boivin et al 2006, Boivin et al 2007). Secondly, as discussed in chapter 2.2, alendronate has been reported to blunt the anabolic properties of teriparatide and if strontium ranelate has anabolic properties then similar blunting may occur (Ettinger et al 2004, Finkelstein et al

2003, Black et al 2003). The inhibition of strontium uptake, leading to reduced x-ray attenuation, and/or reduced bone formation should result in a reduction in the BMD response to strontium ranelate.

This study investigates the effects of prior bisphosphonate exposure on the subsequent treatment response to strontium ranelate. We hypothesise that women previously treated with bisphosphonates will achieve a smaller BMD response to strontium ranelate than bisphosphonate naïve women.

### **Method.**

#### Subjects.

We prospectively recruited women attending for either an outpatient appointment or bone densitometry assessment at the Centre for Metabolic Bone Disease. Two groups of women were recruited: bisphosphonate naïve women and women treated with an oral bisphosphonate for more than 1 year and who had stopped treatment within the last 1 month due to an inadequate response or adverse side effects. All women were aged 50-80 years and had either a T score of less than -2.5 at the hip/spine or a T score of less than -2.0 at either site and one other risk factor for fracture (previous osteoporotic fracture, maternal hip fracture, previous steroid use, body mass index <19). Women were excluded if they had had prior treatment with strontium ranelate or teriparatide, were unable to give informed consent, had impaired mobility resulting in difficulty undergoing

DXA or had a lumbar spine which could not be evaluated by DXA. Women were also excluded if they had current or likely future steroid use or medical conditions associated with bone loss including renal disease (creatinine clearance < 30 ml/min), active malignancy, osteomalacia, hyperparathyroidism and malabsorption syndromes.

Eligible women were enrolled after providing written informed consent. At their first study visit women underwent a full medical history and physical examination. BMD was measured at the spine (L2-4) and hip (total hip) by DXA (Lunar Prodigy, GE Lunar, Madison, WI). Heel (right os calcis) BMD was also measured (Lunar PIXI, GE Lunar, Madison, WI). Blood was collected for bone turnover markers between 9 and 11am after an overnight fast and was transported to the laboratory within an hour for separation and freezing. The bone turnover markers assessed were P1NP (Elecsys 2010, Roche diagnostics, IN, USA), BSAP (Metra BAP, Quidel Corp, CA, USA) and CTX ( $\beta$ -crosslaps, Elecsys 2010, Roche diagnostics, IN, USA).

Intervention and follow up.

All subjects received treatment with strontium ranelate 2g once a day at bed time (2 hours after food) and 1.2g calcium and 800iu vitamin D daily. The women were followed up for 1 year with visits at 3, 6 and 12 months between 9 and 11am. At each visit details regarding compliance (based on returned medication), adverse side effects, concomitant medication and incident fractures were recorded. All women fasted overnight prior to each visit and blood for bone turnover markers was collected at the same time each visit.

Axial and heel DXA was repeated at the 6 and 12 month visits. A VFA was performed at baseline and the 12 month visit to identify incident vertebral fractures.

The primary endpoint was change in axial BMD after 12 months. The average lumbar spine BMD was used for analysis however if there was a prevalent fracture at baseline or an incident fracture during the study in one of these vertebrae then the fractured vertebra was excluded from the analysis. At the hip, total hip BMD was used for the analysis as this region of interest demonstrates the greatest increase in hip BMD in response to strontium ranelate (Meunier et al 2004, Reginster et al 2005) and is the recommended region of interest for assessing treatment response at the hip (Kanis and Gluer 2000). The secondary endpoints were change in heel BMD, the change in bone turnover markers (P1NP, CTX and BSAP) and fracture incidence.

Analysis.

The sample size was determined using data from previous studies of strontium ranelate which demonstrated a mean annual increase in lumbar spine BMD of 7.3% (0.0512 g/cm<sup>2</sup>) with a standard deviation of 4.9% (0.0343 g/cm<sup>2</sup>) (Reginster and Meunier 2003). Allowing for a 10% withdrawal rate, it was calculated that 120 women were needed to detect a 30% difference in BMD gain between the 2 groups with a power of 90%.

The study was analysed on a per-protocol basis rather than as an intention to treat analysis. This was so that the results accurately reflect the changes in BMD in women

who successfully switch from a bisphosphonate to strontium ranelate. Initially, the kolmogorov-smirnov test for normality was used to assess the distribution of the data. Baseline characteristics were then analysed using either a 2 sample T test (with the appropriate assessment of equality of variance (Levene's test)) or Mann Whitney U test depending on the distribution of the data. A Fisher exact test was used for categorical data. The absolute change in BMD at the spine (L2-4), hip (total hip) and heel (right os calcis) after 6 and 12 months of therapy was compared between the groups using a multivariate ANOVA. Within each group a repeated measures ANOVA was used to assess the change in BMD from baseline. For bone turnover markers, a multivariate ANOVA was used to examine the difference between the 2 groups at each visit of the 4 visits. A repeated measures ANOVA was used to assess the overall change from baseline of each bone marker during the course of the study. The significance level chosen was 0.05. The program package used was SPSS for Windows (version 14.0 SPSS, Inc., Chicago, IL).

Study approval and funding.

Ethical approval was obtained from the Hull and East Riding Local Research Ethics Committee. Clinical trial authorisation was obtained from the Medicines and Healthcare products Regulatory Agency, U.K (EudraCT number 2005-003138-16).

## **Results.**

### **Subjects and baseline demographics.**

In total 120 caucasian women were recruited into the study: 60 women were currently taking a bisphosphonate (prior bisphosphonate group) and 60 who had no prior bisphosphonate use (bisphosphonate naïve group). Prior to the first follow up visit at 3 months 8 women discontinued from the prior bisphosphonate group and 4 discontinued in the bisphosphonate naïve group. These women had no outcome data leaving 108 women who made up the study population (52 and 56 women in each group respectively). A further 3 women withdrew between the 6 and 12 month visits so overall 105 of the 108 women in the study population completed the full year.

The prior bisphosphonate group was older (66.9 vs. 62.5 years,  $p=0.001$ ) and had a lower baseline BMD at the spine (0.801 vs. 0.836  $\text{g/cm}^2$ ,  $p=0.03$ ) than the bisphosphonate naïve group. BMD was similar between the groups for total hip and heel BMD. In the prior bisphosphonate group bone turnover markers were significantly lower than in the bisphosphonate naïve group consistent with recent antiresorptive therapy. There were no other significant differences between the groups at baseline. Full baseline demographics are demonstrated in table 7.1.

Table 7.1: Baseline characteristics.

	<b>BP naïve</b> n=56	<b>Prior BP</b> n=52	<b>test used</b>	<b>equal variance</b>	<b>p value</b>
<b>Age (years)</b>	62.5 (6.8)	66.9 (6.8)	t	y	0.001 <sup>a</sup>
<b>Menopause age (years)</b>	47.3 (6.1)	46.8 (6.0)	t	y	0.68
<b>Positive Family history (n)</b>	15 (26.8%)	16 (30.8%)	Fisher's	na	0.68
<b>Prior steroid use (n)</b>	5 (8.9%)	4 (7.7%)	Fisher's	na	1
<b>Current smoking (n)</b>	7 (12.5%)	4 (7.7%)	Fisher's	na	0.53
<b>Alcohol (u/week)</b>	5.4 (9.0)	3.5 (4.7)	u	na	0.63
<b>BMI (kg/m<sup>2</sup>)</b>	24.9 (3.4)	24.3 (3.5)	t	y	0.37
<b>Vertebral # on VFA, (n)</b>	10 (17.9%)	15 (28.8%)	Fisher's	na	0.25
<b>Prior non-vertebral #, (n)</b>	26 (46.4%)	24 (46.2%)	Fisher's	na	1
<b>Vitamin D (nmol/l)</b>	72.9 (31.1)	71.9 (26.6)	t	y	0.86
<b>Parathyroid hormone (ug/l)</b>	31.4 (10.4)	32.3 (11.4)	t	y	0.66
<b>BMD spine (g/cm<sup>2</sup>)</b>	0.836 (0.08)	0.801 (0.09)	t	y	0.03 <sup>a</sup>
<b>BMD total hip (g/cm<sup>2</sup>)</b>	0.780 (0.11)	0.751 (0.11)	t	y	0.18
<b>BMD heel (g/cm<sup>2</sup>)</b>	0.391 (0.07)	0.369 (0.09)	t	y	0.15
<b>P1NP (ug/l)</b>	54.42 (18.9)	29.64 (13.9)	t	y	<0.001 <sup>a</sup>
<b>CTX (ug/l)</b>	0.38 (0.14)	0.18 (0.11)	t	y	<0.001 <sup>a</sup>
<b>BSAP (U/l)</b>	23.16 (6.7)	17.52 (6.6)	t	y	<0.001 <sup>a</sup>

t = 2 sample t test, Fisher's =Fisher's exact test, u = Mann Whitney U, na = not applicable  
 Numbers are n (%) or mean (sd), <sup>a</sup> = significant difference between groups  
 # = fracture, BP = bisphosphonate, VFA = vertebral fracture assessment

In the prior bisphosphonate group the mean (sd) duration of bisphosphonate use was 64.3 (38.5) months. One woman discontinued her bisphosphonate 3 weeks before commencing strontium ranelate, all the remaining women in the prior bisphosphonate groups switched immediately from bisphosphonate to strontium ranelate. Details of prior bisphosphonate usage are contained in table 7.2.



Table 7.2: Bisphosphonate usage before switching to strontium ranelate in the prior bisphosphonate group.

	<b>Immediately prior</b>		<b>Ever used</b>	
	<b>n</b>	<b>%</b>	<b>n</b>	<b>%</b>
<b>Alendronate</b>	27	51.9	39	75.0
<b>Risedronate</b>	24	46.2	29	55.8
<b>Ibandronate</b>	1	1.9	1	1.9
<b>Didronel</b>	0	0.0	15	28.8
<b>Pamidronate</b>	0	0.0	1	1.9

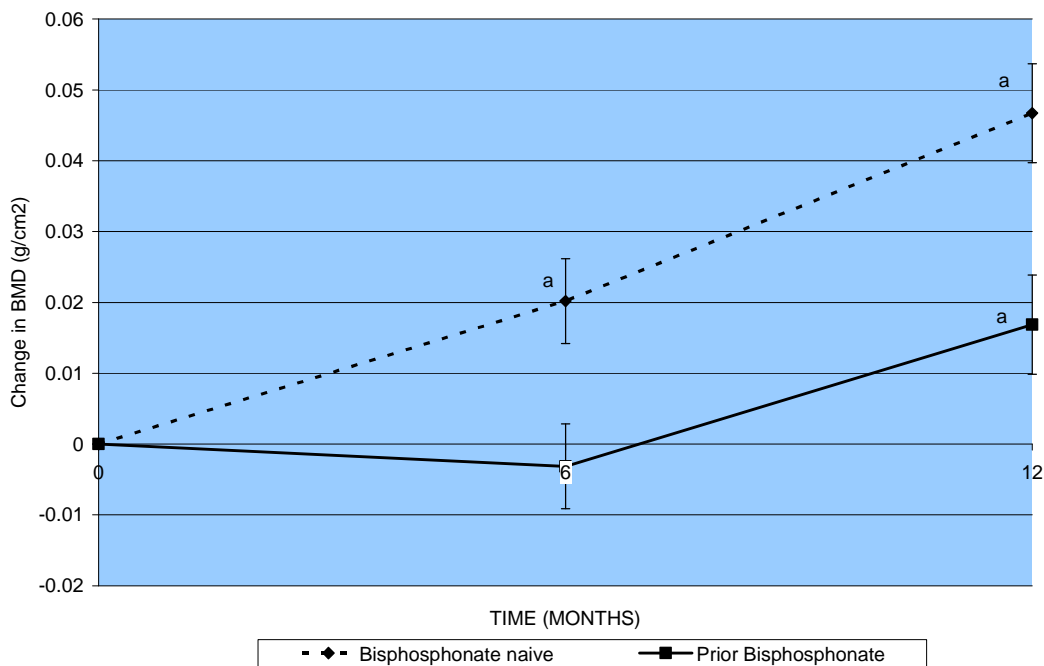
Over the 12 month period the mean level of compliance with strontium ranelate was 95.6% in the bisphosphonate naïve group and 95.0% in the prior bisphosphonate group.

Change in spine BMD with strontium ranelate.

After 6 months of therapy, BMD at the spine had increased by 0.020 g/cm<sup>2</sup> (2.4% increase, p=0.001) in the bisphosphonate naïve group while there was no change in BMD in the prior bisphosphonate group (-0.003 g/cm<sup>2</sup>, p=0.65). After 12 months, BMD at the spine had increased significantly by 0.047 g/cm<sup>2</sup> (5.6%, p<0.001) in the bisphosphonate naïve group and by 0.017 g/cm<sup>2</sup> (2.1%, p=0.002) in the prior bisphosphonate group. These changes are demonstrated in figure 7.1. The increase in BMD was significantly greater in the bisphosphonate naïve group than in the prior bisphosphonate group at both 6 months (difference 0.023 g/cm<sup>2</sup>, p=0.005) and 12 months (difference 0.030 g/cm<sup>2</sup>, p=0.003). After adjusting for the baseline differences in age and BMD, the

bisphosphonate naïve group maintained a greater gain in spine BMD at both 6 (difference 0.028 g/cm<sup>2</sup>, p=0.002) and 12 months (difference 0.036 g/cm<sup>2</sup>, p=0.001). In contrast to the lack of change in BMD in the prior bisphosphonate group during the first 6 months of the study, between months 6 and 12 there was a similar gain in BMD at the spine in each group (0.027 vs. 0.020 g/cm<sup>2</sup>, p=0.40).

Figure 7.1) Mean ( $\pm$  standard error) change from baseline in BMD at the lumbar spine after 6 and 12 months treatment with strontium ranelate in bisphosphonate naïve women and in women with prior bisphosphonate exposure.

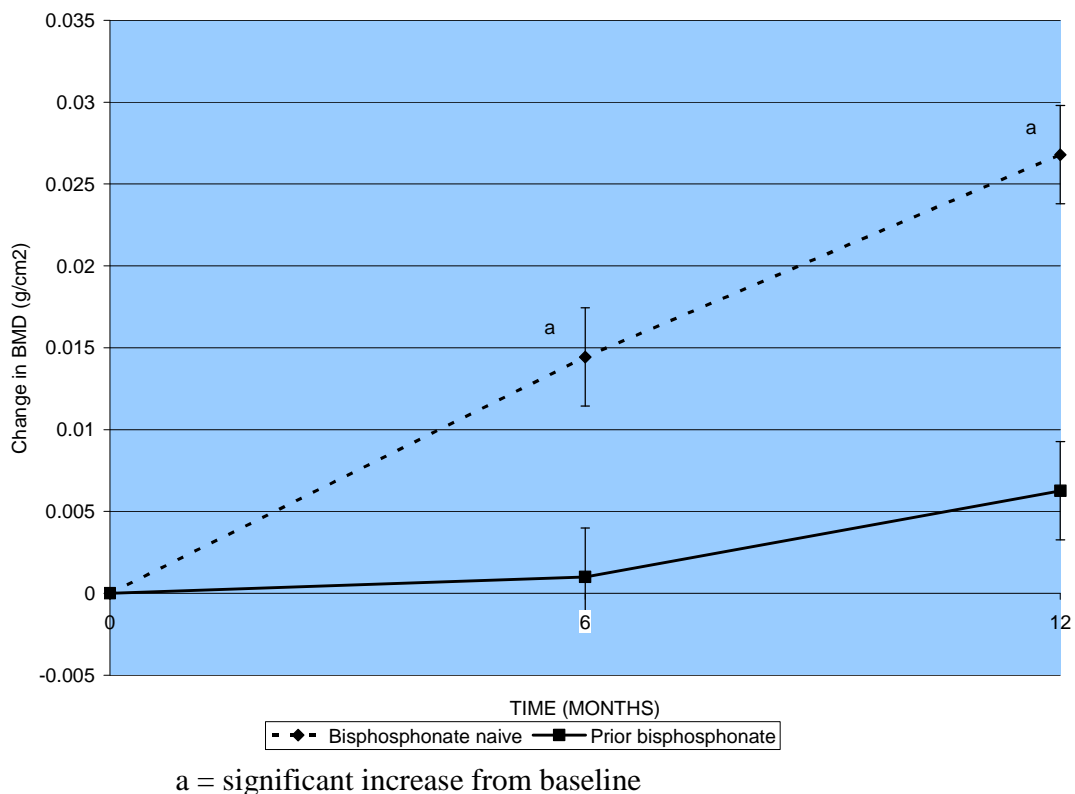


a = significant increase from baseline.

### Change in total hip BMD with strontium ranelate.

In the bisphosphonate naïve group total hip BMD had increased by 0.014 g/cm<sup>2</sup> (1.9%, increase, p<0.001) at 6 months and by 0.027 g/cm<sup>2</sup> (3.4% increase, p<0.001) at 12 months. In the prior bisphosphonate group there was no significant change in total hip BMD during the 12 months (0.006 g/cm<sup>2</sup> (0.8%) increase, p=0.096). These changes are demonstrated in Figure 7.2. The increase in total hip BMD was significantly greater in the bisphosphonate naïve group at 6 months (difference 0.013 g/cm<sup>2</sup>, p<0.001) and 12 months (difference 0.021 g/cm<sup>2</sup>, p<0.001). After adjusting for the baseline differences in age and BMD, the difference in total hip BMD between the 2 groups remained significant at both 6 (difference 0.014 g/cm<sup>2</sup>, p<0.001) and 12 months (difference 0.020 g/cm<sup>2</sup>, p<0.001).

Figure 7.2) Mean ( $\pm$  standard error) change from baseline in BMD at the total hip after 6 and 12 months treatment with strontium ranelate in bisphosphonate naïve women and in women with prior bisphosphonate exposure.

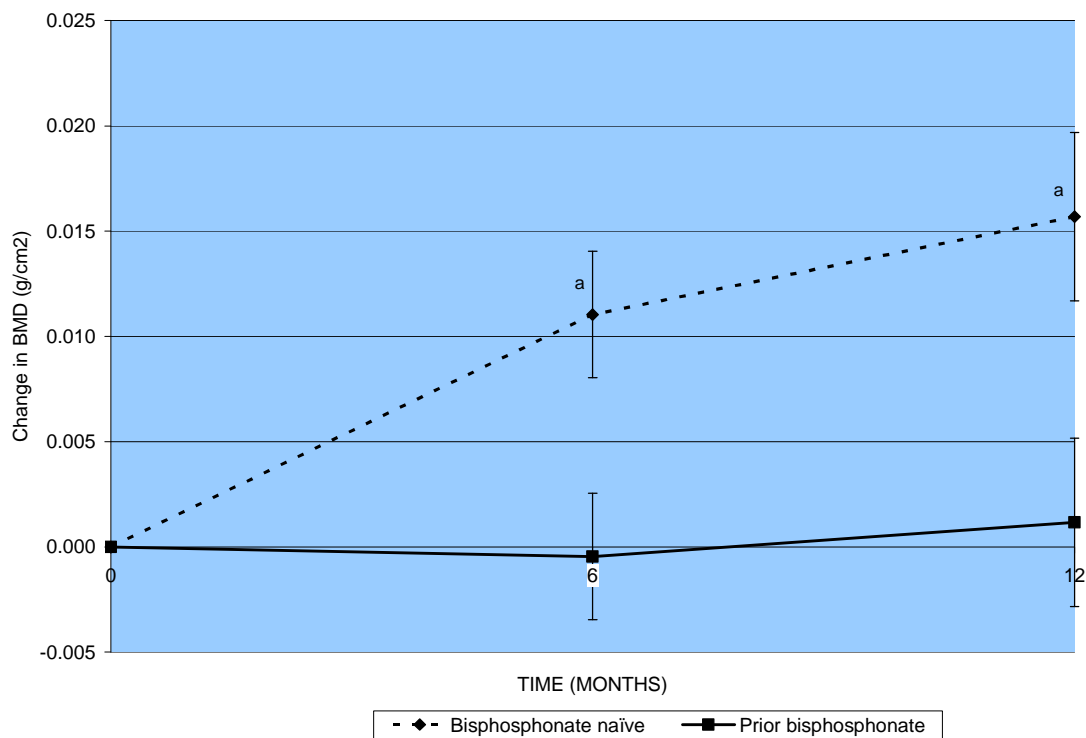


Change in heel BMD with strontium ranelate.

In the bisphosphonate naïve group, heel BMD had increased by 0.011 g/cm<sup>2</sup> (2.9%, p=0.002) after 6 months and 0.016 g/cm<sup>2</sup> (4.0%, p<0.001) after 12 months. In the prior bisphosphonate group there was no change in heel BMD over the 12 months (0.001 g/cm<sup>2</sup> (0.3%) increase, p=0.93). These changes are demonstrated in Figure 7.3. The increase in BMD was significantly greater in the bisphosphonate naïve group at 6 months (difference 0.011 g/cm<sup>2</sup>, p=0.013) and 12 months (difference 0.015 g/cm<sup>2</sup>, p=0.012).

After adjusting for the baseline differences in age and BMD, the bisphosphonate naïve group maintained a greater gain in heel BMD at both 6 (difference 0.013 g/cm<sup>2</sup>, p=0.006) and 12 months (difference 0.015 g/cm<sup>2</sup>, p=0.010).

Figure 7.3). Mean ( $\pm$  standard error) change from baseline in BMD at the heel after 6 and 12 months treatment with strontium ranelate in bisphosphonate naïve women and in women with prior bisphosphonate exposure.



a = significant increase from baseline.

Change in bone turnover markers with strontium ranelate.

At baseline all bone markers were significantly lower in the prior bisphosphonate group consistent with recent antiresorptive therapy. In the prior bisphosphonate group, 12

months after switching to strontium ranelate there was a significant increase of 55.1%, 61.0% and 46.3% in P1NP, CTX and BSAP respectively. There was no longer a significant difference in bone turnover markers between the 2 groups by 3 months for BSAP and 6 months for P1NP and CTX. However, with CTX the difference between the 2 groups remained borderline at 12 months compared to P1NP and BSAP where the difference was negligible. The change in bone markers at each visit is provided in table 7.3.

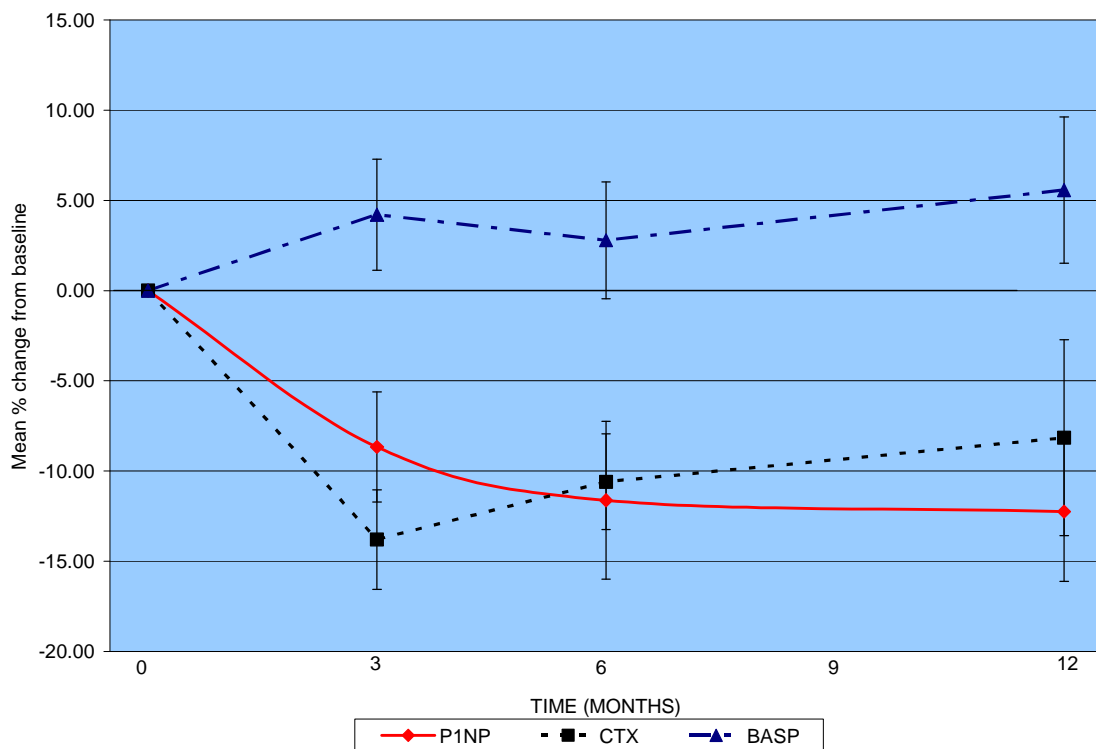
Table 7.3: Changes in CTX, P1NP and BSAP in response to strontium ranelate in women with and without prior bisphosphonate exposure.

		Month				12 month change p value
		0	3	6	12	
CTX (ug/l)	Prior BP	0.18	0.26	0.29	0.29	<0.001
	BP naïve	0.38	0.32	0.34	0.35	0.004
Between group p value		<0.001	0.016	0.069	0.046	
P1NP (ug/l)	Prior BP	29.64	38.00	41.54	45.98	<0.001
	BP naïve	54.42	49.70	48.09	47.75	0.011
Between group p value		<0.001	0.001	0.065	0.603	
BSAP (U/l)	Prior BP	17.52	21.06	23.86	25.64	<0.001
	BP naïve	23.16	24.14	23.81	24.45	0.498
Between group p value		<0.001	0.055	0.976	0.465	

BP = Bisphosphonate

In the bisphosphonate naïve group, after 12 months of treatment with strontium ranelate there was a significant decrease of 8.1% in CTX and 12.2% in P1NP (Figure 7.4). There was an increase of 5.6% in BSAP although this was not significant.

Figure 7.4. Mean ( $\pm$  standard error) percentage change from baseline in P1NP, CTX and BSAP in response to strontium ranelate in treatment naïve women.



Fracture incidence during therapy with strontium ranelate.

During the year there were significantly more women who suffered an incident vertebral fracture in the prior bisphosphonate group (2 vs. 8 women,  $p=0.047$ ). During the study 1 woman suffered a wrist fracture in the bisphosphonate naïve group while 4 women

reported non-vertebral fractures in the prior bisphosphonate group (2 rib fractures, wrist and humerus). All fractures were confirmed on x-ray or VFA with the exception of rib fractures. Fracture incidence is summarised in table 7.4.

Table 7.4. Fractures occurring during 12 months treatment with strontium ranelate.

	Number of women suffering a fracture		p value
	Bisphosphonate naïve	Prior Bisphosphonate	
<b>Any fracture</b>	3	12	0.014
<b>Vertebral fractures</b>	2	8	0.047
<b>Non-vertebral fractures</b>	1	4	0.194

Adverse events and subject withdrawal from the study.

There were a total of 6 serious adverse events during the study (4 prior bisphosphonate, 2 bisphosphonate naïve) none of which were felt to be likely to be related to the study medication or lead to withdrawal from the study. For analysis adverse events were divided into gastrointestinal (GI) (predominantly nausea, altered bowel habit and bloating), central nervous system (CNS) (predominantly headache and lethargy), musculoskeletal (arthralgia or leg cramps) and skin (itching or rashes). Only adverse events considered by the investigators to be probably or definitely related to the study medication were counted. Of the 12 women who withdrew from the study prior to visit 3 the reasons for withdrawal were GI (n=4), CNS (n=3), musculoskeletal (n=3), skin (n=1) and one woman requested to change back to weekly therapy with bisphosphonates. Of the



108 women in the study population the numbers of reported adverse events were: GI 26 (24.1%), CNS 3 (2.8%), musculoskeletal 1 (0.9%) and skin 1 (0.9%). The majority of these (23/31, 74.1%) occurred in the first 3 months and settled without withdrawing medication. The 3 women who withdrew from the study population between months 6 and 12 did so because of lost contact (n=1), disliked the taste of strontium ranelate (n=1) and dyspepsia (n=1).

### **Discussion.**

This is the first study to investigate the BMD response to switching osteoporosis therapy from a bisphosphonate to strontium ranelate. In this study the bisphosphonate naive group achieved increases in BMD at the spine and hip, which are comparable to those seen in the phase 3 SOTI study (Meunier et al 2004). However, the prior bisphosphonate group had significant blunting of the BMD response to strontium ranelate at all 3 sites studied confirming our hypothesis. More than 50% of the BMD response to strontium ranelate is thought to be due to the attenuation artefact caused by strontium's high atomic mass (Blake et al 2007). Therefore a large proportion of the blunting of the BMD response to strontium is likely to reflect poor strontium uptake into the bone. This is likely to occur because the bisphosphonate induced suppression of bone turnover reduces the formation of new bone, which is the site at which strontium is predominantly deposited (Boivin et al 2006, Boivin et al 2007). Also, if strontium ranelate does have anabolic properties, then part of the blunting of the BMD response may also be due to reduced gains in bone mass as discussed in chapters 2.2 and 6. Reassuringly the bone

turnover markers all increased significantly after bisphosphonate discontinuation, reflecting increased bone turnover, and by 6 months all bone markers were similar in the 2 groups. This suggests that the blunting of the response to strontium is likely to be temporary. This is supported by the observation that the increase in BMD achieved at the spine during the second 6 months of the study was the same in both groups.

In contrast to the spine, those women with prior bisphosphonate exposure had no increase in total hip or heel BMD over the 12 months of the study. Therefore the blunting of the BMD response appears to be more persistent at the heel and hip than the spine. The hip is predominantly cortical bone, which is less metabolically active than trabecular bone (Nobel and Reeve 2000). As such bone turnover may take longer to recover after bisphosphonate therapy resulting in a more prolonged blunting of the BMD response to strontium ranelate. Furthermore, the preferential incorporation of strontium into new bone, compared to old bone, is greater in cortical than trabecular bone. This has been demonstrated in monkeys with the strontium content in new cortical bone being 3-4 times greater than that of old cortical bone while the new trabecular bone only contained 2.5 times more strontium (Boivin et al 1996). Therefore reduced new bone formation may cause a greater impedance of strontium uptake at cortical sites than trabecular sites.

The heel, like the spine, is predominantly comprised of trabecular bone. In contrast to the spine, in those women with prior bisphosphonate exposure there was no increase in heel BMD throughout the whole year. The more persistent bisphosphonate induced blunting of the BMD response at the heel may reflect the fact that the heel is a site of yellow

(fatty) bone marrow while the spine has greater red bone marrow content (Liney et al 2007). Red bone marrow is the source of both osteoclasts and osteoblasts as well as a variety of cytokines including macrophage colony-stimulating factor and receptor activator of nuclear factor KB ligand which influence osteoclast differentiation (Rosen and Bouxsein 2006). Therefore, the relative lack of these cells and cytokines in the yellow marrow of the heel may lead to more prolonged suppression of bone turnover after bisphosphonate discontinuation which may account for the longer lasting blunting of the BMD response to strontium ranelate.

The clinical consequences of this blunting of the BMD response by prior bisphosphonate therapy are uncertain as it is difficult to assess whether this has any effect on the ability of strontium ranelate to reduce fracture incidence. Theoretically, if strontium uptake into the skeleton is reduced then it is plausible that this will reduce the effect of strontium on bone strength. However, it is also likely that prior bisphosphonate therapy will have a period of residual effect on fracture risk (Black et al 2006) which may provide protection from fractures while the strontium has time to overcome the blunting effect. While there were significantly more fractures in those women with prior bisphosphonate exposure, it is important to remember that this was not a randomised trial. The prior bisphosphonate group were older and had a lower spine BMD at baseline suggesting that they had a greater risk of fracture, which may account for the observed differences in fracture incidence.

The blunting of the BMD response to strontium ranelate may have other consequences for clinical practice. Firstly, in treatment naïve women, strontium ranelate causes a large increase in BMD making it possible to detect a treatment response as early as 1 year after the initiation of therapy. However, the 2.1% increase in BMD at 1 year observed in the prior bisphosphonate group is less than the most optimistic estimate of least significant change for spine BMD (Delmas 2000). Therefore in clinical practice it may be necessary to allow a greater time period before performing a follow up DXA scan to assess a woman's treatment response to strontium ranelate if there is a history of recent bisphosphonate use. Secondly, if bisphosphonates inhibit the response to strontium ranelate then it may be appropriate to consider strontium ranelate as a first line treatment, especially in patients likely to tolerate strontium ranelate better than bisphosphonates, such as women with coexisting gastrointestinal disease or other medication associated with dyspepsia, and in women over 80 in whom strontium has very good evidence for fracture reduction (Seeman et al 2006). Conversely, if a woman is intolerant of generic alendronate, the first line bisphosphonate recommended by NICE, after more than 12 months on treatment then it may be prudent to try a better tolerated bisphosphonate or an intravenous bisphosphonate before switching to strontium ranelate. Whether bisphosphonate exposure for less than 12 months results in blunting of the BMD response to strontium ranelate is uncertain as such women were excluded from our study.

This study also uses bone markers to provide insight into the changes in bone turnover in each group of patients. CTX and BSAP were measured as these markers allow comparison of our results with the SOTI study (Meunier et al 2004). P1NP was measured

as it is potentially a better marker of bone formation, as it is derived directly from type I collagen synthesis and has the lowest degree of analytical and biological variability (Seibel 2005). Unsurprisingly, in the prior bisphosphonate group all 3 bone turnover markers were significantly suppressed at baseline and increased progressively throughout the study. This is consistent with the increase in bone turnover, which has been observed after the withdrawal of bisphosphonate therapy (Bone et al 2004, Black et al 2006). In the bisphosphonate naïve group the change in CTX and BSAP were comparable to the findings of the SOTI study, which reported an increase in BSAP and a reduction in CTX (Meunier et al 2004). In our study similar divergent changes in these markers were observed. The 5.6% increase in BSAP was not significant in our study but is of a similar magnitude as the 8.1% increase reported in the SOTI study. The reduction observed in CTX was also somewhat smaller in our study (8.1% vs. 12.2%) but was still significant. Using these markers our study supports the theory that strontium ranelate is a “dual action bone agonist”.

The change in P1NP in the bisphosphonate naïve group is unexpected and interesting. Like BSAP it is a marker of bone formation however, in contrast to BSAP, P1NP reduced progressively throughout the study with a significant 12.2% reduction after 12 months. Previous studies with antiresorptives and anabolic agents demonstrate that changes in BSAP and P1NP usually mirror each other (Chen et al 2005, Black et al 2007). BSAP is produced by osteoblasts and is a measure of osteoblast activity and number (Seibel 2005). The increase in serum BSAP is consistent with reports that strontium ranelate increases osteoblast proliferation and differentiation and increases osteoblast expression of alkaline

phosphatase (Bonnelye et al 2007). P1NP is a direct quantitative measure of type 1 collagen synthesis (Seibel 2005). The reduction in P1NP in the face of increased BSAP suggests that collagen synthesis is not actually increased despite the increased osteoblast activity. In fact the P1NP response is similar to the CTX response. This would be more consistent with a mild antiresorptive effect leading to a reduction in bone turnover with reduced collagen breakdown and synthesis. This is somewhat at odds with the histomorphometry data, which suggests that there is an increase in bone formation parameters as well as evidence of increased osteoblast proliferation and differentiation (Marie et al 1993, Buehler et al 2001, Arlot et al 2005). Furthermore, in-vitro studies suggest that strontium increases collagen synthesis (Canalis et al 1996), which would be expected to increase P1NP. Further studies of the effect of strontium ranelate on P1NP are required but if our findings are confirmed then this suggests that strontium cannot have an overall anabolic effect as bone cannot be formed without increased type 1 collagen synthesis. Instead strontium ranelate's effects on bone strength may arise from a mild antiresorptive effect coupled with an added effect on the crystalline structure of bone.

There are limitations to this study. This was not a randomised study as women were allocated into one of the 2 groups according to their prior bisphosphonate use. The lack of randomisation did result in baseline differences in age and BMD. However, adjustment for differences at baseline had no effect on the results and otherwise the 2 groups were well matched. Another limitation was that different bisphosphonates, predominantly alendronate and risedronate, were used immediately prior to enrolment in the study.

Alendronate suppresses bone turnover for several years after discontinuation (Bone et al 2004, Black et al 2006) whereas with risedronate bone turnover normalises within one year (Watts et al 2004). This difference in off-set time may mean that women with prior alendronate use may experience greater blunting than those with risedronate. As this study assesses the first year after discontinuation, the effects of this should be minimised as even bisphosphonates with a rapid offset of action are still likely to cause blunting for a large proportion of the first year. Furthermore, data with teriparatide suggests that the BMD response to teriparatide is the same after risedronate and alendronate (Boonen et al 2006b). Finally, for ethical reasons, the majority of women in the prior bisphosphonate group were switched to strontium ranelate on the basis of a poor clinical response to therapy. As such there may have been selection bias leading to the recruitment of women into the prior bisphosphonate group who, for some reason, were more resistant to treatment which could explain the smaller gains in BMD observed. While this cannot be ruled out, the baseline bone markers do demonstrate that the bisphosphonates were successfully suppressing bone turnover prior to the study, suggesting a therapeutic effect and compliance with treatment. Also against this is the observed increase in spine BMD during the second 6 months of the study. Furthermore causes for a poor treatment response, such as malabsorption and conditions affecting bone metabolism, were excluded at baseline and the compliance with strontium ranelate was the same in each group.

In conclusion, this study demonstrates that after the discontinuation of bisphosphonates and switching to strontium ranelate there remains a significant suppression of bone

turnover for 3-6 months. This is associated with a blunting of the BMD response to strontium ranelate for 6 months at the spine and for longer at the hip and heel. The clinical consequences of this in terms of fracture are uncertain but it does imply that after switching from bisphosphonates to strontium ranelate a greater time period should be allowed before performing a follow up DXA to assess the treatment response. It may also be prudent to switch women with intolerance of alendronate to an alternative antiresorptive or bisphosphonate and to consider strontium ranelate as a first line treatment in certain groups of women. Finally, this study casts some doubt on the claims that strontium ranelate may have anabolic properties due to the observed reductions in P1NP.



**Chapter 8:**  
**The safety and efficacy of vertebroplasty**  
**using Cortoss cement.**

## **Introduction.**

Vertebral fractures are a significant consequence of osteoporosis, as well as trauma and malignancy, and are associated with a substantial degree of morbidity (Nevitt et al 2000, Cauley et al 2000). Chapter 4 demonstrates that there is a high prevalence of vertebral fractures in our local population. After an acute fracture pain often eases with time but not uncommonly patients are left with persistent pain (Matthis et al 1998, Bianchi et al 2005). Increasingly vertebroplasty is being performed as a means of treating persistently painful vertebral fractures, or lesions which are refractory to analgesia. In large case series (see table 2.4.1) this relatively minimally invasive procedure has proven to be very successful at rapidly relieving pain with a low complication rate.

To date the majority of studies assessing vertebroplasty use PMMA cement. Recently, a bis-GMA resin has been developed as an alternative cement (Cortoss™, Orthovita, PA, USA). Cortoss has several potential advantages over PMMA, which are discussed in chapter 2.4. Yet, despite these advantages, PMMA is more widely used and there is little in the current literature regarding the clinical outcomes of Cortoss vertebroplasty. In this study we aim to assess the safety and efficacy of vertebroplasty using Cortoss cement.

## **Method.**

Patients with vertebral fractures or other painful vertebral lesions were reviewed in either the osteoporosis or neurosurgical outpatient's clinic. A full medical assessment was

performed including measurement of BMD (Lunar Prodigy, GE Lunar, Madison, WI) and screening for other causes of metabolic bone disease. Patients were considered potentially eligible for vertebroplasty if their symptoms were consistent with the site of the fracture/lesion and either they had pain despite analgesia or they were unable to take adequate analgesia due to adverse effects. All potentially eligible patients underwent a STIR sequence MRI of their spine to assess the age of the vertebral fracture/lesion and the local anatomy.

The MRI results and case history were subsequently discussed at a multidisciplinary team (MDT) meeting between bone physicians, neurosurgeons and the musculoskeletal radiologist. Patients were confirmed as eligible for vertebroplasty if the MRI demonstrated bone oedema, suggesting acute or ongoing changes, in a vertebral fracture/lesion which was consistent with the site of their pain (Figure 8.1). The only absolute contraindication to vertebroplasty was an inability to tolerate the procedure, usually due to respiratory disease.

After written consent, all vertebroplasties were performed with the patient in the prone position by the same radiologist using c-arm fluoroscopy guidance. Local anaesthetic and mild sedation with fentanyl and midazolam was used in all cases. An 11 gauge needle was placed via a unipedicular approach into the affected vertebral body and Cortoss cement was injected (Figure 8.2). Patients were given antibiotic prophylaxis and observed overnight as an inpatient. A plain x-ray was performed post procedure to check

the position of the Cortoss cement (Figure 8.3). The patients were subsequently followed up in the outpatient clinic.

Figure 8.1): Sagittal STIR MRI demonstrating bone oedema (arrow) at the superior endplate of T12 prior to vertebroplasty.



All patient details were recorded on a database, which was updated on a regular basis using the patient's medical records. The data collected included medical history, indication for procedure, details of the procedure, complications and pre and post procedure analgesic requirements. The data collection and analysis was performed as part of a service review at our centre and therefore ethic approval was not required although permission was obtained from the local audit committee.

Figure 8.2): Injection of Cortoss into the vertebral body of T12 via a left unipedicular approach.

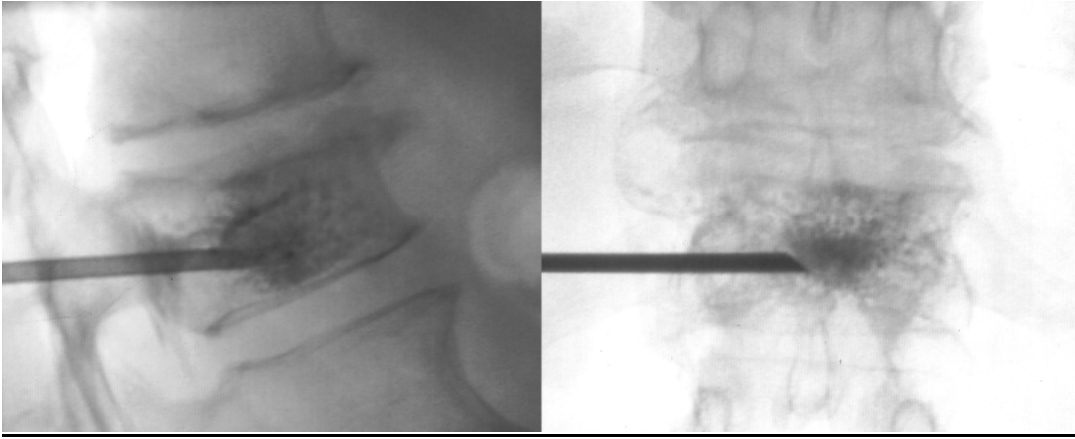
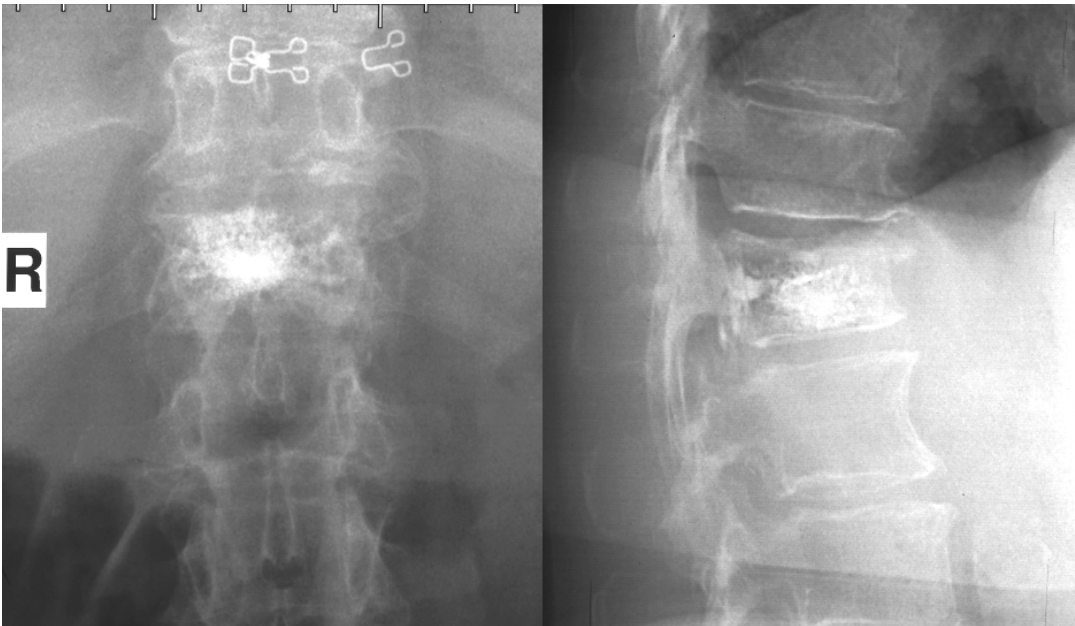


Figure 8.3): Plain X-Ray of T12 post vertebroplasty demonstrating Cortoss distribution.



## Results.

112 patients were discussed at the MDT as possible candidates for vertebroplasty. Of those discussed, 34 (30%) patients had consistent MRI and clinical findings leading to a vertebroplasty being performed on a total of 42 vertebrae. 22 patients were female and 12 male. The mean (sd) age at vertebroplasty was 66.7 (11.2). Patient demographics are summarised in table 8.1. The mean age of the vertebral fracture/lesion was 21.4 months however all lesions had ongoing symptoms and an MRI demonstrating bone oedema within a mean of 4.8 months. All procedures used Cortoss injected by a unipedicular approach (73.5% via left pedicle). A mean (sd) of 2.2ml (0.4) of Cortoss was injected into each vertebra. A total of 5 patients had multiple vertebrae treated during the same session: 2 patients had 2 vertebral levels treated and 3 patients had 3 levels treated.

Table 8.1: Patient demographics, n=34.

<b>Spine BMD, g/cm<sup>2</sup></b>	
Mean (SD)	0.933 (0.215)
Mean T score	-2.2
<b>Total vertebral lesions, n (%)</b>	
Median (range)	2.5 (1-12)
<b>Lesions vertebroplastied, n (%)</b>	
Median (range)	1 (1-3)
<b>Duration of lesion, months</b>	
Overall: Mean (SD)	21.4 (23.5)
Since MRI: Mean (SD)	4.8 (4.7)
<b>Cause of lesion, n (%)</b>	
Osteoporosis	25 (73.5)
Malignancy	5 (14.7)
Trauma	3 (8.8)
Haemangioma	1 (2.9)
<b>Pre-treatment analgesia, n (%)</b>	
None documented	1 (2.9)
Single analgesia	4 (11.8)
Multiple analgesia	29 (85.2)
Strong Opioid	11 (32.4)

### Efficacy of vertebroplasty.

Patients were followed for a mean (sd) duration of 9.5 (4.9) months. In 1 (2.9%) case the effect of vertebroplasty on their back pain was not recorded in the medical records. Of the 33 patients with outcome data, 27 (81.8%) patients reported an overall improvement in symptoms following the vertebroplasty. Of these patients, 5 (15.2%) later reported a reoccurrence of their pain to some degree. 1 (3.0%) patient had a transient worsening of their back pain before it improved. There was no improvement in 5 (15.2%) patients. Only 1 (3.0%) patient reported an overall worsening of their pain although this patient had an asymmetrical distribution of the cement within the vertebral body and is currently awaiting a repeat procedure. Of the 34 patients, 27 (79.4%) required less analgesia post procedure while 7 (20.6%) had the same analgesic requirements.

### Safety of vertebroplasty.

Twenty (58.8%) patients had no complications due to the procedure. In 13 (38.2%) patients there was leakage of Cortoss, 11 extraosseous and 2 static venous leaks. In all cases Cortoss leakage was asymptomatic. There were 4 (11.8%) significant complications. During one procedure venous embolisation of cement was noted on fluoroscopy and a subsequent CT pulmonary angiogram confirmed a pulmonary embolus but there were no associated clinical features or decline in lung function. One (2.9%) patient developed a generalised rash, which settled with chlorphenamine and hydrocortisone. One (2.9%) patient developed a transient radicular leg pain although no

nerve root compression due to Cortoss was demonstrated on CT. Finally, one year after a vertebroplasty, one patient (2.9%) with malignancy suffered further metastatic spinal disease resulting in retropulsion of the Cortoss cement requiring surgical intervention.

### **Discussion.**

To our knowledge, this is only the second report in the literature regarding the outcomes of Cortoss vertebroplasty and the first report of its use in the clinical setting. Cortoss vertebroplasty is effective in reducing pain from a variety of spinal lesions. In this patient series subjective pain reduction was achieved in 82% of patients. Overall, 79% of patients required less analgesia post vertebroplasty. Furthermore the complication rate in our study was low with 88.2% of patients suffering no significant complications.

Palussiere et al (2005) reported on a prospective study using Cortoss. The 53 patients in this study were similar to our study population in terms of age, sex and indications for vertebroplasty although slightly fewer patients were on strong opiate analgesia in our study (32% vs. 41%). In our study a smaller mean volume of Cortoss was used (2.2ml vs. 4.3ml). In contrast to the present study, 60% of the vertebroplasties performed by Palussiere et al (2005) were under general anaesthesia leading directly to the death of one patient and, possibly contributing to, pneumonia in a second. In both studies the commonest complication was leakage of Cortoss although the frequency in our study was lower (38% vs. 76%), possibly related to our use of smaller volumes of Cortoss. In both studies the vast majority of cement leakage was asymptomatic and serious complications



due to Cortoss leakage were uncommon - 1 asymptomatic PE (our study) and 1 soft tissue leakage (Palussiere et al). Other complications were varied and infrequent in either study and occurred in only 2-3% of cases. Palussiere et al also reported significant benefits in terms of pain relief and reductions in analgesic use although Palussiere et al were able to use validated efficacy measures as the vertebroplasties were performed as part of a clinical trial.

Studies using validated efficacy measures confirm that PMMA vertebroplasty reduces pain, reduces disability and improves quality of life as assessed by the visual analogue scale, Barthel index and the SF-36 questionnaire. These measures permit actual quantification of the degree of improvement following a vertebroplasty. Studies which only include osteoporotic vertebral fractures report that 90-100% of patients achieve an improvement in back pain after a PMMA vertebroplasty (Kobayashi et al 2005, Pitton et al 2007). However in those studies which, like our study, included a variety of vertebral lesions, 76-86% of patients reported reductions in pain after a PMMA vertebroplasty (Martin et al 1999, Barr et al 2000, Anselmetti et al 2007). The efficacy of vertebroplasty with Cortoss cement seems comparable with these studies, as 82% of our patients reported an improvement in their pain. The lack of a validated efficacy measure is a limitation of our study however 79% of our patients reduced their analgesic requirements providing further evidence of symptomatic benefit in these patients. This is again comparable to reports from PMMA vertebroplasty in which 71-90% of patients had a reduction in their analgesic requirements (Afzal et al 2007, Diamond et al 2006, Jensen et al 1997).

Asymptomatic Cortoss leakage was noted in 38% of patients in our study. Comparison with the literature from PMMA vertebroplasty is hindered by many studies not reporting asymptomatic leakage rates. Studies using CT scans report that asymptomatic cement leakage is very common occurring in 55-76% of cases (Pitton et al 2007, Kobayashi et al 2005). Studies which, like our study, describe the rates of asymptomatic cement leakage detected by fluoroscopy at the time of vertebroplasty or on a subsequent x-ray report lower asymptomatic leakage rates of 3-50% (Yu et al 2008, Afzal et al 2007). This wide range of leakage rates may in part reflect differing degrees of radiopacity of the different types of PMMA used. The 38% leakage rate with Cortoss in our study does seem to fall within the range reported for PMMA. Palussiere et al (2005) reported a 76% asymptomatic leakage rate for Cortoss which is greater than most PMMA studies. This may be related to the high degree of radiopacity of Cortoss combined with leakage being specifically looked for on fluoroscopy as part of the study design. Other possible reasons for a high rate of cement leakage with Cortoss may be due to differences in viscosity and setting time although it is difficult to assess this without a head-to-head comparative study.

Although a 38% leakage rate is high this is an acceptable complication rate for the procedure due to the absence of any associated morbidity or mortality. However, it is important that Cortoss vertebroplasty has a low incidence of serious complications. In our study there were only a few clinically significant complications of Cortoss vertebroplasty, which is consistent with the reports of PMMA vertebroplasty. A cement pulmonary

embolus is a potentially life threatening complication which has been reported in 0% (Anselmetti et al 2007), 4% (Grados et al 2000) and 7% (Jensen et al 1997) of PMMA vertebroplasties which is comparable to the 2.9% incidence observed in the present study. In our study 1 patient (2.9%) experienced transient nerve root pain which has been reported in 1% (Evans et al 2003), 3.9% (Anselmetti et al 2007) and 8% (Grados et al 2000) of PMMA vertebroplasties. Grados et al (2000) also reported a 4% incidence of a transient increase in back pain, which is again similar to the 3.0% incidence observed in the present study.

Our vertebroplasty service is newly established and the results in this paper are derived from the first 34 patients treated. Prior to the vertebroplasty service the radiologist had limited experience at vertebroplasty. Therefore our results may underestimate the benefits and exaggerate the complication rates, which occur from Cortoss vertebroplasty as the radiologist's technique could improve with increasing experience leading to better clinical outcomes with time. There was no evidence of a secular trend in the benefits and complication rate in this study although this may be due to the short time period and the small number of vertebroplasties studied. Our results however can be expected to represent the results achievable when a vertebroplasty service is first established and may be a conservative estimate of the potential benefit to risk ratio of the procedure.

There are limitations to this study. This study is retrospective and therefore is dependent on the information documented in the medical records. Our results are compared to the published literature rather than a direct comparison with PMMA vertebroplasty. This

would require a head to head comparative study and as yet no such study has been reported. The size of the study population is comparable to many other reports regarding the outcomes of vertebroplasty, however a larger study would better identify the incidence of the less common adverse events (e.g. PE). Finally this study lacks an objective measure of quantifying pain such as a visual analogue scale. This is because we report the outcomes of a clinical vertebroplasty service rather than a specifically designed clinical trial although we do provide results from the “real life” clinical setting.

Vertebroplasty is not a panacea for all patients with back pain but in patients with active vertebral fractures or lesions vertebroplasty provides an effective means of reducing back pain with an acceptable complication rate. Cortoss cement has several potential advantages over PMMA and in the clinical setting the outcomes of vertebroplasty using Cortoss are comparable to those published for PMMA.

**Chapter 9:**

**Thesis conclusion and discussion.**

## **Chapter 9.1:**

### **Summary of conclusions.**

1): Routine VFA screening detects vertebral fractures in 20% of women attending for DXA, the majority of these will have osteopenia and as such the presence of a fracture may directly effect their treatment.

2) Targeted VFA screening greatly reduce the number of women undergoing VFA however only around 10% of women with vertebral fractures are detected.

3): A short course of HRT during the early postmenopausal period has a prolonged benefit in terms of BMD compared to no treatment and may reduce the incidence of fractures even after discontinuation.

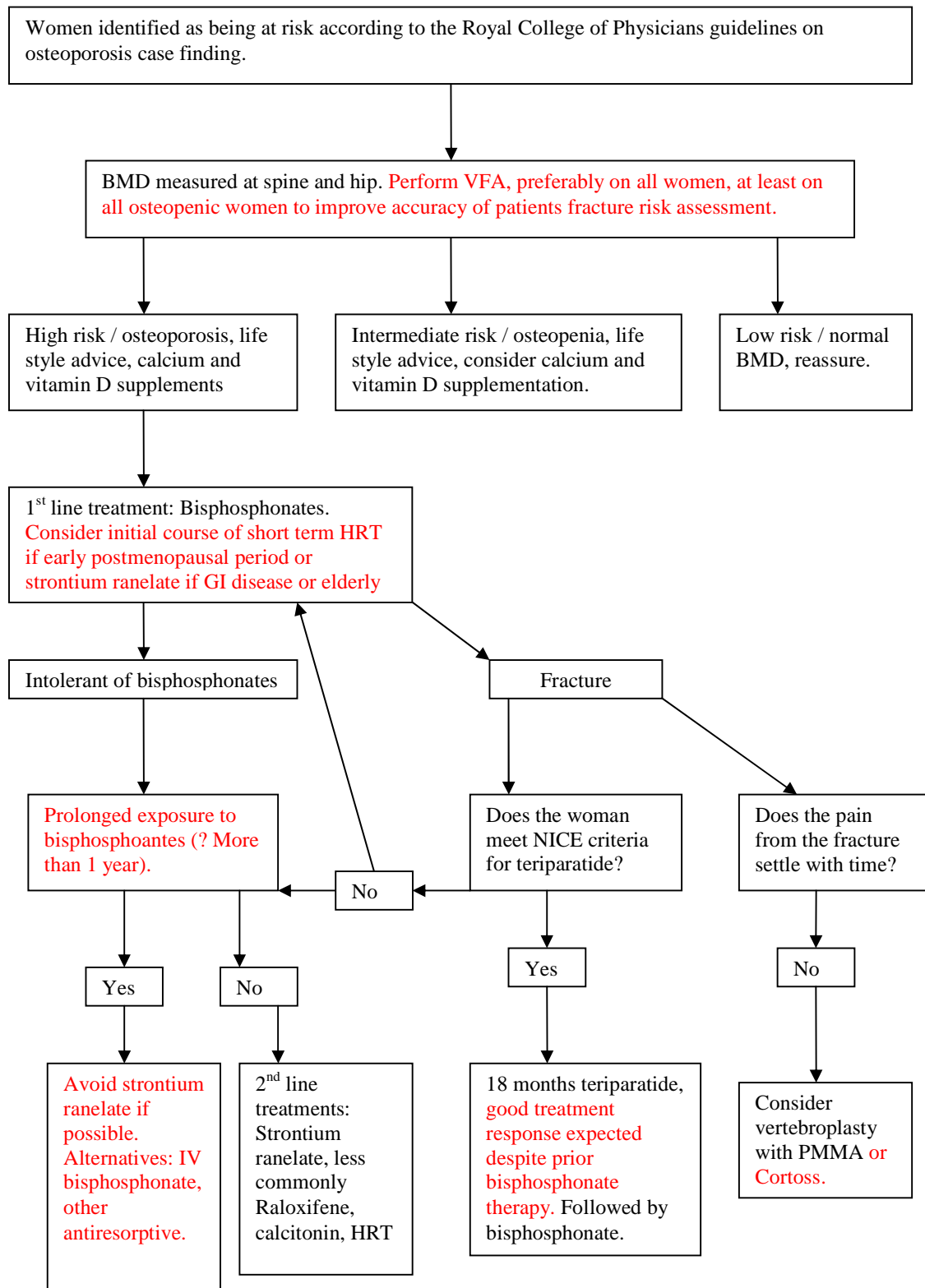
4): Prior bisphosphonate use reduces, but does not prevent, the increase in P1NP in response to teriparatide however this does not result in blunting of the BMD response.

5): The BMD response to strontium ranelate is blunted by prior bisphosphonate use for the first 6 months of therapy at the spine and for at least 12 months at the hip and heel.

6): The P1NP response to strontium ranelate suggests that collagen synthesis is reduced which contradicts evidence supporting its potential anabolic properties.

7): Vertebroplasty using Cortoss cement provides an effective means of reducing pain from painful vertebral fractures with a low complication rate and the results are comparable to the literature for PMMA vertebroplasty.

**Summary, changes to the treatment of osteoporosis suggested by this thesis (in red).**



## **Chapter 9.2:**

### **Discussion of findings.**

This thesis studies several different aspects of osteoporosis management. The early disease period is studied in chapters 4 and 5. Chapter 4 examines the potential for routine VFA to effect the initial decision regarding the need for bone protective treatment. Chapter 5 investigates one of the treatment options available to postmenopausal women in their 50's for whom treatment decisions can be complicated. Chapters 6 and 7 study women with osteoporosis who are on bisphosphonates, the current first line treatment for osteoporosis, and require a change in therapy. These chapters investigate the interactions between different types of osteoporosis treatments and the clinical effects of switching between therapies, an area which is poorly studied. Finally, chapter 8 studies vertebroplasty, which is one of the treatment options for women who suffer a vertebral fracture as a result of their osteoporosis.

One of the most important decisions to make regarding the treatment of osteoporosis is whether or not to initiate treatment. To withhold treatment will allow the age related decline in BMD to continue and may leave the women at a high risk of fracture. However, initiating treatment too freely may result in many women who do not have a high fracture risk being treated. This would expose many women to the potential side effects of bisphosphonate therapy for little gain and would have important cost implications for a health system with finite resources. The key to determining the initial treatment decision is to estimate each individual woman's fracture risk and only treating



those women with a fracture risk, which is deemed to be high. This approach has been adopted by the WHO, which has recently produced a fracture risk calculator (FRAX) ([www.shef.ac.uk/FRAX/tool.jsp](http://www.shef.ac.uk/FRAX/tool.jsp)).

FRAX is designed to estimate an individual's 10 year risk of suffering a hip or other major osteoporotic fracture (clinical spine, forearm or proximal humerus) based on clinical risk factors with or without BMD. The clinical risk factors used by FRAX have been determined to increase fracture risk independent of BMD by meta-analyses of 9 prospective population-based cohorts with a total follow-up of over 250,000 person years (Kanis et al 2008). The risk factors used by FRAX are prior fragility fracture, parental history of hip fracture, current smoking, ever use of long term steroids, alcohol ( $\geq 3$  units/day) and rheumatoid arthritis. BMI is also entered into FRAX although BMD is optional. This provides an overall estimation of an individual's 10 year risk of fracture however the optimum "cut off" level of risk above which treatment should be initiated has not yet been determined.

Vertebral fractures are the commonest osteoporotic fracture however two thirds of women with vertebral fractures are reported to be unaware of them (Melton et al 1993). In chapter 4 the proportion of women with vertebral fractures who were unaware of their presence was even higher at 77%. In these women with undiagnosed vertebral fractures there will be an underestimation of their fracture risk when using FRAX which may consequently lead to treatment being withheld inappropriately. In this thesis I demonstrated that routine VFA screening detects vertebral fractures in 20% of women

screened suggesting that routine VFA will improve fracture risk assessment in up to 1 in 5 women. Furthermore, almost half of all women with vertebral fractures in chapter 4 had 2 or more fractures detected. This knowledge is also important as FRAX states that “fracture probability is underestimated with multiple fractures” so fracture risk assessment should be adjusted to take account of the number of vertebral fractures. Overall routine VFA screening is likely to improve the accuracy of fracture risk assessment by FRAX.

Although routine VFA screening is very much the ideal scenario for risk assessment it has significant implications in terms of DXA scanner resources and not all DXA units will have the capacity to perform VFA routinely. In this situation it will be important to target certain groups of patients to undergo a VFA. However, I also demonstrated that simply targeting women with reasons to suspect a fracture fails to detect 90% of women who have a fracture suggesting that this is not an effective means of targeting VFA. In chapter 4 I discussed the implications of using BMD category to target VFA screening however there are other potential methods of targeting VFA. One option may be to target all women with no prior history of fracture as the detection of an unknown vertebral fracture in these women would increase their fracture risk. Alternatively, it may be beneficial to perform the axial DXA, calculate the fracture risk using FRAX and then target VFA at women who are below but approaching the treatment threshold. Finally it may be possible to use clinical risk factors to determine the probability of a vertebral fracture being detected by VFA and then targeting screening at women above a certain

level of probability. Defining which groups of women should undergo VFA screening is a research area, which requires further work.

One consequence of FRAX is that women in their 50s are unlikely to reach the treatment threshold as increasing age is a major determinant of fracture risk. However, despite a low 10 year fracture risk, a women aged 50 with a T score compatible with osteoporosis has a high life time risk of fracture as, with time, there is a substantial increase in fracture risk due to increasing age and declining BMD. There is also logic to using antiresorptives early while there is bone to prevent being resorbed rather than waiting until there has been a significant decline in bone mass and microarchitecture. Finally withholding treatment from women with perceived “brittle bones” may cause significant anxiety and distress. In clinical practice drug treatments need to be cost effective. As such it may be that a lower treatment threshold can be used for drugs such as generic alendronate and HRT which are considerably cheaper than branded osteoporosis therapies. Interestingly a recent cost effectiveness analysis of generic alendronate demonstrated that it was cost effective (<£20,000/QALY gained) to treat women in their 50s with osteoporosis, even if they had not yet suffered an osteoporotic fracture, despite their low 10 year fracture risk (Kanis et al 2008b).

HRT may still be one of the first line treatment options for those women in the early postmenopausal period who either want or need treatment for their bones. In this age group HRT will not only preserve BMD but it will also relieve menopausal symptoms. It may also delay the initiation of bisphosphonates which may be important in this age

group given the potential concerns regarding long term bisphosphonate therapy discussed in chapter 5. Since the WHI study it is recommended that HRT is only prescribed as a short term therapy. In line with this recommendation, in this thesis, I have demonstrated that even a short period of HRT can have lasting benefits in terms of BMD. Furthermore both my study and Bagger et al (2004) suggest that short term HRT may produce long term benefits in terms of fracture reduction. Therefore, if the treatment threshold for bisphosphonates is set at a level of risk, which denies treatment to most osteoporotic women in their early 50s, then short term HRT may provide an alternative treatment option. This may enable the preservation of BMD and protection from fracture while age, and therefore fracture risk, increases to a level at which bisphosphonates may be used. However, this is an area which requires further research as the recently published WHI follow up study suggests that the HRT benefits in terms of fracture reduction are rapidly lost when HRT is discontinued (Heiss et al 2008). The reason for these contrasting results is uncertain but may reflect the difference between delaying the menopause with early HRT use and inducing an artificial period of increased hormone levels in an already postmenopausal women followed by a second “menopause” when these are withdrawn.

Chapter 5 also demonstrated that with long term HRT BMD continues to increase over a 9 year period which is consistent with the findings from the WHI study. HRT does offer effective bone protection, however the future of long term HRT as a treatment option for osteoporosis depends on its other health effects. The WHI study has cast serious doubts on the health benefits of long term HRT however, as discussed in chapter 2.1.1, the WHI study has certain limitations and as such it is not necessarily the end of HRT. Oestrogen

only HRT may reduce the incidence of breast cancer and there is evidence to support the timing hypothesis which predicts that oestrogen started at the menopause provides long term protection from cardiac events. Furthermore, transdermal oestrogen may not cause the increased risk of venous thrombosis observed with oral therapy (Scarabin et al 2003). Therefore, for osteoporotic women in their early 50s, transdermal oestrogen only HRT may have overall health benefits and reduce menopausal symptoms making it potentially first line treatment. For women with an intact uterus progestogen must also be administered to prevent an increase in endometrial cancer. While the WHI study demonstrated that systemic progestogen is associated with an increased risk of breast cancer and cardiac events this could be negated by the use of topical progestogen in the form of the Mirena coil. Further research is clearly needed on HRT and we await with interest for the results of the KEEPS study which is investigating the cardiovascular effects of starting low dose HRT within 3 years of the menopause (Harman 2006).

My thesis also studies the clinical effects of switching between osteoporosis therapies. Bisphosphonates are currently regarded as first line therapy although women may subsequently switch to other classes of therapy due to side effects or a poor clinical response. Bisphosphonates have a profound affect on bone turnover, which persists after discontinuation. When therapy is switched, the persistent action of bisphosphonates may interfere with the subsequent response to a different class of treatment. However this area of management is poorly studied. To my knowledge there are no such studies with fracture as the primary endpoint as such a study would require thousands of women and would be very expensive. Fracture prevention studies are usually funded by

pharmaceutical companies who have little to gain, and perhaps a lot to lose, by investigating whether their already licensed therapy interacts negatively with other osteoporosis therapies. As such most switching studies, including the 2 studies in this thesis, rely on surrogate markers such as BMD and BTMs. While such surrogate markers are a poor substitute for actual fracture data, they at least provide evidence regarding whether the treatment is having the expected results on bone tissue.

Chapter 6 investigates the effects of switching from bisphosphonates to teriparatide. This is an important area of study for countries like the UK where, due to the NICE guidelines, teriparatide can only be prescribed to women who have already been treated with bisphosphonates. Using teriparatide in this way is outside the evidence base for fracture reduction as in the teriparatide fracture prevention trial the vast majority of women were treatment naive (Neer et al 2001). Chapter 6 demonstrated that prior bisphosphonate users had a lower baseline P1NP and a smaller increase in P1NP. However, reassuringly there was still a 4 fold increase in P1NP in response to teriparatide and the BMD response was the same as both the bisphosphonate naïve group and the published literature. These findings contrasted with the study by Ettinger et al (2004), which was the only similar study available at the time chapter 6 was published. Since then data from the large multicentred Eurofors study has been published which also demonstrates a large increase in BMD at both spine (7.8%) and hip (1.6%) in response to 18 months teriparatide despite prior antiresorptive therapy (Boonen et al 2008). These BMD changes are double those reported by Ettinger et al (2004) suggesting that if the BMD response is blunted by prior bisphosphonates then the effect is small. Boonen et al (2008) also

reported that the response to teriparatide is equivalent in prior users of risedronate and alendronate, which accounted for 79% of the women in my study. Prior didronel users, 8% of my study population, achieved a better BMD response to teriparatide in the Eurofors study which may explain the slightly better BMD response in prior bisphosphonate users reported in this thesis. Overall, in chapter 6 and the Eurofors study there was a good BMD response despite prior antiresorptive therapy. This suggests that bisphosphonates can be used first line, as stated by NICE, with teriparatide, the more expensive treatment, reserved for those patients who suffer a further fragility fracture despite bisphosphonates.

In a similar vein, chapter 7 investigates the effect of prior bisphosphonate use on the subsequent response to strontium ranelate. In contrast to the teriparatide study, chapter 7 demonstrated significant blunting of the BMD response to strontium ranelate at the spine, during the first 6 months, and at the hip and heel throughout the whole year of the study.

So why might prior bisphosphonate use blunt the BMD response to strontium ranelate but not teriparatide? The answer may be due to the different effect that these 2 drugs have on the rate of bone turnover. Both teriparatide and strontium ranelate are thought to induce a positive balance at the level of the BMU leading to an increase in bone mass. However the overall rate at which bone mass is gained is governed by the rate of bone turnover. Teriparatide actually increases bone turnover and will therefore quickly reverse the bisphosphonate induced suppression of bone turnover causing bone mass to be gained rapidly. On the other hand, strontium ranelate has no effect on the rate of bone turnover

(Arlot et al 2005). Therefore, if bone turnover is suppressed by prior bisphosphonate use then any gain in bone mass will occur at a slower rate. Secondly, the persistent suppression of bone turnover, due to the inability of strontium ranelate to increase bone turnover, will reduce the amount of new bone available for strontium uptake, which accounts for a large proportion of the BMD response to strontium ranelate.

When treating a woman for osteoporosis care is required when deciding whether or not to switch her from a bisphosphonate to a different treatment. The type of subsequent therapy to be used is very important. Prior bisphosphonate therapy is unlikely to have a major detrimental effect on subsequent therapy with an alternative antiresorptive or bisphosphonate as the overall effect on bone turnover is similar. This thesis also demonstrates that switching from a bisphosphonate to teriparatide is effective with a significant increase in BMD. However, not all women who are considered for a change in therapy will fulfil the NICE criteria for teriparatide. In these women one must be cautious when considering whether or not to switch them to strontium ranelate. The effect of switching to strontium ranelate on the risk of fracture is not known. However, the risk of a poor response to strontium ranelate, during the first year at least, must be considered and until more information is available it may be better to switch to an alternative bisphosphonate rather than strontium ranelate. Conversely, as discussed in chapter 7, if blunting is going to occur then it may also be prudent to use strontium ranelate first line in certain groups of women.



Finally, this thesis investigates vertebroplasty as a treatment option for women who suffer a painful vertebral fracture. Chapter 8 adds to a large body of evidence demonstrating that vertebroplasty effectively reduces pain due to vertebral fractures with a low complication rate. The role of vertebroplasty in the treatment of osteoporosis is still not entirely clear. The procedure is highly effective at relieving pain and reducing hospital stay when performed acutely however Diamond et al (2006) demonstrated that, compared to conservative therapy, the benefits were marginal at 6 weeks and non-existent at 6 months. This is because the majority of vertebral fractures become non-painful with time. Of more benefit maybe the reduction in pain achieved when vertebroplasty is performed on fractures, which remain painful despite several months of conservative treatment as was the case in chapter 8. However, all studies of vertebroplasty for chronically painful vertebra, including chapter 8, are uncontrolled and therefore the benefit reported relies on the assumption that the vertebra would remain painful if left untreated. A randomised controlled trial comparing vertebroplasty to local anaesthetic injection for the treatment of fractures which have failed to settle conservatively (INVEST trial), is currently underway and hopefully will confirm the benefits of vertebroplasty (Gray et al 2007). Finally, chapter 8 is almost unique in the type of cement used for the vertebroplasty. Although Cortoss has been demonstrated to have potential advantages in-vitro whether or not this translates in to additional clinical benefit needs further investigation, preferably with a head to head comparison to PMMA.

To conclude, osteoporosis and the resulting fragility fractures have significant consequences for both postmenopausal women and society as a whole. Fortunately, in

recent years there have been many advances in the field of osteoporosis leading to an increase in the number of treatments available. While modern treatments are all proven to reduce fractures in treatment naïve women their place in the overall treatment of women with osteoporosis is less well studied. This thesis provides further insight into areas such as improving fracture risk assessment in order to guide treatment initiation, initial treatment options, the effects of switching between treatments and finally the treatment of painful vertebral fractures.

### **Future research:**

Although my MD is now complete I plan to continue my osteoporosis research. All women in the strontium study completed the first year in July 2008 and a final report has been submitted for publication. The strontium study has also been extended for a second year in order to see if the women with prior bisphosphonate use begin to experience an increase in BMD or even “catch up” with the bisphosphonate naïve group. The second year will complete in July 2009. I also have a study underway assessing the effects of strontium ranelate on heel ultrasound although the results will not be ready in time for this thesis. Finally using the large database of women who underwent routine VFA I have recently derived an algorithm, which uses simple clinical risk factors to give a probability score for a vertebral fracture being present on VFA. The use of this probability score to target which women should be selected for VFA screening is soon to be published in *Calcified Tissue International*.

## **Appendix: Publications and presentations.**

### **Full articles and papers:**

- 1): The effects of short-term hormone replacement therapy on long-term bone mineral density. *Climacteric*. 2007 Jun;10(3):257-63.
- 2): The effect of prior bisphosphonate exposure on the treatment response to teriparatide in clinical practice. *Calcif Tissue Int*. 2007 Nov;81(5):335-40.
- 3): The effect of short-term and low dose hormone replacement therapy on long term bone mineral density. *RAD Magazine*. Jan 2008;34(392):19.
- 4): The safety and efficacy of vertebroplasty using Cortoss cement in a newly established vertebroplasty service. *Br J Neurosurg*. 2008 Apr;22(2):252-6.
- 5): Routine versus targeted vertebral fracture assessment for the detection of vertebral fractures. *Osteoporos Int*. 2008 Aug;19(8):1167-73.

### **Poster presentations and abstracts:**

- 1): The implications of the NICE osteoporosis guidelines for women aged 60-70.  
Presented: British Society for Rheumatology, 2006.  
Abstract: *Rheumatology* 2006;45;suppl1;i89;194.
- 3): Vertebral compression fracture, an unusual presentation of Hodgkin's lymphoma.  
Presented: British Society for Rheumatology, 2006.  
Abstract: *Rheumatology* 2006;45;suppl1;i147;373.
- 4): Short term Hormone Replacement Therapy results in long term gains in BMD. †  
Presented: European Calcified Tissue Society, 2006.  
Abstract: *Calcif Tissue Int*:2006;78;suppl1;s147;p422.
- 6): Is serum PTH or vitamin D or both required to assess calcium homeostasis?\*
- Presented: National Osteoporosis Society, 2006  
Abstract: *Osteoporosis internation*:2006;17;suppl3;p132.
- 7): The effect of prior bisphosphonate therapy on the early treatment response to Teriparatide in clinical practice. †  
Presented: European Calcified Tissue Society, 2007.  
*Calcif Tissue Int*:2007;80;suppl1;p380-T;s138.

8): Bisphosphonate exposure prior to Teriparatide for osteoporosis: Does it matter in clinical practice?.

Presented: British Society for Rheumatology, 2007.

Abstract: Rheumatology 2007:46;supp1;i129;335.

9): The safety and efficacy of vertebroplasty using Cortoss cement in a newly established vertebroplasty service. †

Presented: British Society for Rheumatology, 2007.

Abstract: Rheumatology 2007:46;supp1;i132;349.

10): The routine use of lateral vertebral assessment for vertebral fracture detection is more effective than opportunistic screening. † \*

Presented: National Osteoporosis Society, 2007

Abstract: Osteoporosis international 2007:18 (supp3):s74

11): The effect of Strontium Ranelate on heel BMD and ultrasound.

Accepted for presentation: British Society for Rheumatology 2008 and European Calcified Tissue Society 2008

12): The effect of prior bisphosphonate exposure on the treatment response to Strontium Ranelate.

Accepted for presentation: British Society for Rheumatology 2008 and European Calcified Tissue Society 2008

† = Presented at more than one meeting, only first presentation referenced.

\* = nominated for prize.

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