

**METABOLIC BONE DISEASE
AND
ARTHROPLASTY LOOSENING**



Doctorate of Medicine Thesis

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PREFACE

Joint degeneration requiring arthroplasty surgery and the consequences of osteoporosis are the two fundamental pathologies in orthopaedics. There are around 44,000 Medline-indexed journals about osteoporosis, and around 30,000 concerned with arthroplasty. However despite both typically occurring in a similar elderly population, only 350 (less than 0.5%) are cross-indexed.

Aseptic loosening is the commonest cause of hip arthroplasty failure, with revision surgery being the only current treatment. Recent work has increased the understanding of the aetiology of aseptic loosening and studies suggest that this process may be inhibited by the use of drugs that are normally used to treat osteoporosis, such as the bisphosphonates. It has also been shown that the occult incidence of metabolic bone disease may be as high as 40% in patients undergoing primary hip arthroplasty.

This study is a progression of similar work on the aetiology and control of aseptic loosening done in the same department over the proceeding few years. In the first instance a cellular model of aseptic loosening was investigated by Ong and Taylor [published in 2003]. This laboratory based project used mouse bone, and exposing it to interface membrane tissue sampled at the time of revision arthroplasty surgery. This model was described by Reynolds and Dingle in 1970, and shown to activate osteoclasts. Ong and Taylor demonstrated that osteoclast activation could be inhibited with doxycycline, suggesting that matrix metalloproteinases may be important in the pathophysiology of aseptic loosening, and that the process is potentially preventable.

The work was progressed further by Ibrahim and Taylor [2004] who developed a live model of particle induced osteolysis. They measured radio-labelled calcium uptake in mouse femora following implantation of ceramic particles, sham surgery and in controls. This was shown to be a useful model of quantifying osteolysis, although they did not find a difference between the controls and those exposed to ceramic particles.

The original aim of this work was to follow on from the previous work and demonstrate that osteolysis could be inhibited or reversed using pharmacological agents. Ideally this would be done in a human clinical model, and a number of drugs were considered, including doxycycline, bisphosphonates and statins. Such a project would have involved recruiting patients to a clinical trial, followed by either randomisation to treatment or control groups before commencing treatment on participants. The ideal end-point would be revision for aseptic loosening (although radiological development of loosening would be an alternative). Because hip arthroplasty is such a successful operation these end-points are both rare and often not seen for many years. Even if we assume a rather optimistic reduction in loosening of 50% using our agent, we would have to recruit several hundred participants and wait at least 10 years to get meaningful results.

We therefore have had to sacrifice some of the principles of strong research in favour of a project that could be completed with a limited time-frame and a limited budget. We studied patients that had already had an arthroplasty in situ for a number of years, and in view of the multi-factorial nature of loosening (as discussed below), limited this to one type of arthroplasty. The hypothesis of this study is that patients who have an underlying disorder of bone metabolism (such as osteoporosis or vitamin D deficiency) are more likely to develop aseptic loosening. In addition we hypothesise that there are measurable clinical, radiographic and biochemical markers that help predict those likely to develop loosening.

This hypothesis was investigated in 127 patients (78 patients with a loose cemented total hip replacement matched by age, gender, race, prosthesis and time from surgery with 49 patients with a well-fixed stable hip replacement)/ We then conducted four connected studies involving, clinical, radiological, DEXA and biochemical assessment for markers of loosening.

The aims are detailed below, but were principally to see whether patients with loosening are more likely to markers of osteoporosis or poor bone health. Unfortunately, this study takes us no further forward with regard to whether aseptic loosening can be inhibited by specific therapeutic agents, but hopefully it helps us to better understand the pathophysiological processes involved with arthroplasty failure. These can be used in future research to help improve arthroplasty function and longevity.

AIMS

Because the structure of this thesis corresponds closely to its aims, they are listed here at the start. For each of the stated aims, a relevant literature review is discussed in the Introduction, followed by the methodology of assessing each aim, before the results are given and discussed. The study is split into four sections – a clinical, radiological, bone density and biochemical study – each to investigate for bone fragility in patients with either a loose or a stable arthroplasty. The structure of the thesis is coordinated with its aims, so that the introduction, methods, results and discussion of each of the four studies are broken down to be in the same order of the following aims.

A: Do clinical risk factors for osteoporosis predict loosening?

1. Match a cohort of patients with loosening to similar patients with stable implants
2. Do patients with loosening have clinical risk factors for osteoporosis?
3. Is pain is a good screening tool for aseptic loosening, and does it correlated with the degree of loosening?

B: Do pre-operative radiographic markers predict loosening?

1. Do femoral cortical measurements predict loosening?
2. Does the Singh Index predict loosening?
3. Does the classification of osteoarthritis predict loosening?

C: Do patients with loosening have a lower Bone Mineral Density?

1. Do patients with loosening have a lower BMD around their prosthesis?
2. Do patients with loosening have a lower BMD in the wrist and spine?
3. Is there a correlation between BMD and function?
4. How well does the Cortex Ratio correlate to BMD?

D: Do biochemical markers predict loosening?

1. Are patients with loosening more likely to suffer from abnormalities in serum levels of
 - vitamin D and parathyroid hormone?
 - alkaline phosphatase, calcium or phosphate?

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BACKGROUND AND INTRODUCTION

1. BACKGROUND

BONE STRUCTURE

Bone consists of an organic matrix which is later mineralised by the inorganic ions to form functioning bone. Within the bone are the cells involved with its deposition, resorption and growth regulation.

Bone mineral

The mineral content is 70% of the dry weight of bone, consisting of mainly of the crystalline mineral salt, calcium hydroxyapatite ($\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$). The mineral component of bone provides resistance to high compressive forces acting on bone.

Bone matrix

The organic part of matrix makes up around a quarter of the weight of bone and is principally comprised of type I collagen. This is made intracellularly as tropocollagen and then exported to the site of matrix formation where it is arranged into fibrils. The structure of collagen gives bone its tensile strength and also provides an element of elasticity. Type 1 collagen makes up 85% of bone matrix, is a triple helix protein structure rich in hydroxyproline. Type 1 collagen is also found in skin and tendons, and so cannot be used as a specific marker of bone metabolism.

The strands of the collagen are connected by cross-links which join the amino (N) and carboxyl (C) terminal ends of the helix to lysine amino acids in the adjacent helix. The molecules that facilitate cross-linkage are known as pyridinolines and de-oxyypyridinolines and are specific to adult bone. Although not routinely used in clinical practice, the measurement of these molecules is commonly used in clinical trials to monitor response to osteoporosis treatment and may have a role in the detection of aseptic loosening. This is discussed further in chapter 6.

The remaining organic components of bone include proteins such as osteocalcin, osteonectin and osteopontin. Osteocalcin is a non-collagenous protein found in bone and dentin in teeth. It is secreted by osteoblasts and thought to play a role in mineralization and calcium ion homeostasis. It is also thought that osteocalcin may function as an inhibitor of bone formation, although its exact role is unknown. Osteonectin and osteopontin are glycoproteins involved in the alignment and binding of the mineral bone to the organic collagen matrix. Some of these compounds may also be measured as markers of bone turnover, and is discussed in chapter 6.

BONE CYTOLOGY

Osteoblasts and bone formation

Osteoblasts are the cells responsible for bone matrix formation and also play a role in its calcification. They are formed from bone marrow precursor stem cells, and are found in clusters of cuboid shaped cells along the bone surface. They produce uncalcified bone matrix (osteoid) which is later mineralised after a lag of around 10 days. The membrane of osteoblasts is rich in Alkaline Phosphatase, and this can be used as a serum marker of bone formation, as in this study. Osteoblasts also have receptors for parathyroid hormone and oestrogen.

Osteoclasts and bone resorption

The osteoclast is a bone lining cell responsible for bone resorption. Its precise progenitor is not fully identified, although it is known to be of the monocyte-macrophage family of haemopoietic cellular origin. It is a large multi-nucleated cell found within its own bone cavity (Howship's lacunae) created by the effect of its own bone resorption. The characteristic enzyme of osteoclasts is tartrate-resistant acid phosphatase (TRAP) and the process of bone resorption releases calcium, phosphate and hydroxyproline (a breakdown product of type 1 collagen) into the bloodstream. These can all be used to measure bone resorption.

Osteocytes

Osteocytes are small cells, which originally were the bone-forming osteoblasts that have become enshrined within the bone they have created. These cells are found in lacunae which have numerous processes which extend out to allow contact both with other osteocytes and the bone surface. These processes are formed before the calcification of bone matrix and form a network of thin canaliculi. The precise function and physiology of osteocytes is unknown, but they are thought to be involved in the transmission of mechanical loading forces to the periosteum and so play a role in bone turnover.

BONE ORGANISATION

Collagen is strong in distraction and hydroxyapatite is strong in compression, and the resulting bone is strong in both torsion and bending. Bone is structured to have a maximum strength : weight ratio, with an outer solid cortex whose main function is to resist torsion and bending forces, and an inner light web of trabecular bone, particularly at the expanded metaphysis.

This project is concerned mainly with the biomechanics of the proximal femur. This has to resist both compressive forces through its medial side and tensile, distractive forces along the lateral side where the abductor muscles act. The trabeculae are aligned to accommodate these regions of increased force to create distinct bands (Figure 1-1). The principle compressive group transmit across the hip from the acetabulum to the medial cortex of the femur, and the principle tensile group resist the deforming action of the femoral neck angle and abductor muscles. At right angles to the principle tensile group is a secondary compressive group whose function is to support the tensile group. These trabecular patterns form the basis of the Singh Index, the radiological measure of osteoporotic bone loss used in this study.

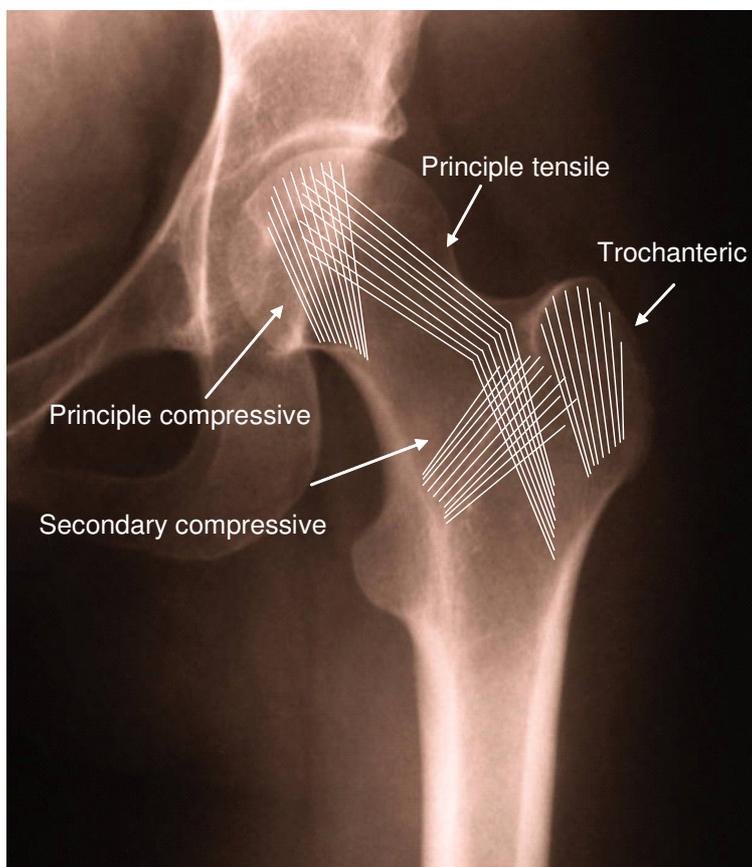


Figure 1-1. Trabecular bands of the proximal femur

ADAPTATION OF BONE TO STRESS

The development of trabeculae is dependent on a number of factors including genetic factors, exposure to oestrogen and mechanical loading, and some of these will be discussed later. The influence of mechanical forces on the development of trabeculae is the basis of Wolff’s law, which states that bone responds to magnitude and direction of load by remodelling the shape and thickness of the cortex and trabeculae (or more concisely as “form follows function”). These adaptations are clearly demonstrated after a fracture (Figure 1-2): initially a disorganised mass of low-strength Woven bone is rapidly put down, with randomly aligned fibres. With time, and as a result of the new forces passing through the bone, the woven bone is often replaced by lamellar bone. This type of bone has fibres aligned in parallel and is much stronger.

Just as bone remodels after a fracture, it also adapts to the changes in forces after a hip arthroplasty. The increased resistance to compressive and tensile forces of the biomaterials used in hip arthroplasty diminish the need for trabecular support. Forces are transmitted directly from the pelvis to the distal prosthesis, bypassing the proximal femur, thus causing a subsequent decrease in bone density in the proximal femur.

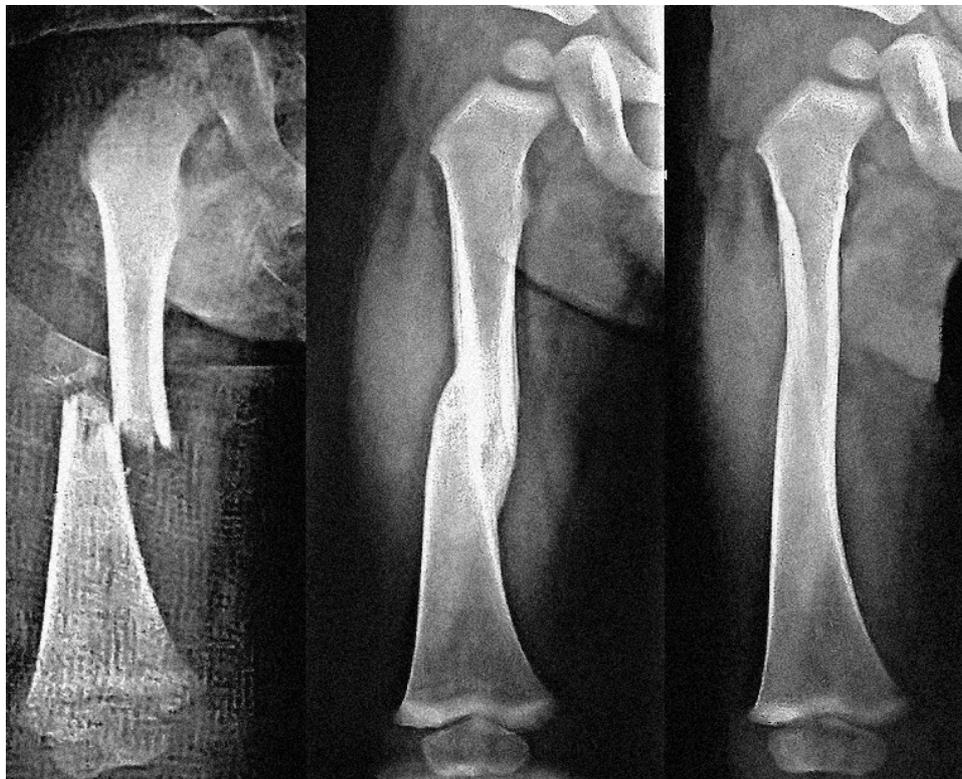


Figure 1-2. Serial x-rays demonstrating remodelling in a child after a femoral fracture

BONE REMODELLING

A change in stress on the axial skeleton creates an equilibrium between bone resorption and regeneration. This cyclical action initiates with osteoclast recruitment, followed by bone resorption (Figure 1-3). Next osteoclasts are inhibited and new bone is deposited. At any one time around 10% of the skeleton is undergoing active remodelling, with the rest of the skeleton in a quiescent phase. This process breaks down in processes such as hyperthyroidism or osteoporosis when the rate of resorption is greater than deposition and there is a net bone loss. Each cycle of remodelling takes around four to six months, of which around two weeks is resorption and the rest of the time being occupied by formation. Because of this prolonged time required to generate bone, processes that increase bone turnover tend to lead to bone loss. An exception to this is the accelerated bone turnover seen in puberty which is matched by accelerated bone formation.

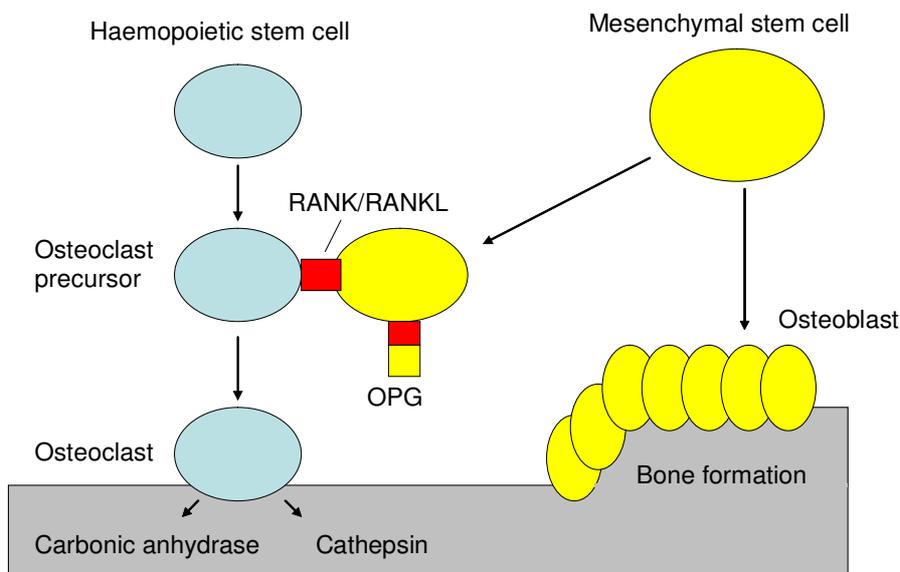


Figure 1-3. Regulation of bone remodelling

Bone remodelling is a complex process, requiring coordinated actions of osteoclasts and osteoblasts. The mechanisms involved are incompletely understood, however several local and systemic factors have been identified that may stimulate or inhibit remodelling. Increased osteoclast activity is seen in many osteopenic disorders including postmenopausal osteoporosis and arthroplasty aseptic loosening. Although many varied factors have been shown to influence bone growth and remodelling, the final common pathway appears to be through the RANK/RANKL/OPG pathway.

INITIATION OF RESORPTION

The remodelling cycle begins with the attraction of osteoclasts precursors (haematopoietic cells of monocyte/macrophage-origin) to the site of resorption. The precursors then differentiate into mature osteoclasts.

Some of the systemic stimulators of bone remodelling include calcitrophic hormones such as parathyroid hormone, PTH-related peptide and (1,25) vitamin D as well as growth hormone and thyroid hormone. Local stimulators include mechanical stimuli (which promote bone formation but inhibit resorption), interleukins 1 and 6, tumour necrosis factor, insulin-like growth factor, prostaglandins and macrophage colony stimulating factor. However, these factors have a wide range of action and none are essential to osteoclast differentiation and activity.

The important molecules appear to be:

- Transcription factor PU-1 is important in early differentiation of osteoclasts from haemopoietic stem cells
- Macrophage colony-stimulating factor (M-CSF), c-fos, nuclear factor kappa B (NFkB) are all important in the later stages of osteoclast maturation.
- Interaction between Receptor Activator of nuclear factor kappa B (RANK) on the early osteoclasts and its ligand on bone marrow stem cells (RANKL) is important for maturation of osteoclasts and their bone resorptive actions.

Interaction between RANKL and RANK activates osteoclasts [Burgess et al., 1999], mediated via intra-cellular biochemical pathways. A number of pathways have been identified that relay RANKL-RANK signals through osteoclasts, and key proteins are thought to be the tumour necrosis factor receptor associated factors (TRAFs), particularly TRAF 6 and c-Src [Wong et al.,1998]. The importance of these relay pathways is seen in the rare autosomal dominant condition familial expansile osteolysis. In this condition, it has been proposed that a defect in the RANK gene results in the RANK relay pathways being activated more easily, causing increased osteoclast activation. This causes focal areas of increased bone remodelling and the development of osteolytic lesions [Hughes et al., 2000].

BONE RESORPTION

Bone resorption is caused by activation of osteoclasts where it is in contact with bone, at the ruffled border. At the edge of the ruffled border is a sealing zone which is in close contact with the bone and thought to isolate the place of resorption. Lysozymes release acid and digestive enzymes: the acid dissolves hydroxyapatite crystals and optimises the pH for proteolytic enzymes to break down the protein matrix (Figure 1-4). These processes are dependent on a number of molecules:

- Carbonic Anhydrase II (CA-II) and a subunit for the proton pump on the osteoclasts membrane encoded by the gene TCIRG1 are necessary for hydrogen ion production
- Cathepsin K – a proteolytic enzyme that degrades the matrix

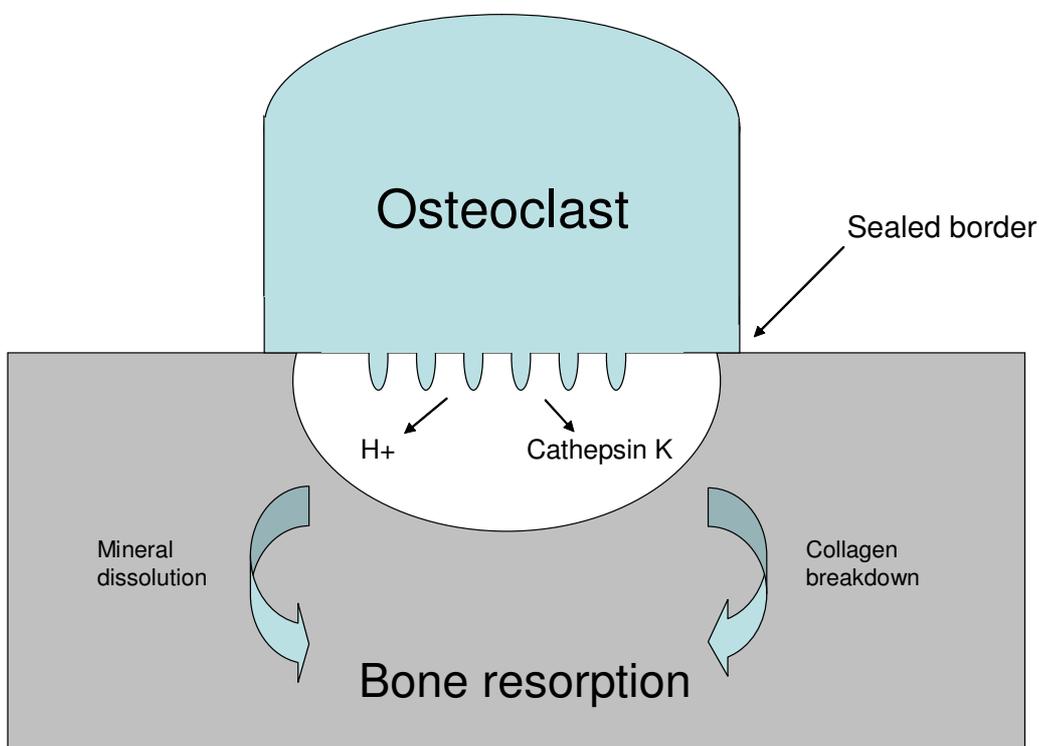


Figure 1-4. Osteoclast bone resorption

INHIBITION OF RESORPTION

Following resorption, osteoclasts undergo apoptosis and this heralds the start of bone formation. Bone remodelling is inhibited by systemic hormones such as oestrogens, androgens, progesterone and calcitonin. Locally acting inhibitors include OPG, interferon gamma, interleukins 4, 10, 13 and 18 and transforming growth factor beta.

The key molecule that inhibits bone resorption is osteoprotegerin (“the protector of bone”, OPG, Figure 1-5) which competitively binds for the RANK binding site with RANKL. This natural decoy prevents osteoclast activation, and so bone loss. Transgenic mice with elevated OPG levels suffer osteopetrosis [Simonet et al., 1997] with excessive bone formation, whereas those with OPG deficiency suffer severe osteoporosis and a high level of fractures [Bucay et al., 1998]. In humans, OPG therapy has been shown to prevent bone loss associated with postmenopausal osteoporosis and cancer metastasis.

It was also noted in this study that OPG deficient mice have a high level of arterial sclerosis, indicating that the OPG/RANKL/RANK pathway may be involved with systemic calcification. A clinical correlation to this has been noted in osteoporotic patients have been shown to have a higher incidence of vascular calcification and cerebral ischaemia accidents [Parhami and Demer, 1997; Jorgensen et al., 2001]. The role of OPG in postmenopausal osteoporosis is supported by studies showing that oestrogen stimulates OPG production (Hofbauer, 1999). Thus in postmenopausal conditions of low oestrogen, there is less of the protective effect of OPG; this could explain one of the mechanisms of bone loss and be a potential avenue for future therapeutics.

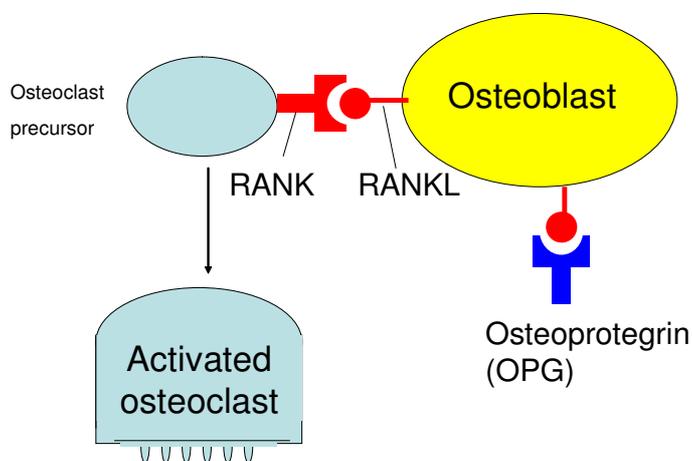


Figure 1-5. RANK/RANKL/OPG interaction

BONE FORMATION

Bone formation begins with the attraction of osteoblast precursors to the bone surface. These are derived from mesenchymal cells from the bone marrow that have the potential to differentiate into a wide range of cell lines. The fate of these stem cells depends on the expression of various molecules, and the key trigger for the genesis of osteoblasts is *cbfa1*.

Cbfa1 is a transcription factor that activates the coordinated expression of a number of genes resulting in the production of type 1 collagen, osteocalcin and alkaline phosphatase. The proteinaceous matrix becomes mineralised after a lag of around 10 days. Some osteoblasts become embedded within the new bone and become osteocytes, whereas others remain on the bone surface to become lining cells.

The other, non-specific stimulators of bone resorption are all mediated through the production of RANKL [Roodman, 1999], with factors such as vitamin D₃, prostaglandin E₂, IL1, IL11, TNF α and glucocorticoid steroids all inducing expression of the RANKL ligand on a number of cells including T cells and osteoblasts. They act on the RANKL receptor, RANK, which is found on a number of cells, including osteoclasts, causing their activation. The over-production of RANKL by T-cells in conditions such as autoimmune conditions, cancers and chronic viral conditions explains why these illnesses are associated with systemic bone loss [Kong et al., 1999].

Bone Morphogenic Proteins (BMP) are a group of cytokines that are known to influence bone (as well as a number of other tissues) growth and development. There are an increasing number of types, but the main ones (BMP 2 to 7), all belong to the transforming growth factor family of proteins. BMP 2 and 7 are thought to be particularly important to bone growth through their differentiation of osteoblasts. They are of particular importance in embryonic development, but recent interest has shown that recombinant DNA preparations may play a role in clinical practice. Clinical studies have shown that they can be used instead of traditional bone grafting techniques, with superior results for the treatment of tibial fracture non unions [Zimmermann et al., 2007].

ARTHROPLASTY

Hip arthroplasty remains one of the major medical breakthroughs of the last century. Its successes and failures have been extensively researched and helped the dynamic development of new techniques and materials. There is considerable variation in outcome of different types of hip arthroplasty [Halen et al. 2007], and for this reason it was important to match for this variable in this study. The final common pathway for arthroplasty failure is loosening of the components with resorption of the host bone.

The normal hip joint is subject to very high forces. Even in a simple single leg stance, it bears between 2 and 3 times the body weight, with this figure more than doubled during running. As well as compressive forces, running mainly along the medial femoral neck and shaft, large tensile forces and torsional forces are also transmitted. These forces are constantly changing in a cyclical manner during locomotion. Any hip prosthesis and its fixation to the host bone has to be strong enough to withstand such forces

The early attempts at joint resurfacing were first described by Smith-Peterson in 1923 using moulded glass as the articulating bearing, and later using Acrylic by Judet. These procedures had limited success, moderately reducing symptoms of pain in the short term, but with less satisfactory results when patients were followed up for longer. Common modes of failure included implant fracture, loosening and infection, and for these reasons arthroplasty was not widely performed.

Subsequently, much of the significant development work was initiated or done by John Charnley (pictured, right) in the late 1960's. He revolutionised and popularised the procedure by developing the concept of a low frictional torque arthroplasty, understanding the implications of surgically altering hip biomechanics, stabilising implant using polymethylmethacrylate cement (PMMA), developing new materials and designs, and realising the importance of operating room asepsis.

Although steady improvements have been made since then, many of his principles including that of having a low friction joint to reduce stress on the prosthesis fixation remain central to implant designs. Debate rages as to whether bone cement is required, and whether harder materials are more durable. Despite this, the use of a relatively small metal head articulating with a polyethylene cup remains the standard global technique.

ARTHROPLASTY SURVIVAL

Rates of implant loosening vary, but a review of multi-centre, non-specialist units have shown that 8.8% of hip replacements show signs of loosening 5 years after surgery [Fender et al., 1999]. Overall 8% of all hip replacements require revision for loosening, which is the cause of 70% of revisions of hip replacements [Herberts and Malchau, 2000]. If left untreated, extensive bone loss is seen, leaving the patient at risk of joint dislocation and peri-prosthetic fracture- both far more serious problems carrying the risk of permanent disability.

Arthroplasty loosening
Radiographic signs of arthroplasty loosening <ul style="list-style-type: none"> - 9% at 5 years - 29% at 20 years
Hip arthroplasty revision <ul style="list-style-type: none"> - 8% of all THR are revised due to loosening - 4% revised because of other causes

Box 1-1. Total hip arthroplasty loosening

The long-term outcome of Charnley total hip arthroplasties is also well documented. Wroblewski et al. [1999] reported 20 to 30 year survival rates of 320 Charnley hip arthroplasties. Clinical outcomes were very good with 94% being rated as "good" with regard to pain and function. However 29% had evidence of stem or socket loosening at follow up, and those with loosening did not complain of worse symptoms compared to those without. Overall 5.3% required revision, of which 0.3% were revised for deep infection, dislocation and fracture each, and 4.4% were revised for aseptic loosening. Kavanagh et al. [1994] reported slightly worse results in his 20 year review of 112 Charnley hip arthroplasties. He found 83% to have survived 20 years, although there was a higher rate of radiographic loosening (17% of the acetabular components and 36% of the femoral components).

AETIOLOGY OF ASEPTIC LOOSENING

The very early attempts at hip arthroplasty were prone to failure. John Charnley revolutionised the practice by identifying that infection and failure of the prosthesis to remain properly bonded to the host bone were the principal causes of failure. He addressed the first issue by adopting strict aseptic techniques, and the second by developing a smaller headed, cement-bonded, low-friction arthroplasty. Initial implants used Teflon as the bearing surface, soon to be replaced by polyethylene with its lower wear-rate characteristics.

Although these changes dramatically improved the longevity of implants, aseptic loosening continued to be a problem and a number of biomechanical and biological causes have since been identified. The first reported causes of aseptic loosening in the post-Charnley era were by Harris in 1976 who attributed it to a reaction to cement. Since then a number of theories have evolved as to why it may occur. There has been progressive research into cement and then other particulate matter as a cause for loosening since the 1980's, with the importance of polyethylene wear increasingly recognised. Later the influence of stress-shielding became known with other mechanical causes of joint failure throughout the 1990's. This included the notion of prosthesis micro motion, changes in fluid pressure and the importance of a sealed interface. In the late 1990's the role of sub-clinical infection and the remnants of bacterial endotoxins came into question. More recently, the importance of patient specific responses to arthroplasty and wear particle generation has been examined, as has the shape of the proximal femur. These are summarised below (Table 1-1). It is likely that a combination of these factors is important in the aetiology of aseptic loosening.

Table 1-1. Evolution of theories of the causes of aseptic loosening

Author	Year	Cause
Harris et al	1976	Cement disease
August et al	1986	Metal particles
Howie et al	1988	Polyethylene particles
Engl and Bobyn	1988	Stress shielding
Ryd and Linder	1989	Micro motion
Barrack et al	1992	Cementing technique
Van der Vliet	1998	Fluid pressures
Ragab et al	1999	Endotoxin
Matthews et al	2000	Individual variations
Kobayashi et al.	2000	Hip structure and shape

BIOLOGICAL CAUSES OF ASEPTIC LOOSENING

Biological causes of loosening have mainly concentrated on the body's response to wear particles. Willert first noted the presence of wear particles around arthroplasty joint capsules [Willert, 1977], a large number of studies since then have examined the influence of wear particles on the development of aseptic loosening. The studies are very heterogeneous, analysing different amounts, types and sizes of particles using a variety of clinical and laboratory models (Figure 1-6).

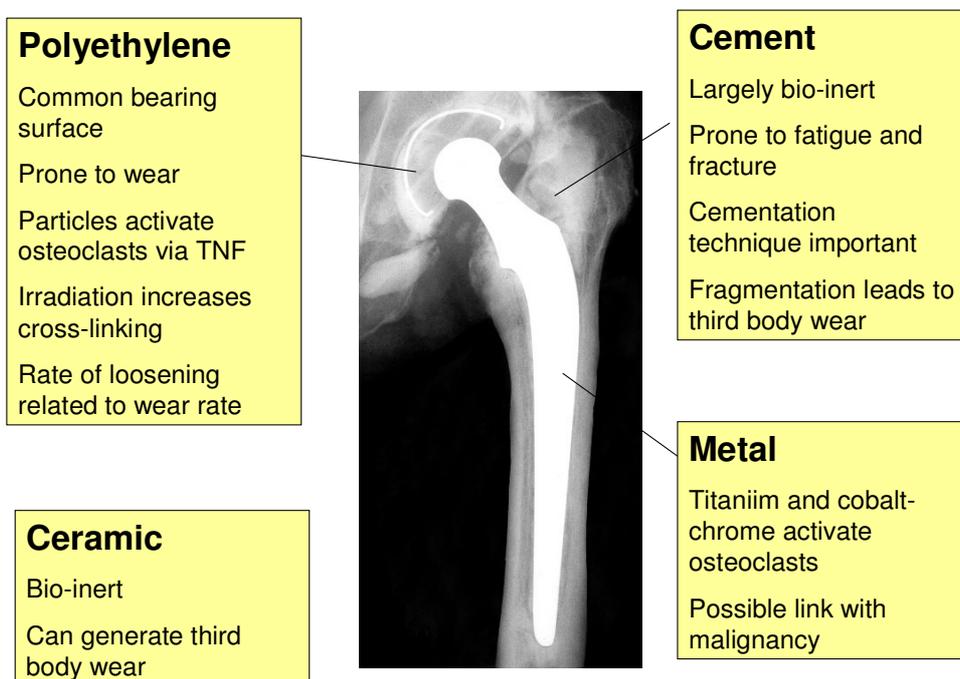


Figure 1-6. Wear debris and its influence on aseptic loosening

Cement

Polymethylmethacrylate (PMMA) cement was first used by Haboush in 1953 as a fixing medium, later to be developed by Charnley in the 1960's. With modern application techniques, such as vacuum mixing, compression, medullary canal plugging and high pressure lavage, it has excellent long term results. A review of cementation techniques [Barrack et al., 1992] assessed the quality of cementation and the influence on 12 year outcomes of hip arthroplasty. He concluded that techniques that enable pressurised infiltration of cement deep into the medullary bone, as far as the enclosing cortex, yielded the best results. Such techniques produced a characteristic "white-out" due to complete filling of the inter-trabecular space with cement.

In prosthetic hip stems, the stresses are mainly shear forces between the prosthesis and the cement, leading to de-bonding of the two. This may occur easily and in an expected fashion in highly polished stems, such as the Exeter prosthesis. This prosthesis has good long term outcomes, and this is thought to be partially due to early subsidence of the stem into a stable position. In roughened stems (such as the Charnley ElitePlus) it may be an undesired event secondary to the failure of the bonding between the cement and the prosthesis to withstand the shearing forces. In such cases the hard rough stem causes wear of the softer cement leading to cement particle generation and eventually breakdown of the cement mantle. Both of these scenarios contribute to the early loosening and failure of the prosthesis.

Harris et al. first reported four cases of excessive bone loss around cemented hip prosthesis' [Harris et al. 1976], postulating that cement reaction played a role in the development of osteolysis. It was thought that cement fragmentation leading to a foreign body reaction was the initial cause of loosening, and that the release of cement into the joint led to polyethylene third-body wear [Willert et al., 1990]. Degradation of the cement occurs the longer it has been *in situ*, and this leads to cement fracture and fragmentation. Recognition of cement being a potential cause for early failure lead to the subsequent development of cementless arthroplasties in the 1980's for younger, more active patients. However cementless arthroplasties continued to develop loosening, and Jasty et al. [1991] concluded in a post-mortem study that cement fatigue and fracture was common, even in stable arthroplasties and that the development of a fibrous interface membrane around a loose arthroplasty was likely to be as a result of loosening, and not the main cause. It can therefore be concluded that PMMA cement does influence loosening, in particular in the way that it is administered, and how the prosthesis interacts with it. However it is not the only cause of failure.

Polyethylene

A number of different bearing surfaces are used for prosthetic joints, however metal on ultra high molecular weight polyethylene (UHMWPE) is the most common material for prosthetic articulation. There is now good evidence that polyethylene wear is a key influence in the development of aseptic loosening.

UHMWPE is a relatively soft compound making it prone to wear, but this happens in a gradual, predictable manner. It is also resistant to fracture (and so rapid catastrophic failure) unlike the harder, but more brittle, bearing surfaces such as ceramics. UHMWPE wear particles cause osteolysis through their interaction with macrophages. This leads to a cascade of inflammatory mediators (in particular Tumour Necrosis Factor), resulting in osteoclast activation and bone resorption. The particles generated vary in size and shape, but the macrophage stimulating effects appear to be optimal in particles smaller than one micron [Green et al., 1998]

The resistance of UHMWPE to fragmentation is due to a number of factors including the manufacturing methods, temperature and pressure during manufacture, methods of sterilisation (gamma irradiation or ethylene oxide), cross linking by gamma irradiation and the storage after manufacture. Most of these relate to the fact that UHMWPE degrades by oxidation, which alters its structural properties. Fatigue wear of polyethylene can lead to de-lamination, and this can be prevented by increasing the number of molecule cross-links by radiation sterilization. Digas et al. [2003] found that increasing the dose of irradiation beyond that used for sterilisation purposes caused highly cross-linked polyethylene. The preliminary 2 year results of their study showed that such bearing material reduced the amount of PE wear by 50%, although the clinical significance is not yet known or if this leads to less aseptic loosening.

Howie et al. [1998] found that exposure of a PMMA plug in rat femurs to UHMWPE resulted in bone resorption in the absence of infection or motion, implicating the key role of polyethylene in the development of loosening. Several clinical studies have demonstrated that the risk of developing osteolysis being proportional to the amount and rate of PE wear [Dowd et al., 2000]. Sochart showed that for every additional millimetre of wear, the risk of acetabular revision in any one year increased by 45% and for the femur increased by 32% [Sochart 1999].

Metal

The influence of polyethylene on aseptic loosening has renewed interest in metal on metal implants. Early attempts at joint arthroplasty utilised metal-on-metal implants, however due to limitations on manufacturing techniques, irregular bearing surfaces generated friction. This led to failure of fixation to bone and high rates of arthroplasty failure. Charnley's realisation of the importance of low friction arthroplasty to allow stable fixation of the prosthesis led to development of cemented metal on polyethylene implants. New manufacturing techniques have improved metal-on-metal articulation and the development of a new generation of prostheses [McMinn and Daniel, 2006] with reasonable outcome studies [August et al., 1986, Steffen et al. 2008].

Titanium [Agins et al., 1988] and cobalt-chrome [Doorn et al., 1998] particles have both been shown to stimulate bone resorption, but both less than polyethylene. Metal particles are typically much smaller (10-400nm) than polyethylene wear and it is thought that the ability of macrophages to ingest more of them, and the fact that they are more likely to be corroded and broken down makes them easier to be cleared from the body. The ingestion of biologically active metal ions has led to concerns that there may be a link between metal implants and malignant disease [Llangkammer et al., 1997], although no link between malignancy and joint prosthesis' has subsequently been shown [Visuri et al. 2003 and 2006].

Ceramic

Particles from ceramic implants are insoluble and bioinert, and the response is more a mechanical result of the particles themselves, rather than the material. Ceramic particles cause a much lower inflammatory response compared to polyethylene or titanium particles, barely more than controls [Warashina et al., 2003], but Hatton [2003] has still described the production of osteolytic cytokines in response to ceramic particles, although the doses required to do this were significantly higher than seen in most ceramic on ceramic joints.

Summary

Wear particles play a significant role in aseptic loosening through a variety of methods. UHMWPE is a strong stimulator of osteoclasts leading to bone resorption. PMMA and ceramic particles are more biologically inert, however in cases where a ceramic head articulates with a polyethylene liner, they still play an important role through the generation of polyethylene debris through third body wear. The influence of metal wear particles is not fully known yet and long term outcome studies will reveal whether it is a more durable material.

BIOMECHANICAL CAUSES OF ASEPTIC LOOSENING

Sealed Interface

Schmalzried, Jasty and Harris came up with the concept of the Effective Joint Space” in 1992. Their histological examination of loose and apparently stable joint replacements revealed the penetration of wear particles around the whole of the cement-bone interface. This suggested that even in stable arthroplasties there is a communication between the bearing surfaces and the entire prosthesis. The entire Effective Joint Space was therefore potentially susceptible to the influence of wear debris and other factors leading to the development of aseptic loosening.

Bobyn et al. [1995] explored this concept after noting that particulate debris penetrated into the effective joint space around smooth implants more than around porous implants. He found that around porous implants there was a higher degree of bony ingrowth. Sundfeldt et al. [2002] explored this experimentally with rabbits, injecting UHMWPE particles around an osseointegrated implant. Although this study showed no increase in osteolysis compared to injecting a saline control, a criticism of the study would be that they did not compare to a non-osseointegrated control. Sundfeldt et al. postulated that early development of a tight seal and preventing micromotion is important to prevent the spread of wear particles around the implant (Figure 1-7).

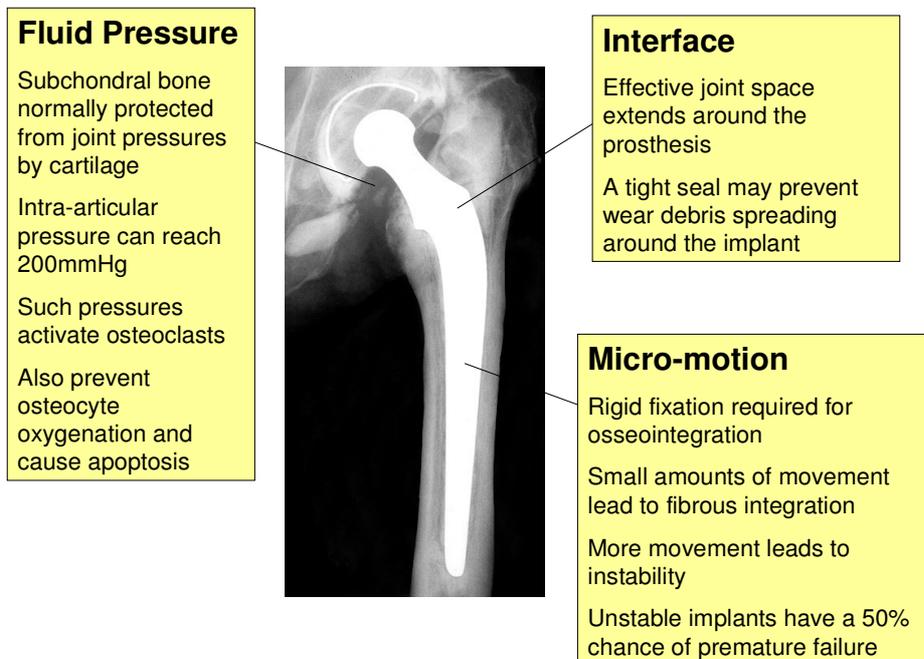


Figure 1-7. Mechanical causes of loosening

Micro-motion

Prosthetic micro-motion is the small movements between a prosthesis (whether cemented or uncemented) and the surrounding bone that is not detectable by conventional radiographic methods. The process of radio-stereometric analysis (RSA) requires taking repeated x-rays at different angles and is regarded as the gold-standard technique for detecting micro-motion. Small amounts of movement are not unusual, and not always associated with loosening. Animal studies in dogs have shown that osseointegration can still occur in implants that move up to 20micrometres, and that stable fibrous integration occurs in implants with up to 40 micrometres of motion [Jasty et al., 1997]. Beyond this range the implant tends to be unstable and this implies that either osseointegration of uncemented implants has not occurred, or that there has been debonding between a prosthesis and its cement mantle (Figure 1-8).

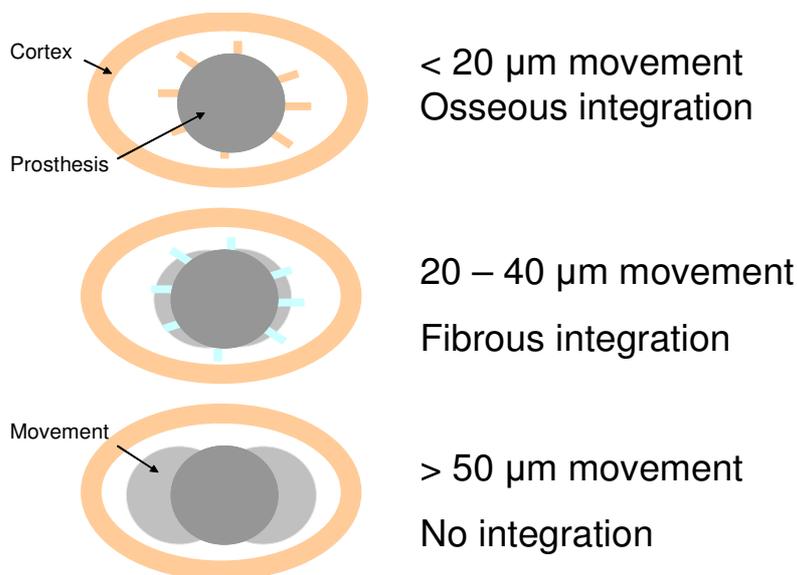


Figure 1-8. Type of prosthesis integration is dependent on micromotion

Karrholm used RSA to show that subsidence of the femoral head of 1.2mm or more two years after surgery was associated with a 50% chance of premature implant failure. One of the key factors determining the stability of an implant is the surgical technique. It has been postulated that one of the reasons for failure of newer modular femoral stems (compared to the original mono-block prosthesis) is movement of the prosthesis within the cement mantle before it has fully hardened during a trial reduction. There is no evidence to support or refute this, but cementation techniques have evolved to ensure the prosthesis is held rigid until the cement has fully set. As discussed above, failure of the ElitePlus stem may be due in part to the change in axial profile of the stem making it less stable to torsion forces.

Fluid pressure

Normal subchondral bone is protected from high intra-articular pressures by hyaline cartilage. In pathological conditions, such as osteoarthritis there is a breakdown of articular cartilage, and the high pressures within the joint can lead to the development of cystic lesions. There is some evidence that it may also play a direct and indirect role on development of cystic lesions around a hip prosthesis [Aspenberg and van der Vis, 1998].

Robertsson et al. [1997] demonstrated mean intra-articular pressures as high as 159mmHg in hips about to undergo revision surgery for aseptic loosening. He also showed using ultrasonography that the joint capsule was significantly more expanded than patients with a stable hip arthroplasty. Similarly, Anthony et al. [1990] showed pressures as high as 200mmHg within an osteolytic lesion. Other studies have shown that cyclical pressure changes (in a similar fashion to the pressure changes seen within a hip joint during walking) [Sampathkumar et al. 2003, van der Vis et al. 1998]. This effect was synergistically increased when the macrophages were exposed to UHMWPE particles.

Such high pressures can therefore cause damage to bone directly by preventing adequate circulation and oxygenation, resulting in osteocyte death as well as indirectly by their effects on macrophages. It is therefore likely that high intra-articular pressures play a part in aseptic loosening in combination with the other factors described.

CHARNLEY ELITEPLUS ARTHROPLASTY

Several studies have looked specifically at the hip joint used in this study, the Charnley ElitePlus (DePuy, Leeds, figure 1.9). This is a relatively new type of arthroplasty, designed with minor modifications to the original Charnley arthroplasty. In particular, the femoral stem is slightly rounder and has a slightly broader shoulder flange compared to the original design. Concerns have been raised whether these changes may make it less stable to rotational forces and less likely to subside into a stable position in the femoral calcar [Hauptfleisch et al., 2006].

Concerns about the failure of the implant were first highlighted by Norton et al. [2002] who had a failure rate of 31% at 5 years in a small series of 29 hips. Since then several other studies have shown a mixed outcome of results. Walton et al. [2005] reviewed 159 hips at a mean of 6 years. Their rates of revision for early loosening were also high at 4%, as was the 27% of patients with radiographic evidence of loosening. In a study conducted in our unit, Rowsell et al. [2006] followed up 368 primary arthroplasties for a mean of 4.5 years. Their rate of failure requiring revision was 1.9% at this early stage with a further 5.8% having radiographic evidence of loosening. Hauptfleisch et al. [2006] reviewed 118 patients, finding 17% had required revision at a mean of 10 years, and a further 24% had radiographic evidence of loosening.

In contrast to these poor results, Kim et al. [2007] reviewed 194 young patients (all less than 60 years old) for a minimum of 10 years. They found radiographic loosening in just 11% of the acetabular components and 14% of the femoral components. Furthermore the rate of revision for loosening was very low, occurring in less than 1%. The authors proposed that the lower incidence of revision could be due the different patient group- unlike the other studies which were conducted in Europe, it was done in Korean with patients who were younger and slimmer, and demonstrated lower rates of volumetric polyethylene wear.



Figure 1-9. The Eliteplus arthroplasty

CHARNLEY ELITEPLUS SURVIVAL

Pooling the data from the 5 studies shows that a total of 868 patients were followed up for 6030 patient years, with a mean follow up of 6.9 years. The pooled incidence of revision was 45 patients, with a rate of 5%; the pooled incidence of loosening was 118 patients, with a rate of 14%. This is summarised in table 1.2 below.

Table 1-2. Incidence of loosening and revision in published series

Study	n	Follow up	% Revised for	% Radiographic
Norton [2002]	29	4	31	Not specified
Walton [2005]	159	6	4	27
RowSELL [2006]	368	5	2	6
Hauptfleisch [2006]	118	10	17	24
Kim [2007]	194	10	1	11-14
Pooled data	868	6.9	5	14

The conclusion from these studies suggests that loosening is common, although frequently asymptomatic and not always requiring revision surgery, and that this type of arthroplasty should be followed up radiographically.

We used the Eliteplus as a study prosthesis because it was a model of established loosening in a relatively homogeneous group. It is acknowledged that the study hypothesis investigates biological risk factors for loosening (ie osteoporosis), and that the principal cause of failure in the ElitePlus is mechanical. In an ideal world we would have used a group of patients, all with an implant with the best possible survival, as this would allow assessment purely of the risk factor in question. In practice this is not practical (due to the success of such implants making loosening very rare and very late).

Our hypothesis is still valid in so far as patients with osteoporosis are probably more susceptible to biomechanical causes of loosening, but we acknowledge the potential conflict.

INTRODUCTION

2. CLINICAL RISK FACTORS FOR BONE FRAGILITY

In this study several variables that are known to strongly and independently influence either osteoporosis or arthroplasty loosening were identified prior to patient selection to enable selection of appropriate controls. These variables were patient age, gender, arthroplasty type and time since surgery. These were used in the matching system. Paradoxically, although increasing age and female gender are well known to negatively influence bone quality, these two variables appear to have a reverse effect on arthroplasty loosening. This is likely to be due to differences in functional demand and prosthetic wear and is discussed in the first section.

In the second section we will study the evidence for other clinical risk factors that will be assessed in this study. These clinical risk factors include a previous history of a fracture, smoking history, body mass index and age of the menopause. Many of these have been thoroughly investigated as predictors of osteoporosis and fragility fractures. Black et al. [2001], developed a Fracture Index using six clinical variables and the BMD measured at the hip to evaluate fracture risk. They found that age, weight, cigarette smoking, maternal hip fracture and prior fracture of the patient as an adult were all independent risk factors for future fracture risk. However, much less work has examined these variables on arthroplasty survival.

In the third section we will look at pain and function as predictors of loosening.

PATIENT AGE

AGE AND FRACTURE RISK

Advancing age has long been acknowledged to be a risk factor for bone fragility. In fact, the first reference to osteoporosis was in the early 19th century when Sir Astley Cooper noted, “the lightness and softness that [bones] acquire in the more advanced stages of life ... favours much the production of fractures”. Bone mineral density changes throughout life, increasing during childhood through to early adulthood to reach a peak bone mineral density at around the age of 25 years. Thereafter there is a steady decline in BMD, which in women declines faster after the menopause, mainly due to the lack of protective effect of oestrogen (Figure 2-1).

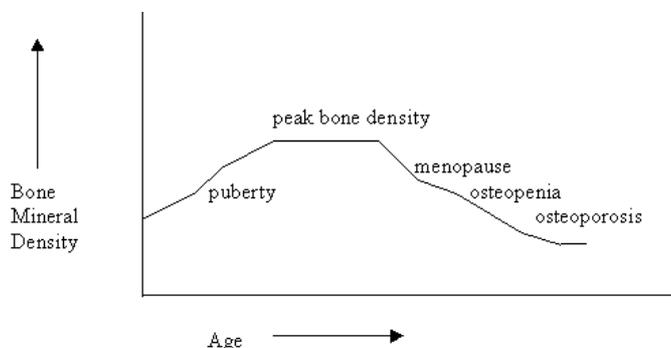


Figure 2-1. Age related changes of BMD

Age related changes in BMD are central to the World Health Organisation criteria for osteoporosis. They define osteoporosis based on the bone mineral density relative to a healthy 25 year old at peak bone mass (the T score). Osteopenia is defined as a BMD between 1 and 2.5 standard deviations below the peak BMD (a T score between -1 and -2.5), osteoporosis is a BMD greater than 2.5 standard deviations below normal and established osteoporosis is defined as a T score less than -2.5 together with a history of a fragility fracture. In addition, they calculate the Z score according to the BMD relative to an age and sex matched population.

The prevalence of osteoporosis is considerable. Currently in the United States and Europe, 45% of women aged 50 or over meet the WHO criteria for osteoporosis, including 29% at the hip. Around 40% of post-menopausal women can expect to sustain a fracture of their hip, spine or distal radius [Boyle et al., 1985; Melton et al. 1992]. Projected forecasts on population age changes suggest that bone fragility is going to be an increasingly common problem. Over the next 40 years, the number of people over 60 years old is expected to increase by 40% and the number over 90 years old is expected to double [Khaw 1999]. With this in mind the projected number of fragility fractures is likely to increase by at least 60% within a similar timeframe.

AGE AND ARTHROPLASTY LOOSENING

Unlike its associated increase in fracture risk, age does not appear to be a significant risk factor for developing arthroplasty loosening. Halen et al. [2007] analysed the 10 and 15 year survival of 11,516 total hip replacements as part of the Norwegian Arthroplasty register. Using revision due to aseptic loosening as an endpoint, they found that although the 10 year outcomes were almost universally very good, the 15 year survival were more mixed. Although the type of prosthesis was a significant factor, age did not appear to be. Similar results were found by Kobayashi et al. [1997] who reviewed only cemented Charnley hip arthroplasties (similar to the type used in our study). They did find that degree of polyethylene wear was an important factor however, and this is likely to be a reason for these results.

Although elderly patients with a hip prosthesis almost certainly have a poorer bone quality that predisposes them to loosening, they also have a lower functional demand and so have less polyethylene wear. Several clinical studies have demonstrated that the risk of developing osteolysis is proportional to the amount and rate of polyethylene wear [Dowd et al., 2000].

Age and bone health
45% post menopausal women meet WHO criteria for osteoporosis
40% post menopausal women will sustain a fragility fracture
40% forecast increase in the over 60's in the next 40 years
Age has a complicated association with loosening as
<ul style="list-style-type: none"> - Older patients have a lower demand - They therefore generate less wear debris - They are also less likely to be fit for revision surgery
Therefore, despite having poorer quality of bone,
Older patients don't have a significantly higher revision rate

Box 2-1. Impact of age on bone health

GENDER

GENDER AND FRACTURE RISK

Gender is also a significant determinant of bone quality. Men reach a higher peak bone mass, with better bone architecture and thereafter undergo less bone remodelling [Guesens et al., 2007]. This and the fact that women tend to live longer means that they are more likely to sustain fragility fractures. Women are around four times more likely to have a fracture of their neck of femur [Nixon et al., 2007].

Women and osteoporosis
Increased remodelling after the menopause
More trabecular bone loss
Poorer bone architecture
Longer lifespan
Higher incidence of fragility fractures

Box 2-2. Effect of female gender on osteoporosis

GENDER AND ARTHROPLASTY LOOSENING

The review of arthroplasty failures by Halen et al. discussed above [2007] found that after adjustment for other variables, men had a 1.3 times higher relative risk of revision for aseptic loosening. Similar findings were found by Munger et al. in 2006. Like younger patients, men tend to have a higher functional demand and so generate more polyethylene wear, and this is likely to be the reason for this finding.

Men and arthroplasty loosening
Higher demand
Higher wear rate
1.3 times higher failure rate

Box 2-3. Effect of male gender on arthroplasty loosening

PREVIOUS FRAGILITY FRACTURE

SUBSEQUENT FRACTURE RISK

Previous history of a fragility fractures (figure 2-1) is an easy way to screen for osteoporosis in an outpatient setting. Placebo arms of controlled intervention trials for osteoporosis have provided good evidence regarding the natural progression of osteoporosis. In such a study, Watts et al., [2003] found that post-menopausal women who have already had one vertebral compression fracture, have a five fold higher risk of having a second one within a year. Women with two incidental compression fractures have a 12-fold increased risk.



Figure 2-1. Typical fragility fracture

The risk was further investigated in a meta-analysis by Kanis et al. [2004]. In this study, they analysed 11 observational studies comprising more than 250,000 patient years, and after stratifying according to age, sex and BMD they found that the relative risk of a further fracture in patients with a previous fracture was 1.9 times greater.

RISK OF ARTHROPLASTY LOOSENING

Despite the above extensive studies, surprisingly little work has investigated the influence of fracture risk factors on aseptic loosening. This includes whether a patient has had a previous low energy fractures or have a maternal history of hip fracture.

Previous fragility fracture
1.9 times increased risk for further fractures
No evidence regarding influence on arthroplasty loosening

Box 2-4. Fracture history and future fracture risk

UNDERLYING DIAGNOSIS

Rheumatoid arthritis patients often have both systemic and localized inflammatory processes. The result of this inflammation is tissue destruction and this translates into bone loss. The pathological nature of the disease activates osteoclasts through the RANK/RANKL (receptor activator of nuclear factor- κ B and RANK ligand) pathway [Wahner and Frgelman, 2004]. Pasco et al. [2006] found that chronic elevated CRP (as a marker of inflammation from a variety of causes) was associated with an increased risk of fracture (risk increased by 23% for each SD higher than the mean).

Rheumatoid arthritis and bone fragility
RANK/RANKL mediated activation of osteoclasts
Common use of glucocorticoids
16% incidence of fracture per patient per year
25% undergo joint arthroplasty
Lower demand but higher rate of arthroplasty revision than non-rheumatoid

Box 2-5. Effects of rheumatoid arthritis on bone fragility

In addition many rheumatoid patients are or have been on glucocorticoid therapy which is also strongly associated with a lower BMD and increased fracture risk. Oral corticosteroid treatment using more than 5 mg (of prednisolone or equivalent) daily leads to a reduction in bone mineral density and a rapid increase in the risk of fracture during the treatment period [van Staa, Leufkens and Cooper, 2002].

As a consequence of this, fractures are very common in rheumatoid patients, as demonstrated in the prospective study by Nampei et al. [2008]. In a prospective study of 209 patients for a median of 1 year they found an incidence of 16 fractures per 100 patient years. In addition to systemic inflammation and steroid use, immobility and subsequent predisposition to falling are reasons for the high incidence. Around a quarter of rheumatoid patients undergo joint arthroplasty [Wolfe and Zwillich, 1998], with 15 year survival rates of around 89% for major joint replacement in young patients [Eskelinen et al., 2006]. Analysis of arthroplasty registers such as the 2007 report of the Swedish arthroplasty register reveals that after adjusting for age, rheumatoid patients have a significantly higher rate of revision.

SMOKING

There are also links between smoking and poor bone health, although the precise causative agent is not known [Wong et al., 2007] and a number of mechanisms have been postulated. Smoking is associated with free radical production, and has also been shown to be associated with inhibited collagen synthesis [Ramp 1991]. There have been reports of earlier menopause amongst female smokers [Wong et al. 2007] (mean age 44 vs. 49 years), although the numbers were small and this was not significant (p=0.30, T test). Other reports show that smokers have a lower body mass [Jones and Scott, 1999] and this predisposes to decreased osteogenic stimulus and conversion of androgens to oestrogens. The same report also noticed a lower vitamin D level in smokers, proposing that this may be explained by increased hepatic metabolism of the vitamin bought about by smoking induction of liver enzymes.

Smoking and bone fragility
Smoking is associated with increased circulating free radicals
Decreases collagen synthesis
Earlier menopause, lower body mass, lower vitamin D levels
25% increased fracture risk
Little evidence regarding arthroplasty

Box 2-6. Smoking and bone fragility

SMOKING AND FRACTURE RISK

Several studies have looked at associations between smoking and fracture risk. A recent meta-analysis [Kanis et al., 2005] reviewed 59,232 subjects in 10 prospective studies. This found a 25% increased risk of fracture amongst smokers, particularly for hip fracture.

SMOKING AND ARTHROPLASTY LOOSENING

There is much less work and no conclusive data assessing the influence of smoking on arthroplasty loosening. A small study (165 arthroplasties) by Meldrum et al., [2005] showed a statistically significant increased rate of revision for aseptic loosening amongst smokers. A similar sized study by Inoue et al. in 1999 investigated the influence of a number of sociodemographic factors on loosening, including smoking. Cox regression showed age, sex, cementation and occupation to be significant factors, but not smoking.

BODY MASS INDEX

Epidemiological studies have shown that increased body mass index is correlated with increased bone density [Zhao et al., 2007]. Although the precise mechanism behind this correlation is unclear, it is thought that the influence of increased loading on bone results in increased bone mass (as described in Wolff's law). Increased oestrogen production in excessive adipose tissue leads to osteoclast suppression [Kameda et al., 1997] and this is thought to be another mechanism. However, other studies have shown a more complex relationship. In particular with the influence of leptin, a hormone released by adipose tissue to control appetite. Whilst some studies have shown leptin to suppress bone growth [Ducy et al., 2000], others have shown it may stimulate new bone formation [Reid, 2002]. A recent study examined the influence of fat mass whilst controlling the mechanical loading effects of body weight [Zhao et al., 2007]. They found that after controlling for body weight, increased body fat was actually associated with lower bone density. This was found in both sexes, and both Caucasian and Chinese populations.

BMI AND FRACTURE RISK

An explanation for this could lie in the fact that adipocytes and osteoblasts are both derived from a common progenitor – pluripotential mesenchymal stromal cells. Their differentiation is dependent on various influences including peroxisome proliferators activated receptor-gamma (PPAR-g). The presence of PPAR-g stimulates differentiation into adipocytes [Pei and Tontonoz, 2004]. This supports the hypothesis that increased body fat is inversely correlated with bone density, although further studies need to assess this in more detail.

BMI AND ARTHROPLASTY LOOSENING

A recent review of the influence of obesity on aseptic loosening of knee and hip prosthesis found inconclusive results [Stukenborg-Colsman, Ostermeir and Windhagen, 2004]. There is some evidence that increased BMI may lead to increased forces across the prosthesis, and so increased production of wear debris and loosening. However there are no good studies that demonstrate a clear correlation between obesity and loosening, with a decrease in activity level amongst obese patients being thought to be the reason.

MENOPAUSE

Fuller Albright [1940] initially described postmenopausal osteoporosis as being a consequence of impaired bone formation due to oestrogen deficiency. Later theories suggested two distinct forms of osteoporosis were thought to exist – one involving menopausal oestrogen deficiency and another involving calcium deficiency. Current belief is that of a spectrum of multiple pathogenic mechanisms converging to cause loss of bone mass and architecture [Riasz 2005].

The menopause and bone fragility

Increased bone remodelling with decreased bone formation

Early menopause associated with a lower BMD and higher fracture risk

No evidence regarding menopause and arthroplasty loosening

Box 2-7. Early menopause and bone fragility

The concept that oestrogen deficiency is critical to the pathogenesis of osteoporosis was originally based on the fact that fragility fractures occurred more commonly in postmenopausal women, who have low levels of oestrogen. Bone remodelling is accelerated during the menopause – as exemplified by an increase in biochemical and histological markers of both bone resorption and formation [Parfitt et al., 1995; Ebeling et al., 1996]. During puberty, when there is a growth spurt with accelerated remodelling, the excessive bone resorption is matched by increased bone formation. However, during post menopausal bone remodelling there is insufficient new bone formation. During oestrogen deficiency there is a diminished response to mechanical loading, suggesting oestrogen is both anabolic and anti-catabolic [Lee et al., 2003].

Oestrogen acts at various stages of the bone remodelling cycle. Its action is mediated by two types of oestrogen receptor (ER α and ER β) with ER α being found primarily in osteoblasts [Lee et al., 2003]. Genetic polymorphisms of this protein have been shown to affect bone mineral density [Albagha 2005]. Other studies have shown that oestrogen may also have an inhibitory effect on osteoclasts [Hughes et al. 1996]. Low dose oestrogen replacement therapy in postmenopausal women prevents bone loss associated with remodelling [Prestwood et al., 2003]. Although clinical studies have shown a relationship between early menopause (before 45 years) and decreased bone mineral density and increased fracture risk [Gallagher, 2007], no studies have looked at the relationship between menopause and arthroplasty loosening.

PAIN AND FUNCTION

There is considerable variation in clinical follow up following hip arthroplasty, with many units discharging patients from review once they have satisfactorily progressed from the early post operative period.

Patients are usually referred back for surgical consultation if there is a change in their hip function or level of pain, and they usually have a plain radiograph to screen for a number of potential complications, including aseptic loosening. A number of other radiographic methods including contrast and digital subtraction arthrography have evolved to further evaluate a painful prosthetic joint (see section "BMD assessment" in chapter 4).

Potential reasons for a loose arthroplasty being painful include micromotion of the prosthesis, instability and low grade inflammatory reactions. Despite the assumption that a painful arthroplasty could well be due to loosening, very little work has correlated level of pain with level of loosening, and even less work to evaluate what proportion of loose arthroplasties are painful. One of the aims of this study is to evaluate if pain is a good screening tool for aseptic loosening, and whether it is correlated with the degree of loosening.

3. RADIOGRAPHIC MARKERS OF BONE FRAGILITY

This chapter is structured so that the first section will analyse the described radiographic markers of bone fragility. This includes cortical and cancellous measurements, bone geometry and finally markers of bone biology. Each section will analyse how these markers relate to biomechanical bone strength, fracture risk and aseptic loosening.

The second section discusses radiographic methods of diagnosing and classifying aseptic loosening that will be employed in this study.

RADIOGRAPHIC MARKERS OF BONE STRENGTH

CORTICAL BONE

A number of studies have used radiographic geometric markers such as the shape of the femoral neck or thickness of the cortex to assess bone quality. The advantage of these types of examination is that they are easy to perform in the outpatient setting, usually without any additional investigations. Most studies correlate findings to the accepted gold standard assessment of bone quality – bone mineral density. This is assessed using a variety of methods, usually DEXA scanning, as discussed in the following chapter. However BMD measurement is a surrogate marker of bone health and there are relatively few studies that have correlated geometric findings with clinical outcomes (such as fractures or arthroplasty loosening) or laboratory assessment of bone strength.

The following diagram illustrates some of the measurements made around the proximal femur, including the one used in this study

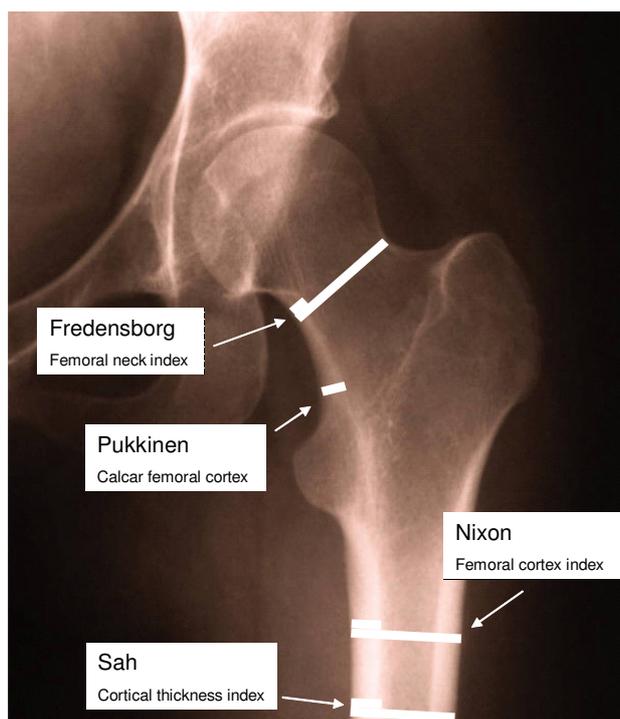


Figure 3-1. The femoral neck and shaft indices

Fredensborg: ratio of femoral neck at the narrowest point to the cortex

Pukkinen: Absolute thickness of calcar cortex

Nixon: Ratio of femoral shaft to cortex, measured 50mm below the lesser trochanter

Sah: Ratio of femoral shaft to cortex, measured at the isthmus

PROXIMAL FEMUR MARKERS

Fredensborg et al. [1977] measured the width of the femoral neck and its most narrow point and divided this by the width of the cortex at the same point to calculate the Femoral Neck Index. He speculated that this may be used to assess fracture risk. Further work has been done by Gruen in 1997, which assessed the femoral cortical thickness in patients prior to hip arthroplasty being performed either for osteoarthritis or due to fracture. He did not assess its influence on outcome, but did show that it was lower in patients having surgery due to a fracture and also in patients with a lower BMI and body weight.

Pulkkinen et al. [2004] measured a number of geometric parameters, including the absolute thickness of the femoral cortex at the level of the calcar in two groups of patients. One group had had a hip fragility fracture and the others were matched controls without a fracture. All patients also underwent BMD assessment. They found that the cortical femoral thickness was strongly correlated to both the fracture risk and femoral neck BMD.

Similar work was done by Sah et al. [2007], who found a reasonable correlation ($r=0.58, p<0.01$) between femoral cortical index and BMD. This was calculated by measuring the dividing the total thickness of the femur at the level of the isthmus by the total thickness of the cortex at the same level. The measurements used in the present study is similar to this, but done at a slightly different level at most patients did not have femur views that included the canal isthmus.

Cortical bone measurements
The cortex contributes to 50% of bone strength
Measurements easy to perform in outpatient setting
Various radiographic measurements described
-cortical thickness
-geometric shape of the proximal femur
Correlated with bone mineral density
May predict fracture risk
Little evidence regarding arthroplasty loosening

Box 3-1. Cortical bone measurements

BONE GEOMETRY

Kobayashi et al. [1997] assessed the femoral shape as a possible influence on arthroplasty loosening. They measured the width of the intra-medullary canal at the level of the greater trochanter and at the level of the isthmus, and expressed the two as a ratio. The divided patients into two groups based on the geometry of the proximal femur. Patients with a relatively wide proximal femur were termed to have a “champagne glass” femur, and found to have a lower incidence of loosening than patients with a wide distal or “stove-pipe” femur. These types are illustrated below (Figure 3-2).

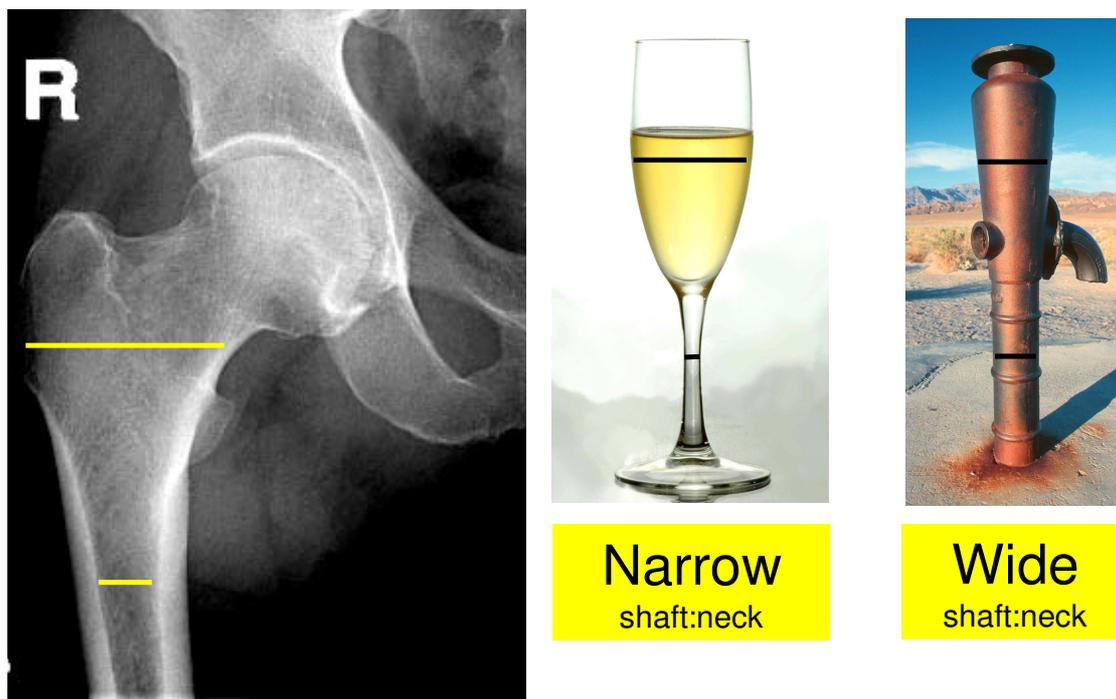


Figure 3-2. Geometry of the champagne glass and stovepipe femur

These studies suggest that the shape of the femur and the thickness of the cortex may be useful indicators of bone fragility. But there is little evidence whether or not these predict arthroplasty loosening.

CANCELLOUS BONE

Singh, Nagarth and Maini described a radiographic method of classifying cancellous bone strength around the femur in 1970. This is widely known as the Singh Index (table 3.1). This is based on the trabecular pattern of the proximal femur, with the key measurements being from the principle tensile group.

Singh Index
Reasonable inter-observer correlation
Good correlation with biomechanical properties and BMD
Little prospective evidence for fracture prediction
Little evidence effects arthroplasty loosening

Box 3-2. Clinical use of the Singh Index

The trabeculae bands in the proximal femur are arranged into distinct patterns as shown in Figure 3-3 below. The principle compressive group is the most important region for transmitting load from the acetabulum to the femur. Because the femoral head is offset from the shaft, there is a continual deforming force pushing the neck into varus during weight bearing. This deforming force is prevented by the principal tensile group which is itself supported by the secondary compressive group. The greater trochanter group, also known as the secondary tensile group are important for the function of the hip abductors which insert here. A break in the principal tensile group indicates osteoporotic bone according to the Singh Index. Ward’s triangle is a distinctive gap in the trabeculae.

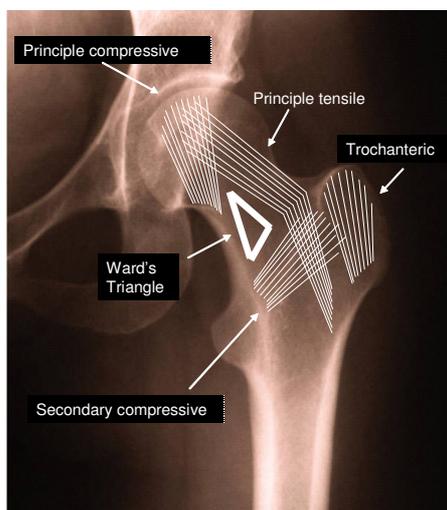
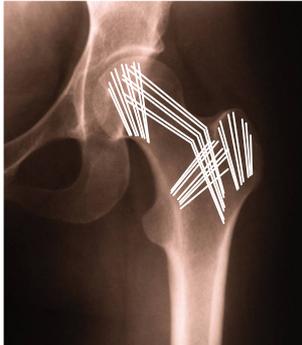
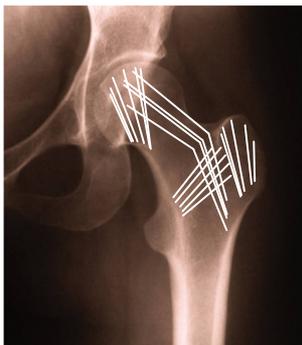


Figure 3-3. Trabecular bands in the proximal femur.

Table 3-1. The Singh Index of osteoporosis

<i>Index</i>	<i>Description</i>	<i>Example</i>
VI	<ul style="list-style-type: none"> - All normal trabecular groups are visible - Upper end of femur fully occupied by cancellous bone 	
V	<ul style="list-style-type: none"> - General loss of trabecular tissue - Principal tensile & compressive trabeculae appear accentuated - Ward's triangle appears prominent; 	
IV	<ul style="list-style-type: none"> - Principal tensile trabeculae markedly reduced - Can still be traced from lateral cortex to upper femoral neck 	

<i>Index</i>	<i>Description</i>	<i>Example</i>
III	<ul style="list-style-type: none"> - Discontinuity of the principal tensile trabeculae - Occurs opposite the greater trochanter - This grade indicates definite osteoporosis 	
II	<ul style="list-style-type: none"> - Only principal compressive trabeculae prominent - Remaining trabeculae have been essentially absorbed 	
I	<ul style="list-style-type: none"> - Principal compressive trabeculae are markedly reduced in number and are no longer prominent 	

THE SINGH INDEX AND BONE FRAGILITY

Several studies have compared the Singh Index with biomechanical and BMD assessments. However, as with the cortical measurements, few studies have prospectively followed up its influence on fragility fractures or on the development of arthroplasty loosening.

Radiographic markers are not regularly used in clinical practice, having been superseded by DEXA assessments, however it is still a reasonable assessor of bone health. Masud et al. [1995] showed that there was reasonable inter- and intra-observer correlation when measuring the Singh Index (kappa values of 0.64 and 0.61 respectively), and that mean femoral and lumbar BMD increased with increasing Singh Index score. However, they did note that there was a high degree of overlap of BMD between Singh Index grades.

A number of studies have compared the Singh Index to biomechanical strength of bone. Watcher et al. [2001] and Krischak et al. [2003] measured the biomechanical properties of bone harvested during total hip arthroplasty and correlated this to CT determined BMD and the Singh Index. They found good correlations between both assessment of BMD and Singh Index and Young's modulus and strength.

There are a number of other similar surrogate studies, but little evidence to show that the Singh Index predicts fracture risk. Yamanashi et al. [2005] prospectively followed up post-menopausal women in Japan following a hip fracture and found no correlation between the Singh Index in their un-fractured hip and the likelihood of fracturing it at a mean follow up of 2.4 years.

The only published study looking at the influence of the Singh Index on aseptic loosening was done by Kligman and Kirsh in 2000, who compared the outcome of 22 osteoporotic patients (Singh Index 1-3) with 48 non-osteoporotic patients (Singh Index 4-6). They found no cases of loosening after hydroxyl-apatite coated THR in either group, although the follow up was relatively short (2-7 years).

From this we can conclude that although the Singh Index may not be the best investigation to screen for osteoporosis, it may still provide a reasonable estimation of bone quality in a study population such as ours that have already had a pelvic radiograph.

BIOLOGICAL CLASSIFICATION OF OSTEOARTHRITIS

The type of osteoarthritis has been classified into hypertrophic, normotrophic or atrophic using the system described by Bombelli [1983]. The underlying mechanism of the different classes is thought to be due to the reaction of osteoblasts to osteoarthritis. Histological studies have shown that in the hypertrophic type of osteoarthritis there is a predominance of osteoblasts and a tendency to develop osteophytes [Saito et al. 1987]. This is sometimes termed "the osteoblastic response to osteoarthritis". In contrast, the atrophic type of osteoarthritis has a predominance of osteoclasts and little development of osteophytes. Table 3-2 below shows the classification system.

Table 3-2. The Bombelli classification of osteoarthritis

<i>Type</i>	<i>Description</i>	<i>Example</i>
Hypertrophic	<ul style="list-style-type: none"> • large osteophytes (>5mm) • predominance of osteoblasts 	
Normotrophic	<ul style="list-style-type: none"> • moderate osteophytes (2-5mm) 	
Atrophic	<ul style="list-style-type: none"> • absent or small osteophytes (<2mm) • predominance of osteoclasts 	

BOMBELLI CLASSIFICATION AND ARTHROPLASTY LOOSENING

Several studies have looked at the classification of osteoarthritis and its influence on arthroplasty outcome. Saito et al. [1987] first also looked at the influence of Bombelli’s criteria on the survival of 63 cemented hip arthroplasties followed up for 7.5 years. They found unsatisfactory results, with evidence of radiographic loosening in 32% of those with atrophic OA. They also performed histological examination at the time of surgery, revealing the osteoblastic response in hypertrophic OA and the osteoclastic response in atrophic OA. The authors concluded that patients with atrophic OA may not be good candidates for standard arthroplasty techniques due to the high rate of loosening.

Similar findings were later found by Hernandez-Vaquero et al. [1996] who followed up 71 uncemented hip arthroplasties for 5.5 years. In a larger study, Kobayashi et al. [1997] performed multivariate analysis on 293 Charnley hip arthroplasty patients to identify risk factors for failure. They found that degree of polyethylene wear, the atrophic classification of OA and a stovepipe shape of the medullary canal were all factors associated with early aseptic loosening.

In the most recent study, Nishii et al. [2001] followed up 91 uncemented arthroplasties for 7 years. In this study however, they found no difference in prosthesis survival or development of aseptic loosening in the different types of osteoarthritis.

Classification of Osteoarthritis
Bombelli classification described in 1983
Atrophic, normotrophic and hypertrophic groups
Relates to the degree of osteophyte formation
Degree of osteoblastic response to OA
Conflicting evidence whether it is risk factor or loosening

Box 3-3. Summary of evidence on the Bombelli classification

DIAGNOSIS OF ASEPTIC LOOSENING

A number of methods have been used to screen for aseptic loosening. Movement of the prosthesis within the bone may cause pain which typically is felt radiating down the thigh, although this is not a reliable marker, and is investigated as one of the methods of detecting loosening in this study.

In grossly loose arthroplasties, the following signs are normally seen on plain radiographs:

- endosteal bone scalloping,
- extensive radiolucency between the prosthesis or cement and the bone
- prosthesis subsidence or movement.

The accurate diagnosis of a less markedly loose prosthesis can be more difficult. In addition to plain radiographs, several different modalities have been used to assess for prosthetic loosening, including nuclear arthrography, subtraction arthrography and bone scintigraphy.

A recent meta-analysis compared the sensitivity and specificity of these four modalities in 32 studies [Temmerman et al., 2004]. They found no significant difference in the sensitivity or specificity of the different methods in detecting loosening (Table 3-3). Although contrast subtraction arthrography was the most sensitive and specific method, they recommended the use of plain radiography because of the increased morbidity in the other methods. For the purposes of this study, the diagnosis of aseptic loosening was made purely using plain radiographs, by comparing the latest radiograph with the initial post operative film.

Table 3-3. Comparison of four methods to detect prosthetic loosening

<i>Method</i>	<i>% Sensitivity</i> <i>(95% C.I.)</i>	<i>% Specificity</i> <i>(95% C.I.)</i>
Plain radiography	82 (76-87)	81 (73-87)
Nuclear arthrography	85 (75-91)	83 (75-89)
Contrast subtraction arthrography	86 (74-93)	85 (77-91)
Bone scintigraphy	85 (79-89)	72 (64-79)

CLASSIFICATION OF LOOSENING

Many classifications systems have been developed to classify the bone loss associated with aseptic loosening. All are based on radiographic findings, with some also based on peri-operative findings. Classifications that help guide management such as the Paprosky and AAOS are most commonly used in clinical practice, whereas quantitative classifications, such as the Dall classification are used more for research purposes.

CLINICAL CLASSIFICATIONS

The most commonly adopted in clinical practice is the Paprosky classification, which has been applied both to femoral [Della Valle and Paprosky, 2004] and acetabular loosening [Paprosky et al., 1994]. This classification is based on a combination of radiological and peri-operative findings to determine the degree and type of bone loss and in particular, the inherent stability of prosthesis components. Based on these findings, the authors gave advice on the best way to manage the condition. The American Academy of Orthopaedic Surgeons has also devised classifications for femoral [D'Antonio et al., 1993] and acetabular [D'Antonio et al., 1989] bone loss. These are far more complicated systems of describing the type and characteristics of bone loss, and are less used in clinical practice. Other clinical classification systems include those described by Chandler and Penenberg [1994] and Engh and Glassman [1988]. Whilst these systems are useful in clinical practice, they are less useful for research purposes.

RESEARCH CLASSIFICATIONS

The classification system used in this study was that described by Dall et al. [1992] because of the strict criteria it gives for measuring precise degrees of loosening and subsidence at different regions around the prosthesis. In this way it provides a useful numerical quantification for the degree of loosening which is useful for grading the severity of loosening, and its progression with time. It was devised after reviewing 811 primary Charnley hip arthroplasties, in which 6.9% (56) required revision surgery for aseptic loosening. A separate socket and stem score is calculated, scoring a maximum of 10 and 15 points respectively, as detailed in table 4-4 below.

The Socket score is dependent on the extent and width of cement-bone radiolucency in the three DeLee-Charnley zones and the degree of migration of the cup. The stem score is dependent on the extent and width of cement-bone radiolucency in the seven Gruen zones, resorption of the cortical shaft and subsidence of the stem together with and within the cement mantle.

Table 3.3. Dall Classification of radiological loosening

Acetabular abnormality			Femoral abnormality		
		Score			Score
Cement-bone radiolucency	No zones	0	Cement-bone radiolucency	None	0
	1 zone	1		1 zone	1
	2 zones	2		2 zones	2
	3 zones	3		3+ zones	3
Maximum cement-bone radiolucency	None	0	Maximum Cement-bone radiolucency	None	0
	1 mm	1		1 mm	1
	2 mm	2		2 mm	2
	3 mm	3		3 mm	3
Amount of stem migration	None	0	Subsidence within cement	None	0
	1 mm	1		1-2 mm	1
	2 mm	2		3-4 mm	2
	3+ mm	4		5+ mm	3
Maximum score		10	Subsidence with cement	None	0
				1 mm	1
			2 mm	2	
			3+ mm	3	
			Resorption of shaft (cortical thinning)	None	0
				1 zone	1
				2 zones	2
				3+ zones	3
			Maximum score		15

We used the criteria that 1mm represents a suspicion or a very thin line, 2mm is a definite demarcation and 3+ mm a more severe change

Based on the Dall classification, we split patients into the following groups:

Group	Characteristics
Stable	No changes since the initial post-operative radiograph
Mild	Minor changes, with the total Dall score less than 10
Severe	Advanced changes scoring >10 or having required revision surgery
All loose	Combination of mild and severe groups

4. BONE MINERAL DENSITY AND BONE FRAGILITY

The first part of this chapter examines the theoretical basis of using DEXA scanning to measure bone mineral density, in particular looking at

- Units of measurement
- Modes of action of photon and x-ray absorptiometry
- Radiation dose exposure,
- Regions assessed
- Adjustments needed for artefacts.

The second examines the accuracy and clinical implications of DEXA to assess:

- Biomechanical bone strength
- Osteoporotic fracture risk
- Effects of arthroplasty on BMD
- Disuse osteoporosis

CLINICAL ASSESSMENT OF BMD

UNITS OF MEASUREMENT

It is important to review some of the units used in measuring bone mineral density. The results of a DEXA scan are expressed as Bone Mineral Content (BMC, in grams), from which the Bone Mineral Density (BMD in g/cm^2) is calculated. As well as an absolute value, results are expressed as standard deviations scores from an age-matched population (Z score) or to a peak bone mass population (T score). The WHO criteria for osteoporosis is greater than 2.5 standard deviations below the normal peak bone mass in a sex matched population (a T score greater than -2.5).

The energy released from an ionising radiation source is described in electron volts (eV). This is defined as the amount of energy equal to the energy gained by one electron when it is accelerated by one volt. The energy released from an x-ray source is described as kilovolt peak (kVp). This is the crest value of the potential wave in kilovolts in an alternating current cycle.

The unit that is used for describing the absorption of radiation by the human body is the *sV*, named after Siewert, (a Swiss chemist). This is the SI unit of ionizing radiation that produces the same biological effect as 1 gray of high energy x-rays; 1.0 *sV* is the equivalent of 1.0 joule/kilogram or 100 rem.

BMD ASSESSMENT

A number of methods have been developed to calculate the Bone Mineral Density, including the use of quantitative CT, ultrasound and absorptiometry techniques (such as dual-x-ray absorptiometry (DEXA)). All these modalities attempt to determine the quality of trabecular cancellous bone, and correlate this to bone fragility and fracture risk.

Numerous studies have assessed the ability of each of these modalities to predict fracture risk and this is discussed in more detail below. There are a number of different techniques, but most studies suggest that CT, ultrasound and DEXA have comparable results [Frost, Blake and Fogelman, 2002; Grampp et al., 1995]. A recent meta-analysis suggested that DEXA has the strongest predictive value for fracture risk, and is especially useful at predicting hip fractures [Johnell et al., 2005].

In addition to being reliable, DEXA is quick, cheap, applicable to multiple anatomical sites, associated with a low radiation dose and easy to perform in a standardised manner, and has therefore emerged as the most commonly used technique (Figure 4-1). It is the locally available modality for assessing BMD, and so was used for this study, and so is discussed in more detail below.

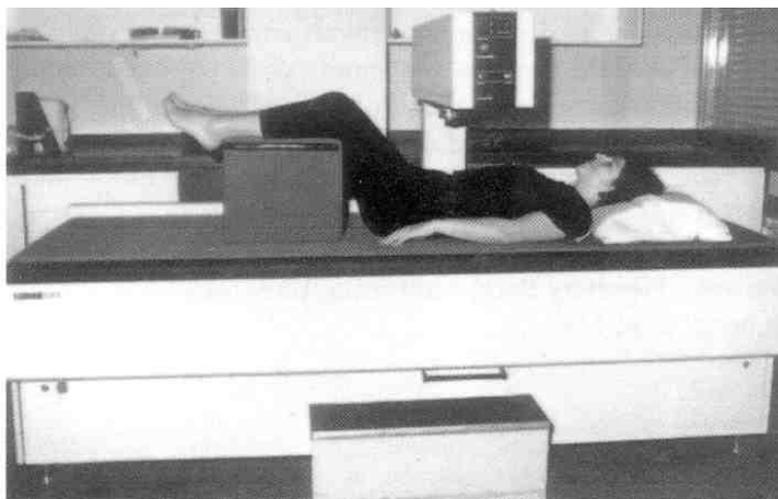


Figure 4-1. Bone Mineral Density assessment at the lumbar spine

SINGLE PHOTON ABSORPTIOMETRY

The early methods of assessing bone densitometry using absorptiometry were developed in 1963 (figure 4-2). Initial techniques used Single Photon Absorptiometry, whereby a single gamma ray energy source was transmitted through an anatomical site (usually the forearm) and a scintillation detector on the other side assessed how much energy had been absorbed. The usual gamma energy source was 125 Iodine. In order to correct for overlying soft tissue, the site being analysed had to be surrounded by water. This having a similar density to the soft tissues enabled a more accurate assessment of bone density in patients with variable soft tissue morphology. Because of this restriction, single photon absorptiometry was best suited for peripheral skeletal sites.

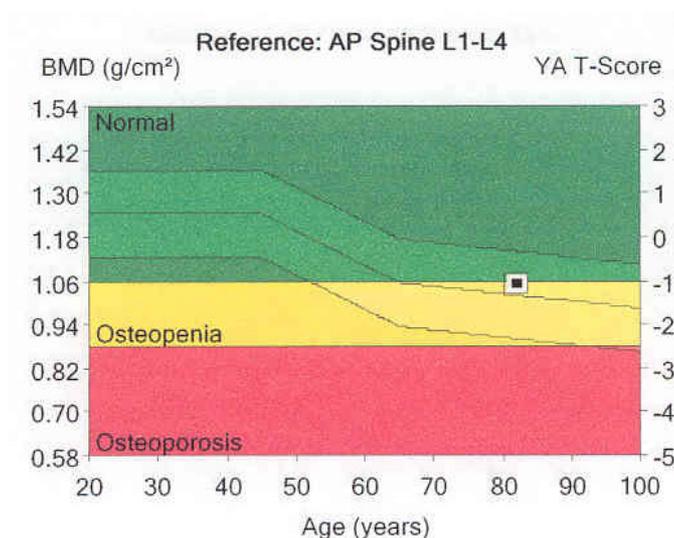


Figure 4-2. Absorptiometry of the lumbar spine

DUAL PHOTON ABSORPTIOMETRY

To allow the assessment of axial sites, Dual Photon Absorptiometry was developed. This involved transmitting gamma radiation at two different energies, one which was absorbed by bone, the other by soft tissues. This allowed the calculation of bone mineral density at sites where there is a variable degree of overlying soft tissue (such as the spine, hip and whole body). The source of the photon energy was usually the radionuclide, 153 Gadolinium which provided energy at 44keV and 100keV. Although this technique provided useful research data, it was limited by the long time to perform scans (up to 40 minutes) due to the low rate of photon emission, and the need to regularly replace the radionuclide source.

SINGLE ENERGY X-RAY ABSORPTIOMETRY

The use of a low dose X-ray tube instead of a radionuclide source led the way to Single and Dual Energy X-ray Absorptiometry (SEXA and DEXA). These techniques were much faster to perform and provided a far better spatial resolution and are now the most widely applied method of bone densitometry [Wahner and Fogelman, 1994].

With SEXA there is a single x-ray beam projected onto the patient's arm submerged in water to allow for correction for the soft tissues. Results are expressed as bone mineral content (BMC) in grams or bone mineral density (BMD) in g/cm². Studies show that the accuracy of SEXA is 3% (i.e. how close it is to the true value), its precision 1% (i.e. how reproducible it is) and the effective radiation equivalent dose is less than 0.1uSv. It is also reasonable quick with scanning taking around 5 minutes [Wahner and Fogelman, 1994].

Photon absorptiometry	Dual X-ray absorptiometry
Developed 1963	Developed 1987
125 Iodine or 153 Gadolinium source	High and Low energy x-ray beams
Limb submerged in water (single)	Axial and non-axial sites measurable
Measured with scintillation counter	High resolution pictures
Expensive, slow, high radiation	Cheap, fast, safe

Box 4-1. Photon and x-ray absorptiometry techniques

DUAL ENERGY X-RAY ABSORPTIOMETRY

DEXA was introduced in 1987 and is now the most widely used technique for clinical bone densitometry techniques. Energy is released at two frequencies, selected to optimise the separation of mineralised and soft tissue components of the sites scanned. Energy switching scanners release energy from an x-ray tube which oscillates between 70 and 140kVp at a rate of 60 times per second. K-edge Filtration scanners use a filter to separate the X-ray beam into "high" (70-80keV) and "low" (40-50keV) energy photons. The dual frequency prevents the need to submerge the arm in water.

Calculation of the relative amounts of energy at the two different frequencies allows estimation of the amount of energy absorbed by bone and soft tissue, and from this the BMC (measured in g) and BMD (measured in g/cm²) can be estimated.

RADIATION EXPOSURE

Radiation exposure to patients from a DEXA scan is relatively low compared to other radiological investigations involving ionising radiation [Lewis et al. 1994, Huda W et al. 1996]. The radiation dose for a DEXA is 1 μ Sv per site scanned, compared to 60 μ Sv exposure from a chest x-ray or 700-2000 μ Sv from a lateral lumbar spine plain radiograph. The scatter dose exposure for the operator is negligible, with accurate levels difficult to detect or quantify [Patel et al. 1996]. There is always a small risk associated with any ionising radiation, but the following list demonstrates how the risk of 1 μ Sv compares to the risk of death from a variety of other risks [Pochin et al. 1974]:

- Exposure to background radiation for 4 hours
- Smoking 1 tenth of a cigarette
- Travelling 3 miles in a car
- Travelling 15 miles by air
- Rock climbing for 5 seconds
- Canoeing for 20 seconds
- Working in a factory for half a day

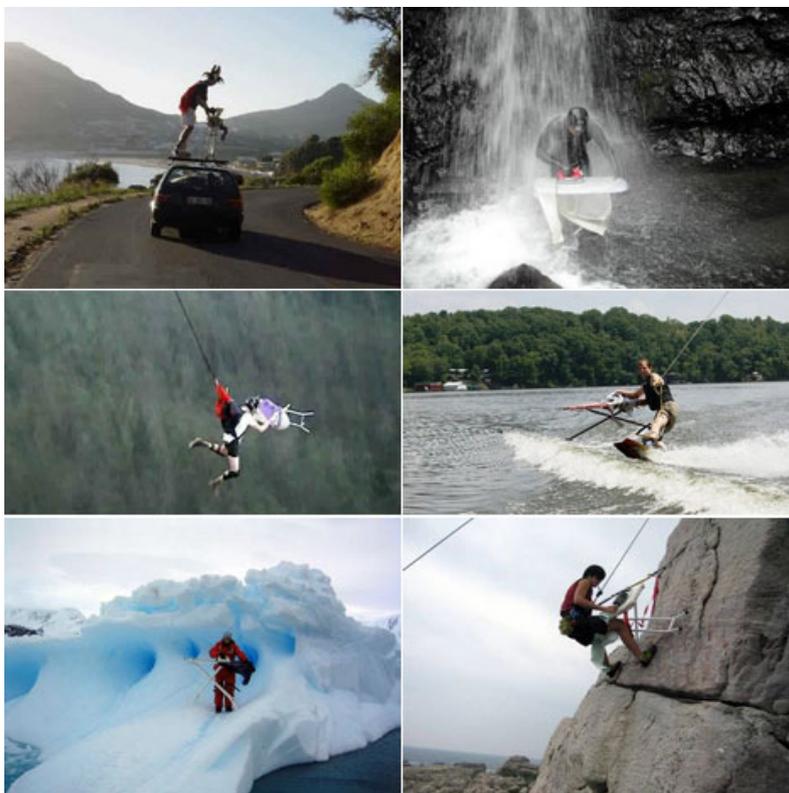


Figure 4-3. DEXA scans - not as dangerous as extreme ironing

ANATOMICAL REGIONS SCREENED FOR OSTEOPOROSIS

DEXA measures the trabecular and cortical bone mass as BMC or BMD. The ratio of cortical to trabecular bone is 80:20 in the whole body. In the lumbar spine it is 50:50, 60:40 in the proximal femur. For this reason the lumbar spine and hip are the areas usually scanned in clinical practice as this is where trabecular bone loss is best seen. DEXA is usually applied to the L1-L4 lumbar vertebrae, the proximal femur, the wrist and the whole body. The methodology for screening is described in more detail in the Methods section.

ANATOMICAL REGIONS SCREENED AFTER ARTHROPLASTY

Gruen and DeLee described discrete anatomical zones around a hip prosthesis [Gruen et al. 1979, DeLee and Charnley, 1976]; these are routinely used to describe the regions of loosening around a prosthesis. The femur is divided into seven zones in the AP view: the proximal, middle and distal thirds of the region around the prosthesis (as measured from the shoulder to the tip) both medially and laterally, and the zone distal to the tip of the prosthesis. Modifications have since described seven similar zones on a lateral projection. The acetabulum is divided into three AP zones based on horizontal and vertical projections arising from the centre of the cup, as shown in figure 4-4.

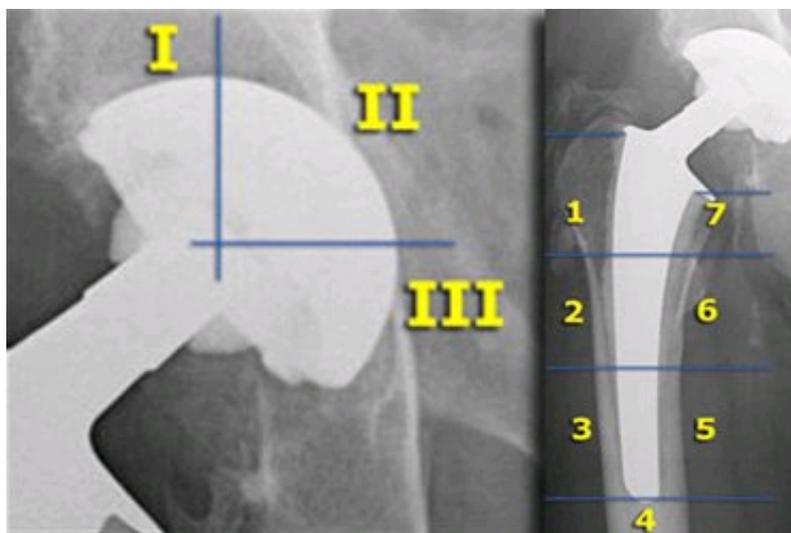


Figure 4-4. The three DeLee and seven Gruen zones around a hip prosthesis.

BMD assessment after hip arthroplasty is not a routinely performed investigation, and usually done as a research tool. Modern scanners have built in software capabilities that can automatically define and then calculate the BMD in each Gruen/DeLee zone.

ARTEFACTS AND ADJUSTMENTS

There are a number of osseous and non-osseous factors that must be taken into consideration to prevent an artefactually increased bone mineral density. These are listed in table 4-1. The way each of these factors was accounted for is detailed later.

Table 4-1. Factors that may confound DEXA BMD measurements

Osseous	Non-osseous	Prosthetic
Severe degenerate disease	Orthopaedic devices	Prosthesis subsidence
Vertebral fractures	Metal buttons, zips etc	PMMA cement
Aortic calcification	X-ray contrast media	Different prosthesis shapes
Paget's disease	Recent contrast studies	
Sclerotic bone tumours	Marked ascites	
Scoliosis	Patient movement	
Calcified nodes	Patient positioning	

BONE MINERAL DENSITY AND BONE FRAGILITY

BIOMECHANICAL STRENGTH

The bone mass of an individual increases throughout adolescence and young adulthood, reaching a peak bone mass in the late 20's. Thereafter there is a gradual decline with increasing age and in women, this decline accelerates after the menopause. There is considerable variation between individual's peak bone mass, it being dependent on gender and race, but it appears to be a strong prospective predictor of a patient's future fracture risk [Ross et al., 1990] and is the baseline value for calculating the T score.

Laboratory studies have shown that BMD is a good predictor of biomechanical strength [Krischak et al., 1999; Järvinen et al., 1998]. In the study by Krischak, they divided 33 femurs each into 39 cylindrical segments of cancellous bone (total 689 segments). The BMD was assessed using quantitative CT, and each segment was subjected to a compressive force using a stainless steel punch. Strength was measured as the total force required to cause collapse of the bone, and the Young's modulus of elasticity was also measured. Strength had a very strong Pearson's correlation coefficient of 0.86, and elasticity also having a good coefficient of $r=0.68$ (both $p<0.001$). Cody et al. [1996] found comparable predictive values of DEXA and 3D quantitative CT at assessing femur biomechanical strength.

FRACTURE RISK

There is fairly strong clinical evidence that low bone mass is a good predictor of bone fragility and subsequent fracture risk. Cummings et al. [1993] showed that a low BMD measured at various anatomical sites predicted hip fractures, but the strongest predictor was the BMD at the hip itself. A large meta-analysis of 12 studies and a total 39,000 patients, confirmed that BMD was the strongest predictor of fractures, with each drop of one standard deviation in BMD increasing the relative risk of fracture by 2.9 in both men and women [Johnell et al., 2005]. They also found that the relative risk was dependent on age: a low BMD was more important in younger patients. The reason for this finding is not known, but it is speculated that with advancing age, other factors become more important (such as general immobility and a tendency for falls).

EFFECTS OF HIP ARTHROPLASTY ON BMD

Implantation of a prosthesis alters the pattern of stress distribution in the femur and pelvis. Modern prostheses attempt to preserve as much bone as possible, yet despite this the altered strengths and plasticity of the prosthesis compared to bone means that the prosthesis transmits forces preferentially. This alteration of forces through bone inevitably results in changes in the morphology of bone (in accordance with Wolff's Law, 1870) and is one of the causative factors in development in arthroplasty loosening.

McCarthy et al. showed [1991] that up to 50% of the femoral bone mineral density can be lost following hip arthroplasty, with bone loss beginning proximally around the lesser trochanter and developing distally. Venesmaa et al. [2001] followed up 22 patients with serial DEXA scans for 3 years after total hip arthroplasty. They found that there was significant bone loss all around the prosthesis in the first year, greatest in zone 7 at the medial calcar (a reduction of 23%). Subsequently there was a slight restoration of BMD in the second year, which plateaued in the third year. Similar results were found by Aldinger et al. [2003] who reviewed patients after 7 years.

The physical properties of an implant are likely to affect the degree of stress shielding, and these depend on its length, thickness, material and size relative to the femoral canal. Engh and Bobyn [1998] found that these factors influenced the degree of bone resorption around an implant. Harvey (1999) found that highly flexible stems had more fibrous and less bony ingrowth than rigid ones - a finding likely to be due to the increase in micromotion (as demonstrated by Jasty et al. in 1997). However Harvey could not demonstrate any difference in stress shielding between these two types of stem.

Maloney et al. [1996] did an autopsy study of cemented and cementless arthroplasties to examine the bone mineral density and cortical thickness. They found a strong correlation between the BMD of the contra-lateral (non-operated) femur and the amount of bone loss around the operated hip. Engh et al. [1992] showed in another autopsy study that there is between 7% and 52% loss in bone mineral content after arthroplasty, and that the degree of this loss is proportional to the BMD of the contra-lateral hip. Both these studies draw similar conclusions to the hypothesis of our study that patients with osteoporotic bone are more likely to develop aseptic loosening.

DISUSE OSTEOPOROSIS

However the bone loss after arthroplasty is not purely due to stress shielding. Bryan et al. [1996] showed that bone loss is also seen in regions not affected by stress shielding, with bone loss apparent throughout the whole of the operated limb (such as in the femur distal to the prosthesis or in the proximal tibia), with gait analyses showing a tendency to avoid weight-bearing on the operated side. Adolphson et al. showed a similar post-operative loss in BMD in the lumbar vertebrae [1994]. These studies indicate that an element of the bone loss is probably due to disuse or post-traumatic osteoporosis.

BMD and hip arthroplasty
Stress shielding alters BMD after hip arthroplasty
Generalised reduction in body BMD seen
Up to 50% reduction of femoral BMD after THR
Greatest around the medial calcar
Greatest loss in the first year after surgery
Degree of loss dependent on prosthesis design
Also dependent on BMD of contra-lateral hip

Box 4-2. Effects of arthroplasty on BMD

5. BIOCHEMICAL MARKERS OF BONE FRAGILITY

The first section of this chapter will examine how the metabolism of calcium is controlled, and how these biochemical markers can provide information about bone fragility, and in particular fracture risk and aseptic loosening.

Calcium and phosphate are essential in providing structural support to hard tissues (such as bone and teeth) as well as for important intra-cellular signalling pathways. Because of the latter functions, the intra and extra-cellular levels of calcium need to be tightly regulated. In conditions such as chronic vitamin D deficiency and secondary hyperparathyroidism the mineralisation of bone is sacrificed to maintain extra-cellular levels.

The two key important hormones involved in regulating calcium and phosphate are parathyroid hormone (PTH) and 1,25 dihydroxy-vitamin D, although several other hormones also help regulate their haemostasis.

PARATHYROID HORMONE

Through their secretion of parathyroid hormone (PTH) the parathyroid glands are primarily responsible for maintaining extra-cellular calcium concentrations. The secretion of PTH, an 84–amino acid polypeptide is regulated directly by the plasma concentration of ionized calcium. Low circulating extra-cellular calcium is detected by Ca-sensing receptors on the chief cells of the parathyroid glands. This stimulates the chief cells to produce pre-pro-PTH, which is converted to pro-PTH and then to PTH prior to secretion. This is cleaved into a biologically active 34 chain protein either in the PTH gland or in the tissues (Figure 5-1).

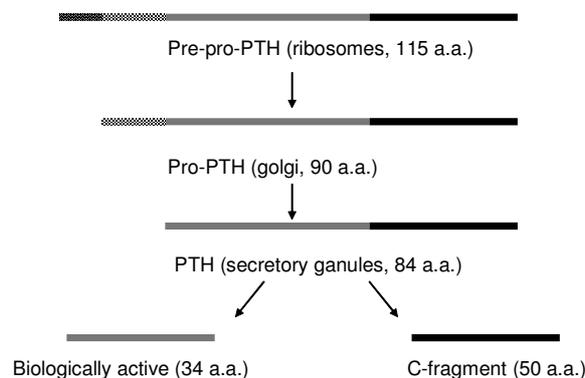


Figure 5-1. Parathyroid hormone metabolism in the chief cells

Mutations in the gene that encodes the Ca-sensing receptor can result in conditions such as familial benign hypocalciuric hypercalcaemia syndrome [Attie et al., 1983]. In this condition high circulating calcium does not inhibit PTH production (causing hypercalcaemia), and inhibits renal excretion (causing hypocalcuria).

Parathyroid hormone
84 amino acid protein
pre-pro PTH converted to pro PTH which is converted to PTH
Increases serum calcium
- increases renal calcium resorption and vitamin D activation
- increases osteoclast bone resorption

Box 5-1. Parathyroid hormone (PTH)

ACTIONS OF PARATHYROID HORMONE

Secreted PTH has a short half life (<5mins), which has implications on measuring it. High serum calcium also has the ability to inhibit PTH release – this is brought about by repression of the PTH gene in chief cells, which ultimately reduces the amount of PTH produced. The main effects of PTH are to increase the concentration of plasma calcium by actions on the bone and the kidneys. PTH also acts indirectly on the intestine through its activation of vitamin D. The actions of PTH are mediated through the actions of the PTH receptor, found in the proximal and distal renal tubules and osteoblasts. PTH-receptors are also found in other developing organs,

In the bone PTH increases the release of calcium and phosphate from bone matrix by stimulating the release of osteoclasts-activating factors such as IL-6 from osteoblasts. In the kidneys, PTH directly increases calcium levels by increasing resorption in the cortical thick ascending tubules and indirectly by causing hydroxylation of 1,25-dihydroxyvitamin D-3 (calcitriol) in the proximal convoluted tubule which subsequently allows increased intestinal absorption of calcium. PTH also directly stimulates calcium resorption in the kidney and excretes phosphate, thereby decreasing serum phosphate levels. Thus, overproduction of PTH results in elevated levels of plasma calcium (Figure 5-2).

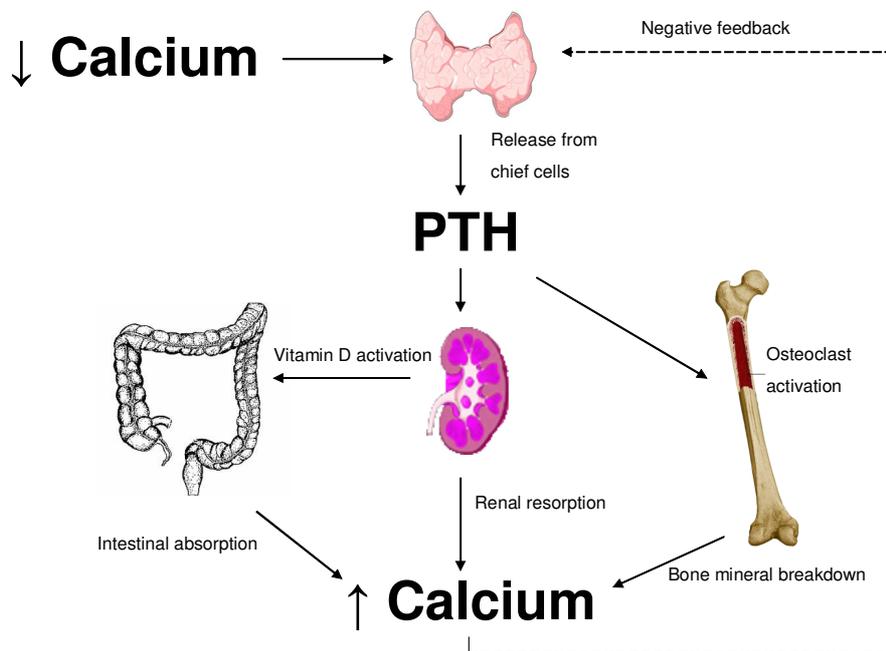


Figure 5-2. PTH increases calcium via gut, renal and bone metabolism

SECONDARY HYPERPARATHYROIDISM

Several studies, including the one by Bruce et al. [1999] have observed hyperparathyroidism and vitamin D deficiency in elderly patients with hip fractures (Figure 5-3). Sahota [1999] measured vitamin D and PTH levels in community dwelling elderly women. They found that the two were inversely proportional ($r=-0.42$, $p<0.01$) and that those with vitamin D insufficiency had significantly higher biochemical markers of bone turnover (for both bone resorption and formation).

Mild undiagnosed hyperparathyroidism may not be an uncommon finding among postmenopausal women [Glowacki et al., 2003]. The condition appears to have no major consequences at least for elderly women, as confirmed in a recent screening programme of 5212 women (average age 80 years). 2.5% of them fulfilled the criteria for mild primary hyperparathyroidism, which was associated with significantly reduced BMD but the incidence of clinical fractures was not affected during the median follow-up of 4 years. This may well be because the number of patients with hyperparathyroidism and the incidence of fractures were too small.

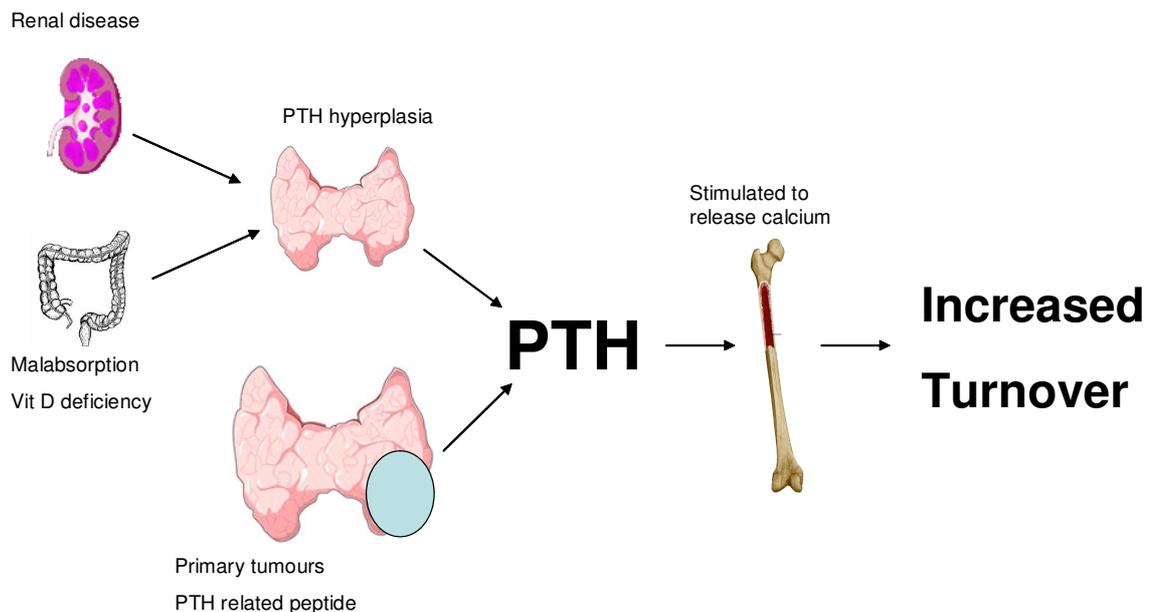


Figure 5-3. Mechanism of secondary hyperparathyroidism.

There is very little evidence correlating parathyroid hormone levels with arthroplasty loosening. The epidemiological study by Glowacki mentioned above found that 4% of women awaiting hip arthroplasty have hyperparathyroidism, but did not correlate this to outcome.

VITAMIN D

In humans, as in other vertebrates, the major role of vitamin D is to increase the absorption of calcium and phosphate for the mineralization of the skeleton. Deficiency in childhood results in the bone cartilage not being calcified, causing rickets. In adults, newly formed bone matrix (osteoid) is not mineralised, causing osteomalacia. Although these two conditions are relatively rare, less severe vitamin D deficiency is common, particularly in the elderly [McKenna 1992]. In addition to intestinal absorption of calcium, vitamin D also plays important roles in bone remodelling and renal absorption of calcium and phosphate.

Vitamin D₃ (cholecalciferol) is synthesized in the skin by the action of ultraviolet light. Its precursor, 7-dehydrocholesterol is first converted into previtamin D₃, which slowly isomerises into vitamin D₃. Vitamin D binding protein (DBP), a liver produced glycoprotein binds around 85% of vitamin D and transports it in the bloodstream. Around 0.4% of vitamin D is transported free, with the rest bound to other proteins. Vitamin D₃ may also be found in some food sources (including fatty fish, eggs and dairy products). Vitamin D₂ (ergocalciferol) has a similar metabolism to D₃, and is frequently added to dairy products and vitamin supplements. It is formed by UV irradiation of ergosterol, frequently found in plants.

Vitamin D is hydroxylated first in the liver into 25-hydroxyvitamin D (25(OH)D) and then in the kidney into its major active metabolite 1,25-dihydroxyvitamin D (1,25-(OH)₂D,). The production of 1,25-(OH)₂D is under tight feedback control. The final renal hydroxylation is by the enzyme 1- α hydroxylase. High levels of PTH stimulate this enzyme's transcription, but the reverse effect is caused by high levels of calcium, phosphate and 1,25-dihydroxyvitamin D. In these circumstances 25-hydroxyvitamin D is instead hydroxylated into 24,25-dihydroxyvitamin D. The function (if any) of this metabolite is unknown (Figure 5-4).

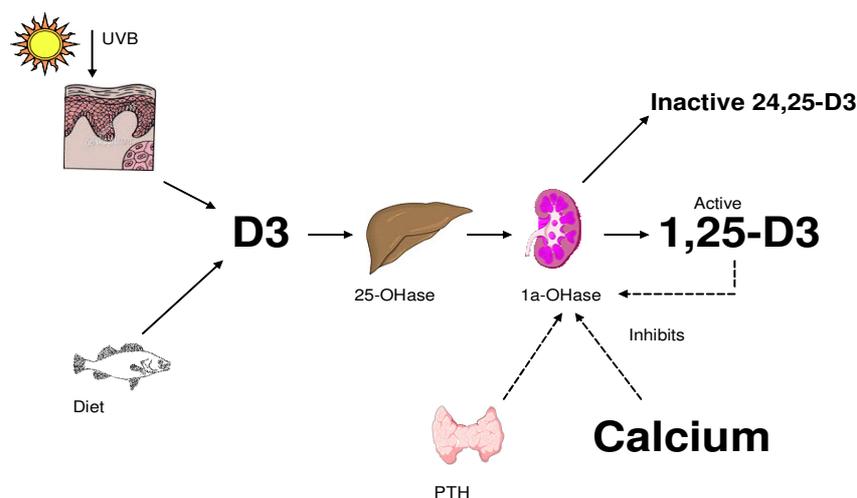


Figure 5-4. Metabolism of vitamin D

ACTIONS OF VITAMIN D

99% of the active metabolite, $1,25\text{-(OH)}_2\text{D}$, is bound in the plasma to either DBP or albumin. It exerts its action by interacting with the vitamin D receptor (VDR), present in various sites. When $1,25\text{-(OH)}_2\text{D}$ binds to VDR it acts directly on DNA as a transcription factor, stimulating gene expression. In the intestine it stimulates the production of several proteins which participate in the transport of calcium from the intestinal lumen into the bloodstream (Figure 5-5).

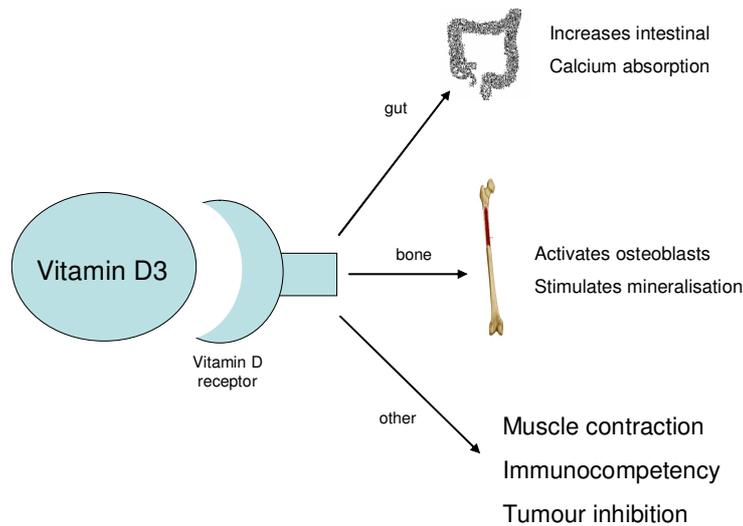


Figure 5-5. Actions of vitamin D

As well as in the intestine, VDR is present in a number of other tissues including muscle, bone, pancreas and the pituitary. Its effects on bone are incompletely understood, but it does stimulate osteoblasts to produce osteocalcin and alkaline phosphatase. It also causes bone matrix production and by increasing serum calcium and phosphate levels it also indirectly stimulates mineralization [Lips 2007]. Other studies, however, suggest that vitamin D itself may have an inhibitory effect on bone production, with animal and *in vitro* studies showing it to inhibit collagen production and stimulates bone resorption [Norman et al. 1982, Reichel et al. 1981].

In muscle it stimulates cell differentiation and muscle function. This is of particular importance with regards to fracture risk, as vitamin D deficient patients have been noted to have abnormal muscle contraction and relaxation that is reversed by vitamin D supplements [Boland, 1986]. This leads to problems with coordination and balance, and Vitamin D deficiency has also been related to the tendency to fall in nursing home residents [Stein et al., 1999].

VITAMIN D REQUIREMENTS

Vitamin D₃ production is dependent on a relatively small range of UV light frequency (290-315nm). UV light is absorbed by glass, plastic, clothing, and to a lesser extent, the atmosphere [Lips, 2001]. Because during the winter months in northern Europe, sunlight needs to pass through more of the atmosphere, vitamin D production is virtually absent between October and March. Vitamin D synthesis is also reduced in pigmented skin, thin skin and in the elderly [Clemens, 1982; Holick 1989].

Despite this, the production of vitamin D is efficient and it has been estimated that a 10 minute exposure of the head and arms to sunlight three times a week is enough to produce sufficient vitamin D [Chel et al., 1998].

VITAMIN D DEFICIENCY

Clinically, vitamin D deficiency is associated with symptoms of bone pain and muscle weakness. Serum calcium and phosphate levels are low, due to lack of intestinal absorption, and alkaline phosphatase levels are high, due to an increased PTH-driven bone resorption to maintain satisfactory calcium levels. In the last 25 years, serum measurements of 25(OH)D have made the diagnosis easier, but insufficient international standardisation of assays has led to difficulties interpreting results. Lips et al. [1999] found a 38% variation in the mean values of the same samples analysed in five different laboratories.

Vitamin D deficiency can be defined in two ways: either by population based reference limits of vitamin D assays, or by biological indices such as hypocalcaemia with elevated alkaline phosphatase or PTH levels (health-based limits). A large number of studies have assessed the prevalence of vitamin D deficiency in a variety of patient groups and a variety of reference ranges. The European SENECA (Survey in Europe on Nutrition and the Elderly, a Concerted Action) study suggested lower reference limit of 30nmol/litre (12ng/ml) [Van der Wielen et al., 1995].

Serum levels are lower in European countries than in the United States, which may be due to the fact that milk and other foods are fortified with Vitamin D in the United States. A study in Amsterdam showed a gradual decline in Serum 25(OH)D levels from healthy adults, to independent elderly to institutionalised elderly to hip fracture patients [Ooms, 1994].

Vitamin D deficiency is characterised by a low serum 25(OH)D level and this leads to a decrease in 1,25(OH)₂D and so calcium absorption. The lower serum calcium level leads to an increase in PTH secretion which stimulates an increase in renal production of 1,25(OH)₂D. By this mechanism, 1,25(OH)₂D is kept at near normal level at the expense of a higher PTH concentration. This is termed secondary hyperparathyroidism, and it implies that serum PTH is relatively high for the calcium levels (although it may still be within normal reference limits). It is also thought that 1,25(OH)₂D inhibits PTH synthesis, and so deficiency of this would be another cause of hyperparathyroidism.

The increase in PTH level results in an increase in bone turnover, which usually occurs in cortical rather than trabecular bone. This is thought to be the principal mechanism by which vitamin D deficiency leads to bone fragility.

Vitamin D deficiency
Seasonal variation, dependent on sunlight exposure
Need 30 min sunlight per week for normal levels
Associated with low calcium and phosphate, and an elevated ALP
Poorly defined criteria for deficiency
8-17% elderly population are deficient
Conflicting evidence whether supplementation reduces fractures
Deficiency common in patients awaiting arthroplasty
No evidence whether deficiency influences outcome

Box 5-2. Vitamin D deficiency

VITAMIN D DEFICIENCY AND FRACTURE RISK

Vitamin D deficiency is extremely common [Venning, 2005], particularly in the elderly, with reported incidences of 8% in patients between 65 and 64 years up to 17% in those over 85 years [Semba et al., 2000]. Despite the importance of vitamin D for normal bone physiology there is conflicting evidence as to whether vitamin D supplements are beneficial.

Conflicting evidence exists whether Vitamin D supplements reduce the incidence of fragility fractures. Longitudinal studies of healthy, ambulant women found that severe vitamin D deficiency was rare, and that vitamin D levels are neither correlated to BMD or fracture risk over 11 years. Several placebo controlled randomised trials [Meyer et al., 2002; Lips et al. [1992] found no reduction in fracture risk after administration of vitamin D supplements to nursing home residents. The RECORD study (Grant et al., 2005) found no benefit of giving calcium or vitamin D supplements to ambulant patients following a Colles' fracture.

Contrary to this Chapuy et al. [1992] found that calcium and vitamin D supplements reduce hip fractures by 43% in similar population groups. Other studies suggest that higher doses (800 IUL) of vitamin D are safe and may be more effective [Dawson-Hughes et al., 1997], although such preparations are not readily available in the UK.

VITAMIN D DEFICIENCY AND ASEPTIC LOOSENING

Less work has been undertaken to show whether there is an association between arthroplasty loosening and vitamin D deficiency. There is evidence that vitamin D deficiency is common in patients awaiting hip arthroplasty, but little evidence whether it influences rates of loosening or revision. An epidemiological study by Glowacki in 2003 found that 25% of women awaiting total hip replacement had osteoporosis that was unrecognised prior to their surgery and 22% had vitamin D deficiency. A small study by Tauber in 1989 of 15 patients with aseptic loosening found that only one had vitamin D deficiency, however this study was conducted in Israel which has considerably more sunlight exposure than the UK. It also has more sunlight than Boston, where the study by Glowacki et al was conducted.

BONE TURNOVER MARKERS

Various markers are expressed more in states of bone formation and others in states of bone resorption. Turnover markers are now frequently used as a surrogate marker to study the effect of drugs in the treatment of osteoporosis, and several studies have used them as an indicator of aseptic arthroplasty loosening. Because the resorptive phase of remodelling happens earlier and faster, its markers tend to respond faster and be easier to measure than bone formation markers (Figure 5-6). The detectable levels of bone turnover markers are also affected by diurnal, menstrual, seasonal and dietary factors.

BONE FORMATION MARKERS

Osteocalcin is a non-collagen protein, 49 amino acids long, thought to be involved in the attachment of hydroxyapatite crystals to collagen. Being found only in bone and dentin, it is a reasonably specific marker of bone formation and several studies have shown it to be higher in aseptically loose hips [Li 2004 and Schneider et al., 1997]

Procollagen extension peptides are segments of protein that are cleaved off pro-collagen at the amino and carboxyl terminal ends. They may be measured by immunoassay, but are non-specific, being raised with increased turnover of non-bone tissue such as skin, and have not been shown to be raised in patients with aseptic loosening [Schneider et al., 1997].

Alkaline Phosphatase, for which there is a bone specific iso-enzyme, is an enzyme released by osteoblasts. It is involved with bone mineralisation, although its precise mechanism of action is unknown. Its deficiency leads to the condition hypophosphatasia, characterised by osteomalacia. Its level may be raised in conditions with significant bone deposition like Paget's disease, but it has not been found to be increased in osteolysis [Schneider et al., 1997].

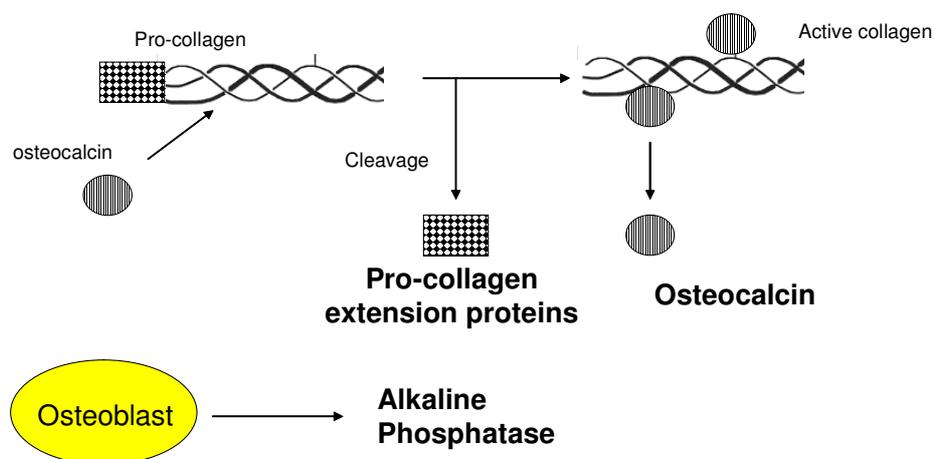


Figure 5-6. Bone formation markers.

BONE RESORPTION MARKERS

Bone resorption markers (Figure 5-7) tend to be breakdown products of type 1 collagen and its associated cross links. The structure of the collagen is not specific to the bone and so cannot be used as an accurate marker of bone turnover. It is arranged as a triple helix with an amino (N) and carboxyl (C) end points. The ends of the helical chains overlap, like bricks, and cross-links found at both the amino and carboxyl ends of collagen secure one triple helix to its neighbour. When the collagen matrix is broken down during bone resorption, fragments of collagen and/or the cross links are released into the blood.

Cross-linked telopeptides (NTX and CTX) are the amino and carboxyl terminal ends of the collagen helix together with their attached crosslink. They are excreted in the urine and can be measured in the urine or serum by immunoassay. As well as being important markers used to prove the inhibition of osteoporosis in pharmaceutical studies, other studies have shown the levels of NTX to be raised in cases of aseptic loosening [Schneider et al., 1997 and 2000, Yamaguchi et al. [2003] and another study has shown that this increase can be reversed by bisphosphonates [Antoniou et al., 2000].

There are two types of cross-link, pyridinoline (PYR) and deoxypyridinoline (DPD) and these may also be measured in the urine. PYR levels are higher, but are less specific to bone cross-links than DPD. Various studies have shown conflicting accuracy of measuring these in aseptic loosening. Schneider et al. [2000] and Wilkinson et al. [2003] found an increase but Witzleb et al. [2001] did not. Forty percent of the hydroxyproline released from type 1 collagen breakdown is excreted in the urine, but as it is also the breakdown product of other types of collagen, only 50% of urinary hydroxyproline is from bone. It is therefore not a useful marker of osteolysis. Tartrate Resistant acid phosphatase (TRAP) is a bone specific isoform of acid phosphatase found on the surface of osteoclasts, and so may also be raised in states of increased bone turnover.

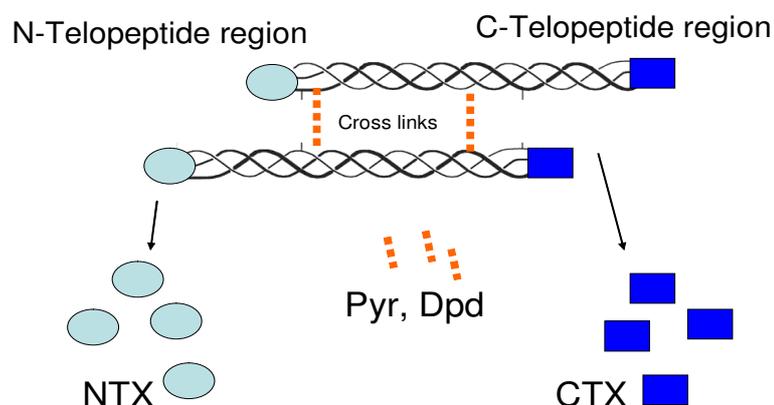


Figure 5-7. Bone resorption markers

METHODS

6. PATIENT SELECTION

PROJECT LOGISTICS

ETHICS

Following submission of a full protocol and the relevant paperwork to the local ethical committee the project was approved to contact and recruit participants and perform the desired investigations.

FUNDING

Funding for the administrative costs and necessary reagents to perform the biomechanical studies was provided by a £2000 grant from the Foxtrot charity. Radiographs were clinically justified to screen for loosening in an established high risk group. DEXA scans were funded by the rheumatology department, but had to be performed on a Saturday to avoid conflict with clinical work.

STATISTICAL ANALYSIS

Choice of statistical tests was made after discussion with a medical statistician at the Trent Institute at Leicester University. Appropriate tests were used for parametric and non-parametric data using Microsoft Excel and SPSS. Statistical significance was taken for p values <0.05 , and statistical trends for $p < 0.1$. Binary logistic multivariate analysis was performed for each study. For this test, the least significant variable was excluded before repeating the analysis until only significant variables remained. The benefit of this type of analysis is that significance levels are re-checked after non-significant variables have been removed.

PATIENT CONTACT AND CONSENT

Each patient was contacted by letter and invited to participate in the study. They were given an information leaflet detailing what the study was about and what was required from them. Willing participants completed a reply slip and were contacted by phone to arrange an appointment with the Principal Investigator.

The outpatient appointments were between March and May 2006 at the Glenfield Hospital. The purpose of the study, what was involved and potential risks were explained to the patients. Providing they agreed to take part, the other parts of the study were arranged. A signed consent form was kept in the study notes and the patient given the Patient Information Sheet to keep. Any participants not prepared to take part in any aspect of the trial were allowed to do so without any pressure being put upon them.

MATCHING OF AGE, SEX AND PROSTHESIS

For accurate matching, two groups of patients needed to be identified – those with and those without loosening. The causes of both osteoporosis and aseptic loosening are multi-factorial, and we aimed to eliminate as many known confounding variables as possible between the two groups. By doing this we aimed to assess the impact of individual variability in bone metabolism on arthroplasty loosening.

The confounding variables can be categorised into those that influence bone metabolism such as age and gender, and those related to the prosthesis itself such as the type of prosthesis, method and time since insertion.

Although hip arthroplasty is a commonly performed operation and aseptic loosening a relatively common complication, it is often difficult to identify a suitable cohort of patients with aseptic loosening. This is because patients are not routinely followed up for long periods of time, and because arthroplasty aseptic loosening is frequently asymptomatic. Those patients with aseptic loosening that are under review tend to have a wide variety of prosthesis's that have been *in situ* for a varying length of times. Frequently, by the time a loose hip becomes painful and the patient re-presents, revision surgery is indicated. It is therefore hard to identify a group of stable, but loose, hips for analysis.

Matching scheme
Aim to eliminate known confounding variables
All patients had same ElitePlus prosthesis
All patients had surgery in the same hospitals
Matched for age, sex and time since surgery

Box 6-1. Summary of the matching scheme used

SELECTION OF PATIENTS WITH LOOSENING

Initially, suitable patients were identified from a previous audit conducted 5 years previously by Rowsell et al. This audit identified that an unusually high number of patients (21%) had developed signs of loosening at a mean of 4 years after surgery. The criteria used in 2001 to describe loosening is shown in table 6.1. From this audit group, patients with loosening were carefully matched by age/sex/time since surgery to stable controls. It was anticipated that in the intervening 5 years that a number of patients from the stable arthroplasties would develop loosening and so change groups. With this in mind, all patients were re-xrayed and the groups adjusted accordingly. To accommodate for this cross-over, two controls were selected from the 2001 audit to ensure roughly equal numbers by the time re-matching had been done. Patients' age, sex and time since surgery were compared after re-matching to ensure they were still comparable.

This group of patients made a unique study group as all the patients had the same cemented prosthesis, all had their operation within a short period of time and all operations were performed in the UHL Teaching Hospitals by a small number of surgeons with similar practices. For these reasons, the number of confounding factors is kept to a minimum and the chances of seeing a statistically significant difference between two groups maximised.

One confounding factor of this study is that although all patients had the same cemented femoral stem, there was a mix of types of acetabular components and bearing surfaces used. Clearly, patients with hard bearing ceramic implants have different degrees and types of wear, and as discussed earlier, this could influence the degree of loosening. This is acknowledged, and would need to be addressed in future studies, but it is still felt that the group is as homogenous as realistically possible for this study.

PATIENT NON-PARTICIPATION

Most patients that were contactable were happy to participate in at least part of the study. Where possible appointments were made at times most suitable for the patients and contact was made by the Principal Investigator. If patients were unable to attend for review they were questioned over the phone.

Table 6-1. Rowsell criteria for arthroplasty abnormality and failure

Criteria	Example
Scalloped endosteal or intra-cortical bone loss.	
Appearances of destruction of bone.	
>2mm radiolucent zone at the cement-bone interface	
Osteolysis in 4+ zones was classed as failure	

NUMBER OF PATIENTS IN EACH GROUP

132 potential participants were identified in 2001, and 127 (96%) had recent radiographs available for examination and classification of loosening. Based on this 49 patients (39%) had a stable arthroplasty, 43 (34%) had mild loosening and 35 (22%) had severe loosening

NUMBER OF PATIENTS IN EACH STUDY

Of the 127 potential participants, 106 (83%) had their pre-operative radiograph and immediate post-operative radiograph available for review, 100 (79%) completed the questionnaire for study A, 75 (59%) had a DEXA scan and 80 (63%) gave a blood sample for analysis. A summary of the patients reviewed is in the table below.

Although there was a good uptake in the clinical and radiological studies, there were significantly fewer patients available for the BMD and biochemical studies. This could influence the validity of any results. It is unlikely the uptake could be significantly improved as only 9% were lost to follow up and 5% were too unwell to attend. The remaining 28% refused to take part in further parts of the study, and no attempt was made to coerce them.

Because of these reasons, slightly different subsets of these patients were available for each part of the study (pre-operative radiograph review, clinical review, bone densitometry, and biochemical analysis, table 6.2). Patients who had died, who were unable to attend for medical reasons or were lost to follow up still had their pre and post op radiographs reviewed.

Table 6-2. Number of patients reviewed in each component of the study

A	Clinical	Completed and returned questionnaire	100 (79%)
		Refusing to take part in study	10 (8%)
		Lost to follow-up	11 (9%)
		Died/ medically unwell	6 (5%)
B	Radiological	Pre-op radiograph available	106 (83%)
		Pre-op radiograph unavailable	21 (17%)
C	BMD	Had DEXA scan	75 (59%)
		Refused to take part in study	35 (28%)
		Lost to follow-up	11 (9%)
		Died/ medically unwell	6 (5%)
D	Biochemical	samples available for analysis	80 (63%)
		Refused to take part in study	11 (9%)
		Lost to follow-up	30 (28%)
		Died/ medically unwell	6 (5%)

7. CLINICAL RISK FACTORS

CLINICAL RISK FACTORS FOR BONE FRAGILITY

The aim of this study were assess whether patients with loosening had any identifiable clinical risk factors for osteoporosis. Secondary aims were to assess if there was a difference between the two groups' level of pain and function. After matching for age, sex and prosthesis, the following additional risk factors for osteoporosis were screened for in a structured interview, conducted by the Principal Investigator.

PREVIOUS FRAGILITY FRACTURE

A careful history of previous fractures was taken. Fragility fractures were defined as sustaining a fracture after a fall from standing height or less, and the occurrence of any of these was recorded. High energy fractures, childhood or early adulthood, and fractures to bones not typically affected by bone fragility (such as midshaft fractures of long bones) were excluded.

UNDERLYING DIAGNOSIS

The underlying pathology was determined by consultation with the patient and reviewing of their medical notes. Pathologies were categorised into being due to primary osteoarthritis (OA), developmental dysplasia of the hip (DDH), Rheumatoid arthritis (RA), secondary to Perthes' disease, avascular necrosis (AVN) or slipped capital femoral epiphesis (SCFE). This was more broadly classified into having primary osteoarthritis (OA) or another pathology (Non-OA). It is acknowledged that the non-OA group includes a number of disease processes such as altered biomechanical loading, joint non-congruity, inflammation and infective arthropathies. These behave in a number of different ways, but the usually common pathway way is development of secondary OA. Because the numbers are relatively small in each group it was decided to analyse them together. Assessments were later made to examine the bone mineral density according to underlying diagnosis (see Study C for details).

BODY MASS INDEX

Body mass is thought to influence bone health. Comparisons were made between Body Mass Index, weight (in kg) and Bone Mineral Density and the degree of loosening. All participants' heights were measured and they were weighed in clinic, using the same set of calibrated weighing scales. The Body Mass Index (BMI) was calculated using the following equation:

- $BMI = \text{weight in kg}/(\text{height in metres})^2$

MENOPAUSE

Bone loss accelerates after menopause in women. To determine whether this was a factor in predicting development of loosening, post-menopausal women were asked the date of their menopause. Early menopause was defined as occurring before the age of 40 years and analysed separately.

PAIN AND FUNCTION

PAIN

Participants were asked about the maximum amount of pain they experienced from their hip during the last 4 weeks. This was on a visual analogue scale from 0 (none) to 10 (worst pain imaginable). This was done by the Principal Investigator so that non-hip originating sources of pain could be excluded.

FUNCTION

The level of function was determined using the Oxford Hip Score, a validated 12 part questionnaire about pain and function due to the hip [Dawson et al. 1996]. All patients were assisted in completing the questionnaire to ensure that the pain or restricted function were attributable to their hip and not another pathology (e.g. lumbar spine or knee problems). It examined the following 12 categories from a scale of 1 (best) to 5 (worst), generating an overall score ranging from 12 (best) to 60 (worst):

- Day to day pain
- Night pain
- Sudden severe pains
- Limping
- Walking distance
- Ability to climb stairs
- Shopping
- Putting on shoes/socks
- Changing position
- Using cars/public transport
- Washing/cleaning
- Work

USE OF A STICK

This was used as a separate marker of function and disability.

8. ASSESSMENT OF RADIOGRAPHIC MARKERS

The primary aim of this study was to assess whether measurements of a patient's pre-operative radiograph could predict patients likely to develop aseptic loosening. The secondary aims were to assess the influence of the Singh Index of osteoporosis and the Bombelli classification of osteoarthritis and on aseptic loosening. Finally multivariate analysis was performed to assess the influence of multiple radiographic factors.

Comparisons were made between patients with stable arthroplasties and those with either mild or severe degrees of loosening (as defined in the introduction) or pooled data from these latter two groups. Statistical analysis was as discussed in the results section.

CORTICAL BONE STRENGTH

An estimation of the cortical bone strength was made by measuring the thickness of the medial cortex of the proximal femur. This being a weight-bearing area should normally have some of the strongest bone of the body. Although this method provides reasonably accurate and reproducible information about cortical bone, it does not assess trabecular bone or provide information about the bone mineral content or abnormalities of bone turnover.

Using a digital calliper, (with a calibration accuracy of 0.1mm) the absolute thickness of the medial femoral cortex was calculated. This was termed the Medial Cortical Thickness, figure 1. Each measurement was made in a standardised fashion, at a measurement of 50 mm below the base of the lesser trochanter.

Many of the radiographs were old and taken at different degrees of magnification with no calibration markers. In addition participants were of varying sizes with different sized femurs. To accommodate for this we also calculated a ratio of the thickness of the medial femoral cortex compared to the thickness of the femoral shaft at the same level (Figure 8-1). This was termed the Cortex Ratio, with a value from 0 to 1:

$$\text{Cortex ratio} = \text{cortical thickness} / \text{shaft thickness}$$

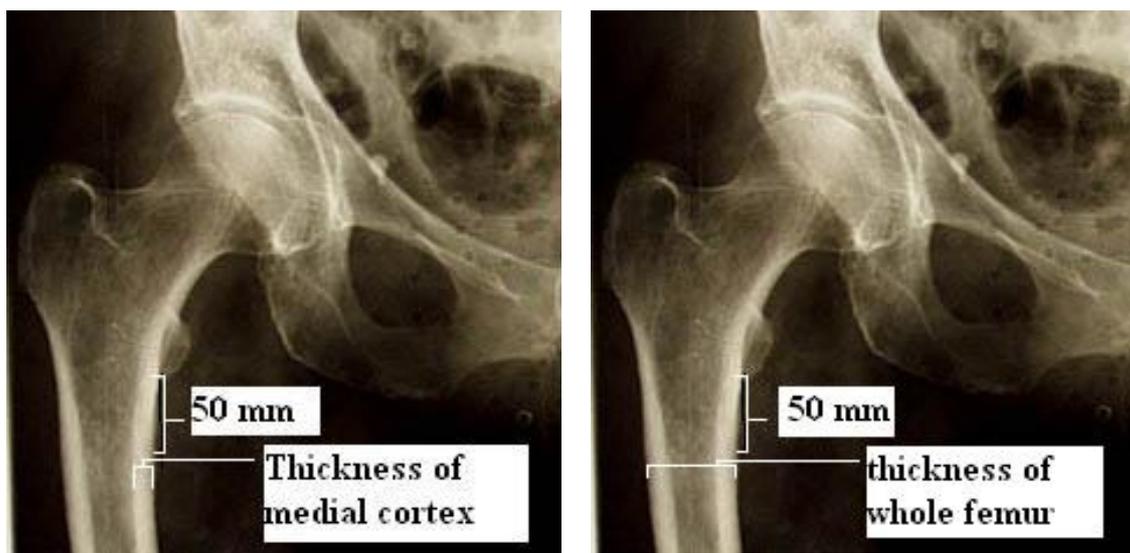


Figure 8-1. The medial femoral cortical thickness, and shaft thickness

NARROW CORTEX RATIO

The following example (Figure 8-2) illustrates a patient with a narrow cortex ratio. In this case the medial cortex measured 5.1 mm, and the shaft 31.2 mm, with a resulting Cortex Ratio of 0.17 (17%).



Figure 8-2. Example of a narrow femoral cortex

WIDE CORTEX RATIO

In contrast, the following example (Figure 8-3) illustrates a patient with a wide cortex ratio. In this case the medial cortex measured 14.6mm, and the shaft 43.4 mm, with a resulting Cortex Ratio of 0.34 (34%).



Figure 8-3. Example of a wide femoral cortex

CANCELLOUS BONE STRENGTH

We had anticipated that assessing the Singh Index on the pre-operative radiographs would help provide an assessment of the cancellous bone strength. However, during review of the available films with a consultant radiologist, a number of difficulties were encountered. It was apparent that due to the presence of degenerate changes within the hip joint and variable degrees of osteophyte formation around the femoral head, it was not possible to accurately assess the Singh Index. This was particularly apparent in patients with hypertrophic OA.

When the contra-lateral side was examined instead, there were less problems with osteophyte artefact, however the radiograph could not be assessed in all patients as a significant proportion (21/106) had had a hip arthroplasty on that side already. Others had degenerate changes present bilaterally.

With these limitations in mind the Singh Index was assessed, but not too much weight was put on the results.

CLASSIFICATION OF OSTEOARTHRITIS

All available pre-operative radiographs were carefully examined by the principal investigator and with a consultant radiologist (Dr Jeyapalan). The type of osteoarthritis was graded into being hypertrophic, normotrophic or atrophic using the classification system described by Bombelli [1983]. The following criteria were used for each group:

- Atrophic – absent or small osteophytes (<2mm, Figure 8-4)
- Normotrophic – moderate osteophytes (2-5mm)
- Hypertrophic – large osteophytes (>5mm, Figure 8-5)

It is accepted that the degree and size of osteophyte formation is a continuous variable, and so most of the analysis compared the hypertrophic and atrophic groups at either end of the spectrum. We also analysed whether there was a correlation between the classification of osteoarthritis and the underlying diagnosis (osteoarthritis, rheumatoid, DDH etc).

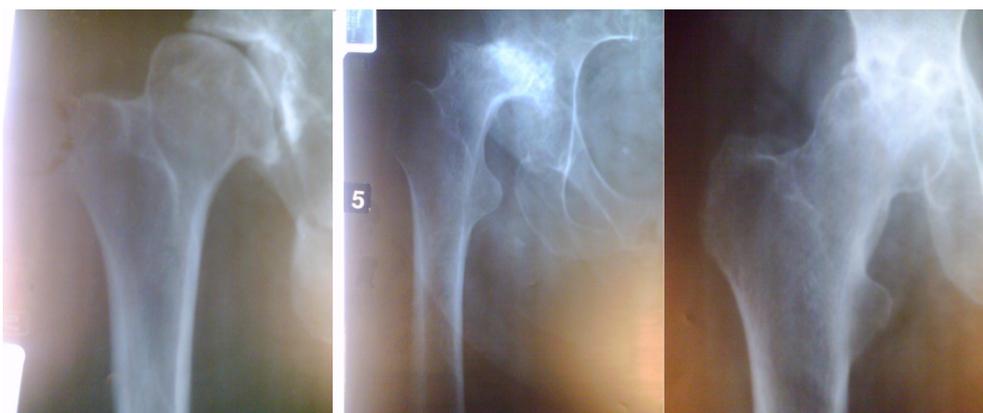


Figure 8-4. Examples of atrophic OA



Figure 8-5. Examples of hypertrophic OA

MULTIVARIATE ANALYSIS

After discussion with a medical statistician, binary logistic regression was performed using a backward LR model. To improve the statistical power, binary outcome measures were assessed (i.e. presence or not of loosening). Independent variables were the Cortex Ratio (CR), Bombelli classification and Singh Index. Because a significant proportion of patients couldn't have their Singh Index assessed the model was run twice, with and without the use of this variable.

REPRODUCIBILITY OF THE RADIOGRAPHIC MEASUREMENTS

Precision of the measurements was made by calculating the coefficient of variance for each measurement. This was done by measuring the medial cortical thickness (MCT) and femur thickness (FT) using the same method 5 times in 3 radiographs (a, b and c). The mean, standard deviation and coefficient of variance (SD/mean) were calculated and listed in table 8.1 below:

Table 8-1. Reproducibility of cortical measurements

	<i>Measurement (mm)</i>					<i>SD</i>	<i>Mean</i> <i>(mm)</i>	<i>CV (%)</i>
	1	2	3	4	5			
Medial Cortical Thickness								
a	7.5	7.8	7.8	7.1	7.2	0.33	7.48	4.4%
b	14.1	14.4	13.8	14.5	13.7	0.35	14.1	2.5%
c	5.2	5.5	4.8	5.2	5.1	0.25	5.16	4.9%
Femoral Thickness								
a	30.5	30.2	30.1	30.9	30.7	0.33	30.48	1.1%
b	36.8	36.5	36.9	36.7	37.0	0.19	36.78	0.5%
c	31.2	31.0	30.8	31.6	31.7	0.38	31.26	1.2%

The Medial Cortical Thickness and Femoral Thickness were measured 5 times in 3 separate radiographs. From the 5 readings the mean, standard deviation (SD) and coefficient of variance (CV) were calculated

The following conclusions can be drawn. The similar standard deviation for the six radiographic parameters reflects a high level of reproducibility, likely to be due to the use of a digital calliper throughout. The coefficient of variance (CV) is higher in the MCT than the FT measurements. This reflects the lower absolute values between the 2 groups, but because the standard deviation is the same (due to the same technique of measuring with the calliper), the CV is comparatively high in the MCT group. Finally, all CV values were less than 5%, and so the readings were taken as being reproducible.

9. ASSESSMENT OF BONE MINERAL DENSITY

The primary aim was to assess whether there was a difference in bone mineral density (BMD) between the two groups at the site of the hip replacement, with sub-analysis at seven zones around the femoral component of the prosthesis.

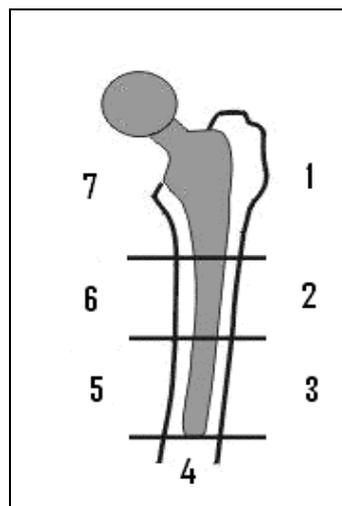
The secondary aim was to assess BMD at distant sites in the lumbar spine and distal radius. Tertiary aims were to assess for correlations between BMD and the various clinical and radiographic assessments made in the other studies

BONE MINERAL DENSITY, T AND Z SCORE ASSESSMENT

Each patient underwent a DEXA scan to assess their BMD. This was performed at the Leicester Royal Infirmary throughout April and May 2006 by a senior radiographer, Leigh Warrilow with the Principal Investigator. Each patient was positioned on the scanning table in the same manner, using pre-cut foam blocks to enable accurate, reproducible measurement of the scanned sites. The radiographer was blinded so as not to be aware whether the patient had a loose or stable arthroplasty. The scanner used was the Lunar Prodigy Advance and this was used to assess the Bone Mineral Content (BMC, g) and Bone Mineral Density (BMD, g/cm²) around the prosthesis and at locations distant to the site of surgery, as shown in table 9.1 below.

Table 9-1. Peri-prosthetic BMD

Region	BMD (g/cm ²)	BMC (g)	Area (cm ²)
1	1.129	16.62	14.72
2	2.012	8.36	4.16
3	1.901	8.92	4.69
4	1.534	8.21	5.35
5	2.046	9.74	4.76
6	1.846	6.96	3.77
7	1.045	3.89	3.73



Example of results given for peri-prosthetic BMD assessment

All patients were weighed and measured, which together with information about their age, sex and ethnicity was used to calculate the T score and Z score for the contra-lateral hip, lumbar spine and distal radius (figure 8.1). These values were calculated by comparison with pooled data supplied by the scanner manufacturers. As there are no standardised results for comparison of BMD around an arthroplasty, so it was not possible to calculate T or Z scores. Instead, for this region results were expressed only as Bone Mineral Content (BMC in grams) or Bone Mineral Density (BMD in g/cm²).

These results were available as BMD, T and Z scores in tabulated and graphical forms (see figure 9-1, table 9-2):

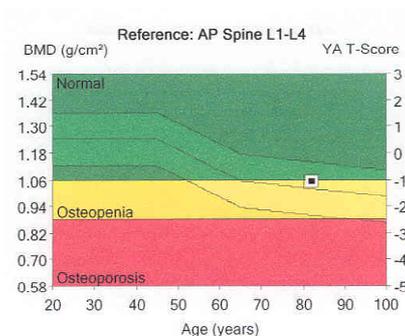


Figure 9-1. Spine, wrist and un-operated hip BMD

Table 9-2. Lumbar BMD

Region	BMD (g/cm ²)	Young adult T score	Age-matched Z score
L1	0.916	-1.8	-0.4
L2	0.913	-2.4	-1.1
L3	1.072	-1.1	0.3
L4	1.262	0.5	1.9
L1-L4	1.052	-1.1	0.3

Example of the data generated for each assessment at the lumbar spine
Shown with a figure of the region assessed

DISUSE OSTEOPOROSIS

In our study we anticipated that patients with arthroplasty loosening may have a more pain or a lower level of function than patients with stable arthroplasties. This may lead to disuse osteoporosis, and so we sought correlations between pain and function and BMD. To investigate this we looked for correlations between visual analogue scores for pain (VAS) and the Oxford Hip Score (OHS) for function and the peri-prosthetic BMD. We anticipated that if disuse osteoporosis was a significant factor, patients with a higher pain score or lower level of function would have a lower BMD. In addition, by analysing the BMD at multiple sites we aimed to get a more accurate picture of the patients general bone health.

BONE MINERAL DENSITY ASSESSMENT AROUND THE HIP

FEMORAL COMPONENT

All femoral components were cemented ElitePlus prostheses. This reduced the chance of having errors generated from having different types of prosthesis, with different methods of fixation. Analysis was performed at the seven antero-posterior zones described by Gruen. The scanner's software was able to automatically calculate the BMD in each zone (Figure 9-2). As well as values for the individual zones, the mean BMD of all zones around the prosthesis was calculated – this was termed the Peri-prosthetic BMD. Comparisons were made between patients with loose and stable arthroplasties.

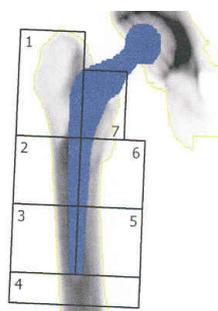


Figure 9-2. BMD assessment in the 7 Gruen zones

ACETABULAR COMPONENT

Unlike the femoral stems, there was considerable variability in type of acetabular components and method of fixation. 65 (51%) patients had uncemented metal Trilogy cups, and 62 (49%) had cemented flanged polyethylene cups. The scanner was not able to accurately discriminate between bone, cement and polyethylene in these regions and so acetabular BMD was not assessed in this study (Figure 9-3).

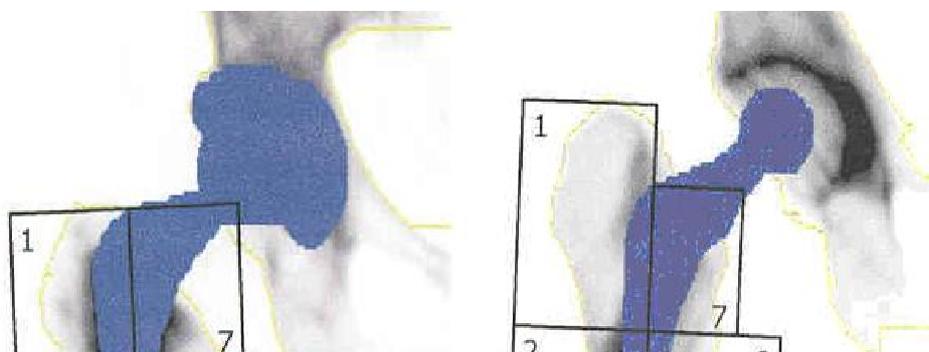


Figure 9-3. DEXA scans for cemented and uncemented acetabular prosthesis

In the first example accurate BMD measurements can be made around the uncemented, metal lines cup. In the second example the scanner can not accurately distinguish between bone, cement and the polyethylene cup.

BONE MINERAL DENSITY ASSESSMENT AT DISTANT SITES**LUMBAR BONE MINERAL DENSITY ASSESSMENT**

Standard lumbar spine BMD assessments were done using antero-posterior views of the 1st to the 4th lumbar vertebrae. The scanner could automatically detect these 4 vertebrae, although manual corrections were made for scoliosis and patches of osteophytes or sclerosis (Figure 9-4). Results were available as BMD (g/cm²) and as T and Z scores, which were calculated using reference data supplied by the scanner manufacturer. The T score was used to determine which patients met the WHO criteria for osteoporosis (a T score greater than -2.5). Comparisons were made between patients with loose and stable arthroplasties.

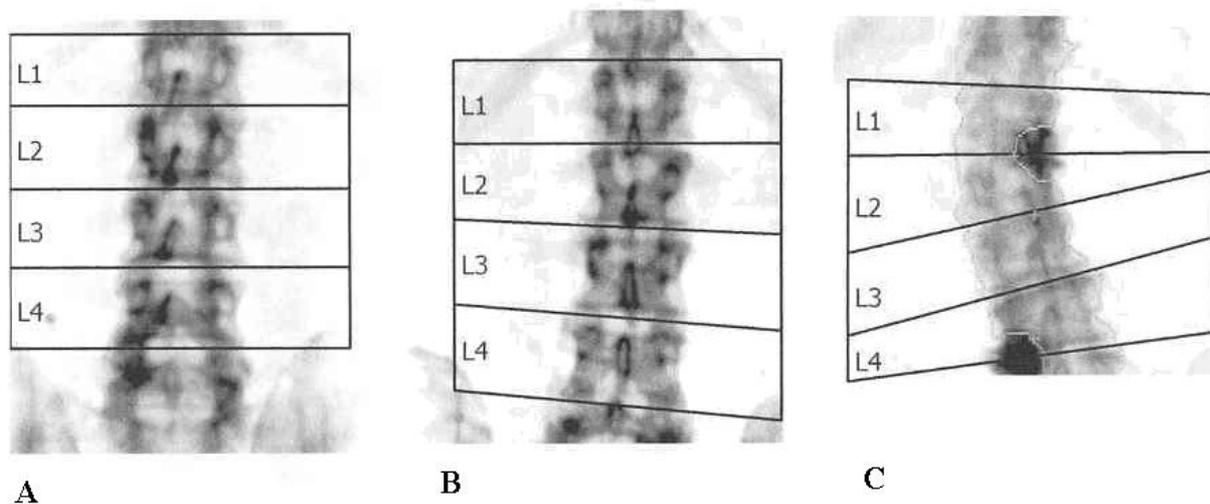


Figure 9-4. Lumbar DEXA measurements

- (A) normal lumbar spine, with no adjustments necessary
- (B) mild scoliosis with adjustments made to re-align the lumbar zones
- (C) Severe scoliosis with exclusion of areas of sclerosis and osteophyte formation.

RADIUS BONE MINERAL DENSITY ASSESSMENT

Standard analysis of the wrist BMD was performed, to calculate the BMD, T and Z scores from the Ultra Distal Radius site (fig 8.5). This site was chosen because it contains the highest proportion of cancellous bone. The non-dominant hand was used, as this hand is less prone to variation due to occupation and recreational activities (such as playing tennis). If, however, the non-dominant hand had previously been fractured, the dominant hand was used, as previous radial fractures may cause deformity of the distal radius that would alter readings.

CONTRA-LATERAL HIP

It was planned to assess the BMD in the contra-lateral hip (Figure 9-5), however 40 (53%) of those that attended for DEXA measurement had had that hip replaced also. Only 35 patients therefore had this assessed. Because the numbers were too small for interpretation, the data was collected, but not used.

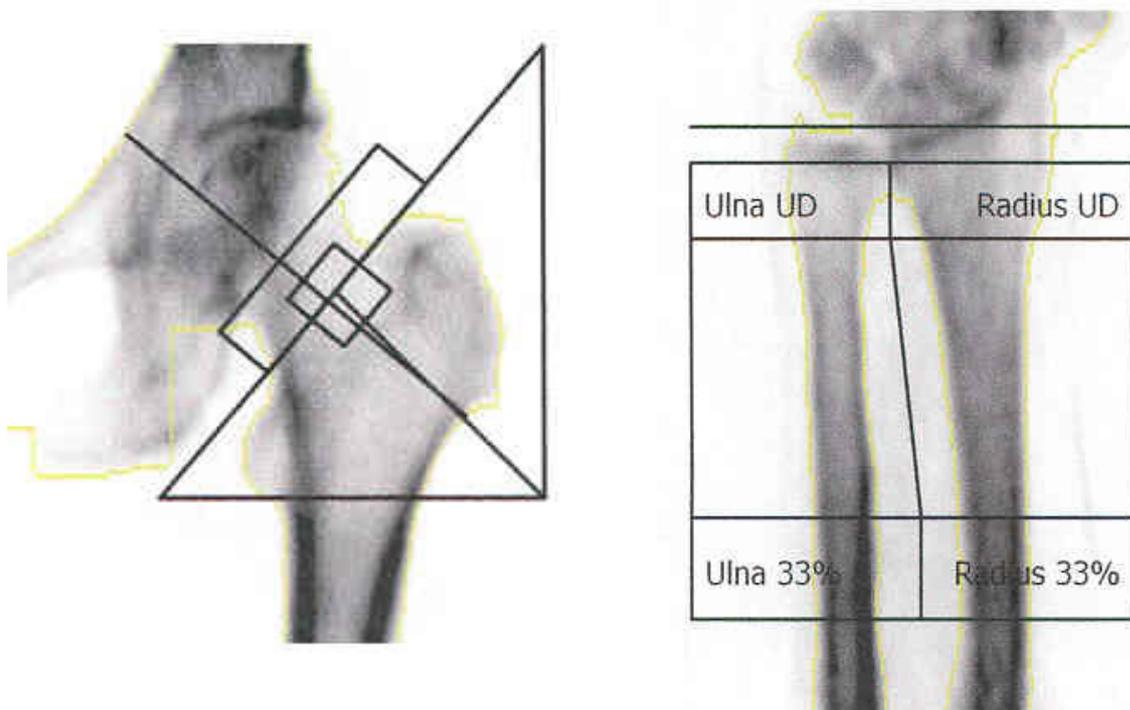


Figure 9-5. BMD measurement of the contra-lateral hip and at the wrist

REPRODUCIBILITY OF BMD MEASUREMENTS

Standardisations were made to minimise the effect of a number of potentially confounding factors. These are listed in the table and text below (table 9.3). All these adjustments were made by the principal investigator (MFN) and a senior radiographer (LW).

Table 9-3. Standardising assessment of Bone Mineral Density

Confounding factor	How accounted for
Osseous	
Degenerate disease	Manual exclusion of region (see text)
Vertebral compression fractures	Manual exclusion of region (see text)
Aortic calcification	Unable to account for
Scoliosis	Manual adjustment of zones (see text)
Calcified nodes	Unable to account for
Non-osseous	
Orthopaedic devices	Not present in study population
Metal buttons, zips etc	Removed prior to examination
Recent radionuclide examinations	Not present in study population
Marked ascites	Not present in study population
Patient movement	Minimised by using foam limb supports
Patient positioning	Minimised by using foam limb supports
Prosthetic	
Subsidence	Manual adjustment of zone 1 (see text)
Cement	Only cemented prosthesis studied
Prosthesis type	Only ElitePlus femoral stems studied

Description as to how osseous and non-osseous confounding factors were accounted for.

ADJUSTMENT FOR PROSTHESIS SUBSIDENCE

An adjustment unique to this particular study was the fact that a number of arthroplasties had subsided within the femur, affecting the accuracy of readings in zone 1. Zone 1 relates to a region around the lateral aspect of the femur from the shoulder of the prosthesis to a third of the way down the prosthesis. When a hip arthroplasty is correctly inserted, the shoulder of the prosthesis sits at the tip of the greater trochanter. Zone 1 therefore normally measures the greater trochanter which contains mainly cancellous bone and so has relatively low BMC and BMD. However, in patients with femoral stem subsidence, the prosthesis slides down into the femoral canal, and so is surrounded by a higher proportion of higher proportion of hyper-dense cortical bone, generating an artificially high reading.

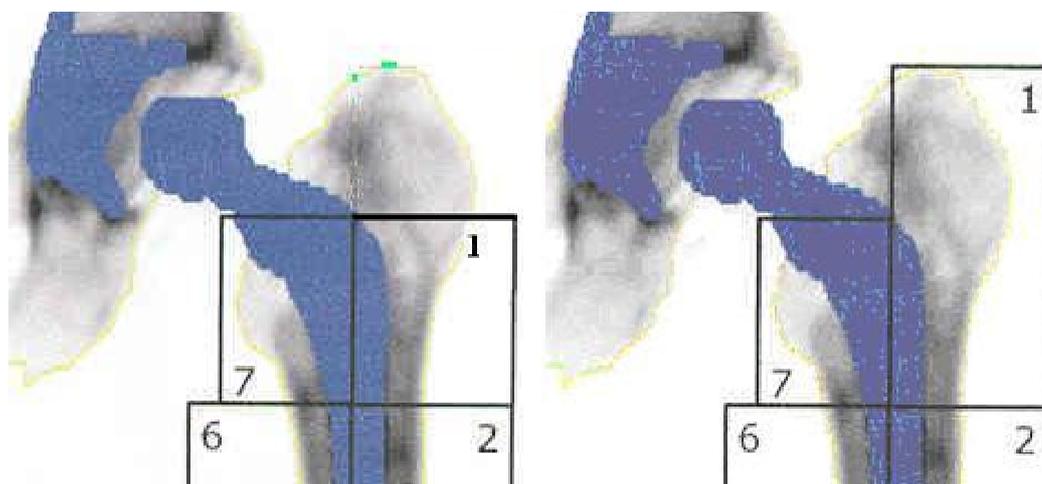


Figure 9-6. Adjustment of zone 1 for prosthesis subsidence.

- (A) With subsidence, zone 1 assesses a higher proportion of hyper-dense cortical bone.
- (B) Extension of zone 1 creates more uniform readings with more cancellous bone.

To address this issue, Gruen zone 1 was manually adjusted in all cases to extend instead from the tip of the greater trochanter to a third of the way down the prosthesis (Figure 9-6). This meant a larger area was analysed, particularly in those with significant amounts of prosthetic subsidence. Because the key measurement was the density of bone mineralization, not bone area. The increased area measured was thought to provide a better comparison of bone quality between those with or without prosthetic subsidence and so more acceptable than using the traditional Gruen zones.

ADJUSTMENT FOR DEGENERATE CHANGES

Degenerate changes could be seen on the scan as areas of increased density due to osteophyte formation and sclerosis (Figure 9-7). Such bone would be measured as having artificially high bone density and so all areas noted to have such changes were highlighted and excluded from the analysis.

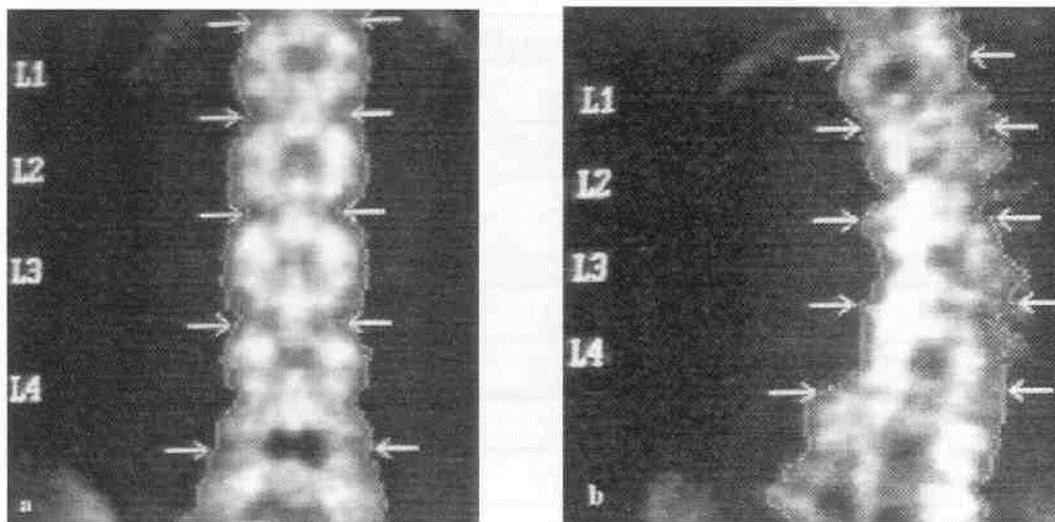


Figure 9-7. Lumbar BMD with artefactual increase in the degenerate and scoliotic spine.

ADJUSTMENT FOR CEMENT

All the prosthesis had the same stem, fixed with radio-opaque PMMA cement. Although the scanner had facilities to exclude selected areas from analysis, the quality of the screening images was not good enough to accurately identify which areas were cement and which areas were bone. It was decided that the errors generated from inaccurately identifying and excluding areas of cement from the analysis would be higher than accepting that all hips had slightly different amount of cement around them. It was therefore decided not to exclude cement from the BMD assessment.

10. ASSESSMENT OF BIOCHEMICAL MARKERS

In the fourth study, our aim was to investigate whether there was a difference in levels of serum markers between patients with loose and stable arthroplasties. The markers measured were vitamin D, parathyroid hormone (PTH), alkaline phosphatase, calcium and phosphate. For each of these the mean, median and SD were calculated and appropriate comparisons made between patients with loose and stable arthroplasties.

Unfortunately, insufficient funds were available to measure bone turnover markers such as NTX and osteocalcin, although serum and urine samples were collected and stored for future use if required.

SAMPLE PROCESSING

COLLECTION

After obtaining consent, two blood samples were obtained during the clinical review of study A. The first sample was used for analysis of calcium, phosphate and alkaline phosphatase, which was done in the UHL biochemistry department using an automated analyser.

STORAGE

The analysis of vitamin D and PTH was done by the principal investigator. Because of the labile nature of parathyroid hormone at room temperature, the second blood sample was immediately kept on ice before being processed for storage and future analysis. Within 30 minutes of venesection, the samples were centrifuged for 6 minutes at a speed of 4000 rpm to separate the serum. Thereafter, 5ml of serum was labelled and stored at -20°C at the university clinical sciences department at the Glenfield hospital.

TRANSFER

All the vitamin D and PTH levels were analysed in one batch together at the biochemistry department at the Leicester Royal Infirmary. This was done by the principal investigator under the supervision of Gayle Thrower, senior MLSO at the biochemistry department. Samples had to be rapidly thawed followed by immediate processing to obtain accurate results. To achieve this they were transferred frozen from the Glenfield hospital to the Leicester Royal Infirmary using dry ice to maintain the necessary temperature.

THAWING

After transfer, the samples were incubated at 40 degrees Celsius whilst being constantly turned to enable rapid, even warming. After defrosting, the samples were centrifuged again at 3000 rps for 5 minutes to remove any freeze/thaw debris.

ENZYME LABELLED IMMUNOMETRIC ASSAY

Following sampling, storage transfer and thawing, 0.75 ml of serum was sampled into pre-labelled tubes and loaded into the Immulite 2500 analyser of analysis of vitamin D and PTH concentration. The Immulite 2500 utilises sandwich chemi-luminescent enzyme-labelled immunometric assay which converts the concentration of vitamin D or PTH into the measurable production of light, as described below.

ISOLATION

The first step is to bind the vitamin D/PTH (termed the substrate from now on) to beads so that it can be measured. This is achieved by mixing 50µL of serum with affinity purified murine antibody beads (the "primary antibody 1"). This antibody is specific for the molecule being assessed, in this case PTH or vitamin D and allows the beads to bind to the free intact substrate. Following this the beads are washed to remove any unbound substrate.

The second step is to bind a second antibody to the substrate which will later be involved in measuring its concentration. This is done by mixing the beads with 11.5ml of affinity purified goat antibody (the "primary antibody 2"). The third wash is of a secondary antibody and this binds to the non-beaded primary antibody, conjugated to this is bovine alkaline phosphatase which remains exposed to act as a chemi-luminescent indicator. The process of binding two antibodies to the substrate is gives the process the name sandwich assay.

Finally the beads are then washed again to remove any remaining serum or unbound reagent. At this point, the amount of alkaline phosphatase is therefore directly proportional to the concentration of PTH. The isolation is technique is illustrated in Figure 10-1 below.

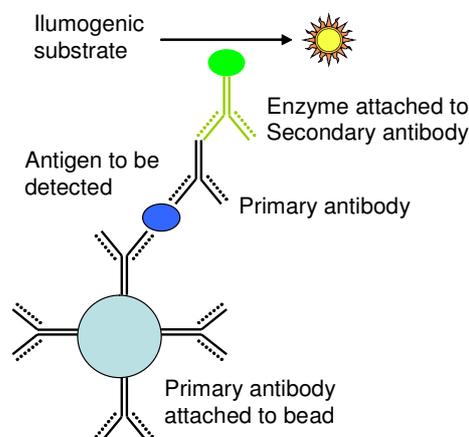


Figure 10-1. Mechanism of action of the sandwich chemi-luminescent assay.

ASSESSMENT OF CONCENTRATION

The next step is to use the exposed alkaline phosphatase to perform a measurable chemical reaction, in this case generation of light. The luminogenic substrate we used was dioxetane phosphate. After adding this to our bead/antibody/substrate/antibody/ALP mixture, the dioxetane phosphate is taken up by the alkaline phosphatase.

The dioxetane is dephosphorylated into an unstable intermediate, which subsequently decomposes into dioxetane, releasing light at the same time (Figure 10-2). The amount of light generated is proportional to the amount of alkaline phosphatase available to catalyse the reaction.

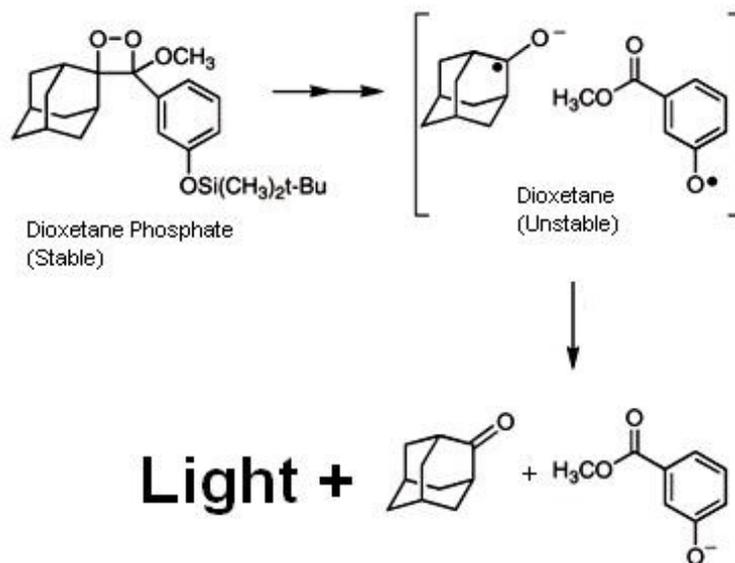


Figure 10-2. Chemical reaction of the chemi-luminescent substrate

To accurately measure the amount of light generated, five minutes after adding the luminogenic substrate, the sample is placed in front of the photomultiplier tube to magnify the reaction. The amount of light produced is quantified by the Immulite analyser, and measured as counts per second (CPS).

Using this method, the amount of vitamin D or PTH is correlated to the CPS of light produced.

REPRODUCIBILITY OF BIOCHEMICAL MEASUREMENTS

The substrate concentration can be predicted by comparing the number of photons of light emitted to reference data supplied by the manufacturer. Such performance data is generated by doing repeated intra- and inter-assay precision tests.

INTRA-ASSAY PRECISION

The intra-assay tests involved repeated analysis of a single sample 20 times using the same reagents. The mean CPS, standard deviation (SD) and coefficient of variance (CV) are calculated for each test. The CV is measured by dividing the SD by the mean, and is expressed as a percentage. A CV of less than 5% represents a reproducible and reliable result (i.e. it is precise). The intra-assay test is performed at low, middle and high substrate concentrations and shown in table 10.1 below.

Table 10-1. Manufacturer's intra-assay precision

Substrate concentration	Mean count (CPS)	SD	CV (%)
Low	72	4.1	5.7
Middle	258	11.0	4.3
High	662	28.0	4.2

The same sample is tested 20 times with the same reagents, repeated at 3 concentrations

INTER-ASSAY PRECISION

Inter-assay tests involved analysing a single sample 20 times in different runs, with different batches of reagents. This was repeated at low and high substrate concentrations (table 10.2). The higher inter-assay CV represents the slight biological variations in assay components – because of this it is important to recalibrate the equipment between batches of assays.

Table 10-2. Manufacturer's inter-assay precision

Substrate concentration	Mean count (CPS)	SD	CV (%)
Low	54	3.4	6.3
High	387	34.0	8.8

The same sample is tested 20 times with different reagents at 2 concentrations

LOCAL CALIBRATION

Because of variability between different analysers and reagents it is also vital to calibrate results locally to those supplied by the manufacturer. Two reagents of known concentration (a low adjustor and a high adjustor) were analysed 4 times each. The mean photon counts per second (CPS) was calculated along with the standard deviation (SD) and the coefficient of variance (CV), see table 10.3. Again, a CV of <5% for both the high and the low adjustor is the target.

Table 10-3. Local calibration

Substrate concentration	Test	Local CPS	Local Mean CPS	Manufacturer Mean CPS	CV (%)
Low	1	25676	26952	24448	4.1
	2	26795			
	3	26937			
	4	28400			
High	1	1141247	1122311	1273942	2.2
	2	1139156			
	3	1121394			
	4	1087447			

Comparison of manufacturer's and local results (measured as counts per second, CPS)

ASSAY LINEARITY

To enable assessment of a spectrum of substrate concentrations, a known concentration is repeatedly diluted by known amounts. When analysed, you would expect the observed and the predicted to be directly and equally proportional (linearity of 100%). In practice there is a slight discrepancy, and the values are not quite equal. Determination of the linearity allows a substrate concentration to be calculated by plotting its position along a best-fit regression line (table 10.4).

Table 10-4. Manufacturer's assay linearity

Substrate concentration	Dilution	Observed (CPS)	Expected (CPS)	Linearity (%)
Low	8 in 8	158	-	-
	4 in 8	82	79	104
	2 in 8	42	40	105
	1 in 8	22	20	110
Medium	8 in 8	253	-	-
	4 in 8	132	127	104
	2 in 8	67	63	106
	1 in 8	33	32	103
High	8 in 8	533	-	-
	4 in 8	274	267	103
	2 in 8	141	133	106
	1 in 8	71	67	106

Calculation of linearity at low medium and high substrate concentrations

Linearity calculated by dividing observed/expected counts per second (CPS)

RESULTS

11. CLINICAL RISK FACTORS OF LOOSENING

The first section analyses the matching of patients with loosening to similar patients with stable implants. It assessed the number of patients in each group based on the most recent radiograph, and how well matched for age, sex and arthroplasty age.

The second section assesses whether patients with loosening have clinical risk factors for osteoporosis (fracture history, BMI, menopause, smoking history), and the third section whether pain or hip function is different in the two groups. A summary of the findings from this study are listed in the box below.

Summary of study A findings

- Patients with loosening are 4x more likely to have had a fragility fracture.
- The underlying diagnosis doesn't influence the likelihood of developing of loosening.
- Patients with loosening tended to be active smokers
- Body Mass Index is correlated with Bone Mineral Density
- BMI and weight did not influence development of loosening.
- Patients with loosening tended to have an earlier menopause.
- Only patients with advanced loosening complain of significantly higher levels of pain or have a significantly worse level of function.
- Simply asking whether a patient uses a walking aid is as good as the Oxford Hip Score at determining reduced function.

Box 11-1. Summary of clinical risk factors for loosening

MATCHING CRITERIA

PATIENT AGE

Patient age was calculated from their date of birth until the time of the last hip radiograph. Because this is a variable that patients were matched for, we expected there to be no difference between groups. Table 11.1 below breaks down ages of participants in each category with basic descriptive statistics, the data was normally distributed, and so we performed parametric tests.

Table 11.1. Patient Age

	All	Stable	Loose		
			Mild	Severe	All *
Number	127	49	43	35	78
Mean	68.1	67.2	68.9	68.8	68.9
Median	69.0	68.0	70.0	69.0	69.0
St Dev	9.7	9.1	9.6	10.6	10.0

Age (in years) for patients with varying degrees of loosening

*Patients with "all" loosening were a combination of the "mild" and "severe" groups

There was no significant difference in mean age between those with and without loosening (68.9 vs. 67.2 years, $p=0.3$ T-test), or between those with the none, mild or severe loosening (67.2, 68.9 and 68.8 years respectively, $p=0.6$, ANOVA). This is shown in Figure 11-1 below.

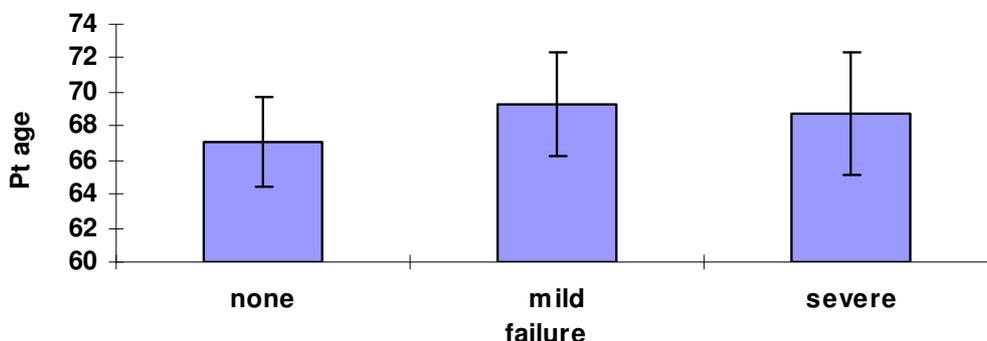


Figure 11-1. Mean patient age in years with 95% confidence intervals

Difference in means: $p=0.6$, ANOVA

ARTHROPLASTY AGE

The second criteria patients were matched by was arthroplasty age. This was measured from the date of surgery to the last available follow up radiograph, ranging from 6 to 10 years. Because this is a variable that patients were matched for, we expected there to be no difference between groups. Table 11.4 below breaks down ages of participants in each category with basic descriptive statistics. The data was normally distributed, and so we performed parametric tests.

Table 11-2. Arthroplasty Age

	All	Stable	Loose		
			Mild	Severe	All *
Number	127	49	43	35	78
Mean	7.9	7.7	8.0	7.9	7.9
Median	8.0	8.0	8.0	8.0	8.0
St Dev	0.9	0.9	0.9	0.9	0.9

Arthroplasty age (in years) for patients with varying degrees of loosening

*Patients with "all" loosening were a combination of the "mild" and "severe" groups

There was no significant difference in mean arthroplasty age between those with and without loosening (7.9 vs. 7.9 years, $p=0.9$, T-test), or between those with the none, mild or severe loosening (7.7, 8.0 and 7.9 years respectively, $p=0.4$, ANOVA). This is shown in figure 11.2 below.

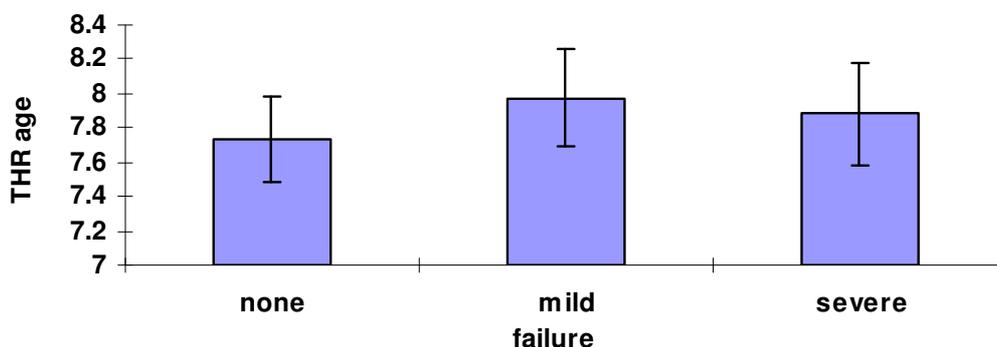


Figure 11-2. Mean arthroplasty age in years with 95% confidence intervals

Difference in means: $p=0.4$, ANOVA

From this we conclude that patients were well matched for arthroplasty age.

GENDER

The third matching criterion was gender. Because this is a variable that patients were matched for, we expected there to be no difference between groups. Table 11.3 below shows the gender distribution in each group. Because it was categorical data, chi-squared two-by-two analyses were used.

Table 11-3. Gender

	All	Stable	Loose		
			Mild	Severe	All *
All	127	49	43	35	78
Male (n,%)	38 (30)	12 (24)	12 (28)	14 (40)	26 (33)
Female (n,%)	89 (70)	38 (76)	30 (72)	21 (60)	51 (67)

Gender distribution for patients with varying degrees of loosening

*Patients with "all" loosening were a combination of the "mild" and "severe" groups

Overall, 89 (70%) of patients were female and 38 (30%) were male. Analysis of different degrees of loosening revealed slight differences in sex distribution: 24% of those with stable arthroplasties were male, compared to 28% of those with mild loosening, and 40% of those with severe loosening. These did not reach statistical significance (p=0.3, chi square). This is shown in figure 11.3 below.

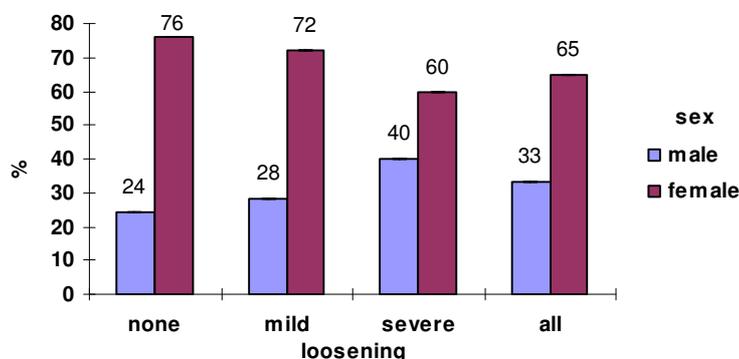


Figure 11-3. Gender distribution for patients with varying degrees of loosening

Patients with "all" loosening were a combination of the mild and severe groups

No significant difference between groups (p=0.3, chi square)

CLINICAL RISK FACTORS FOR BONE FRAGILITY**NUMBER OF PATIENTS**

Of the 127 potential participants, six (4%) had died or were unable to complete the form for medical reasons, 16 (12%) were lost to follow up and 10 (8%) refused to participate. The remaining 95 (76%) had a clinical review. 22 of these patients were too frail to attend hospital, and a telephone consultation was conducted, in these patients it was not possible to make measurements to calculate the body mass index. Other adjustments to the number of participants are stated in the relevant sections.

The good response rate allows us to interpret the results of this part of the study with a reasonable degree of validity. Analysis of the non responders showed there was no difference between responders to the questionnaire with regard to sex (percentage male: 30/100 vs. 10/32 respectively, $p=0.9$ chi-square), time since initial surgery (mean years: 7.8 vs. 7.9 respectively, $p=0.2$, T-test) or patient age (both 68 years, $p=0.9$, t-test).

PREVIOUS FRAGILITY FRACTURE

A past history of a fragility fracture was associated with development of aseptic loosening. Table 11.4 below breaks down incidence of fragility fracture in each category. Because it was categorical data, chi-squared analyses were used.

Table 11-4. Incidence of fragility fracture

	All	Stable	Loose		
			Mild	Severe	All *
All	95	36	28	31	59
Yes	18	3	8	7	15
No	77	33	20	24	44

Incidence (with percentage) of fragility for patients with varying degrees of loosening

*Patients with "all" loosening were a combination of the "mild" and "severe" groups

Of the 95 participants questioned, 18 (19%) had a history of a fragility fracture. This was more common amongst those with a loose than a stable arthroplasty (15/59 vs. 3/36, $p=0.04$, chi square. Odds Ratio = 3.75, 95% CI 1.1 to 13.1). This difference was more significant for those with mild loosening than severe loosening (3/36 vs. 7/31, $p=0.03$ and 3/36 vs. 15/59, $p=0.1$, both chi square), and is illustrated below (fig 11.4).

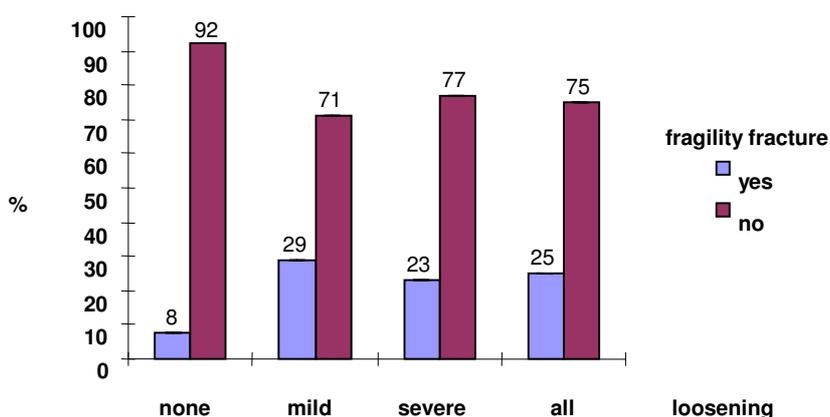


Figure 11.4. Incidence of fragility for patients with varying degrees of loosening

*Patients with "all" loosening were a combination of the mild and severe groups

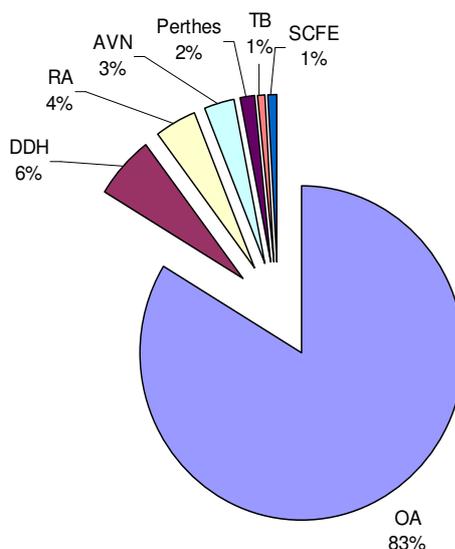
UNDERLYING DIAGNOSIS

There were seven underlying diagnoses prior to hip arthroplasty, as determined from the clinical notes, patient consultation and pre-operative radiographs. Because of the high predominance of osteoarthritis (103 patients, 83%), and relative infrequency of other diagnoses (20 patients, 17%), patients were grouped into either osteoarthritis (OA) or their pathologies (non-OA).

The frequency of developmental dysplasia of the hip (DDH) was 6%, rheumatoid arthritis (RA) 4%, avascular necrosis (AVN) 3%, Perthes’ disease 2%, tuberculosis (TB) 1% and slipped capital femoral epiphysis 1%. This is shown in table 11.5 below. As noted previously (p.89), these non-OA conditions are due to a number of different disease processes, but this normally manifests itself as secondary arthritis.

Table 11-5. Underlying diagnosis prior to hip arthroplasty

Category	N
All	123
Osteoarthritis	103
Non-Osteoarthritis	20
Development Dysplasia Hip	7
Rheumatoid Arthritis	5
Tuberculosis	1
Avascular necrosis	4
Perthes	2
Slipped upper femoral epiphysis	1



Incidence of each underlying diagnosis amongst all patients with pie-chart of relative frequency

The following table (11.6) and figure (11.5) shows the distribution of diagnoses according to the degree of arthroplasty loosening. There was no significant difference between the groups (p=0.9, chi square).

This implies that in this study, the underlying diagnosis does not appear to influence the likelihood of developing arthroplasty loosening.

Table 11-6. Underlining diagnosis

	All	Stable	Loose		
			Mild	Severe	All *
All	123	49	41	33	74
OA	103	42	34	27	61
Non-OA	20	7	7	6	13

Underlying diagnosis for patients with varying degrees of loosening

*Patients with "all" loosening were a combination of the "mild" and "severe" groups

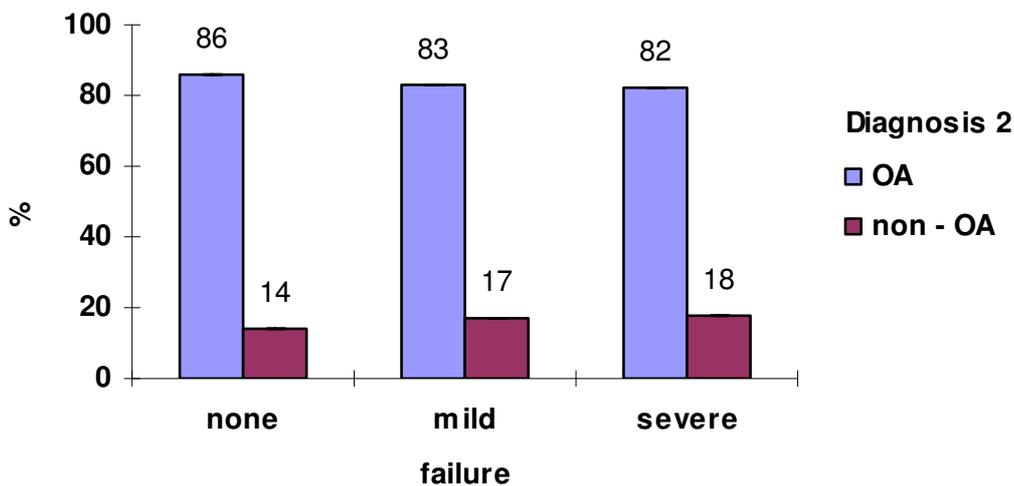


Figure 11-5. . No difference in underlying diagnosis between groups

(p=0.38, chi square)

SMOKING HISTORY

The following table (11.7) shows the frequency of patients who were active smokers amongst those with loose and stable arthroplasties. Ten ex-smokers were excluded. The data was categorical so chi-squared analyses were used.

Table 11-7. Smoking history

	All	Stable	Loose		
			Mild	Severe	All *
All	85	32	26	27	53
Smoker	9	1	4	4	8
Non-smoker	76	31	22	23	45

Smoking history for patients with varying degrees of loosening

*Patients with "all" loosening were a combination of the "mild" and "severe" groups

Active smokers had a non-significant tendency to develop loosening (8/9 (89%) vs. 45/76 (59%), $p= 0.082$, chi square, odds ratio 5.5, 95% CI 0.8 to 38). Individual comparisons of stable arthroplasties with either mild or severe degrees of loosening did not reach significance (both $p=0.1$, chi-squared). This is shown in figure 11.4 below.

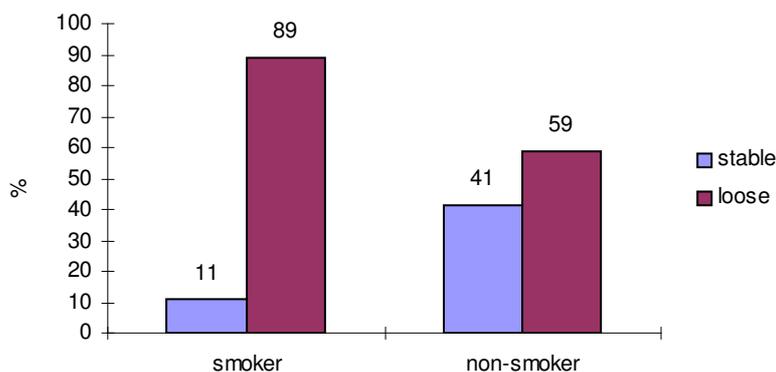


Figure 11-4. Smoking and arthroplasty loosening (p=0.08)

Although firm conclusions cannot be drawn from this study, it appears that smoking may affect the development of loosening.

BODY MASS INDEX AND BONE MINERAL DENSITY

There was a weak correlation but significant correlation between BMI and BMD, with those having a higher BMI tending to have a higher lumbar BMD (Pearson’s correlation = 0.33, $p=0.004$), figure 11.5.

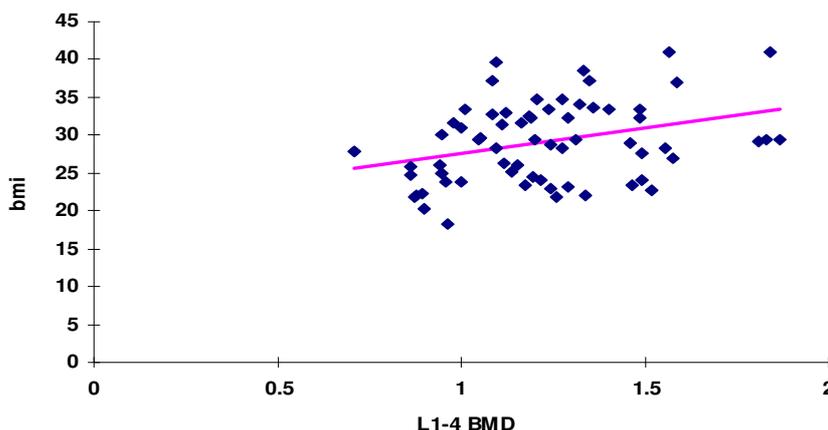


Figure 11-5. Correlation between BMD and BMI ($r=0.33$, $p=0.004$).

Shown with best fit linear regression line.

There was a slightly stronger correlation between weight (in kg) and BMD ($r=0.51$, $p<0.001$), Figure 11-6.

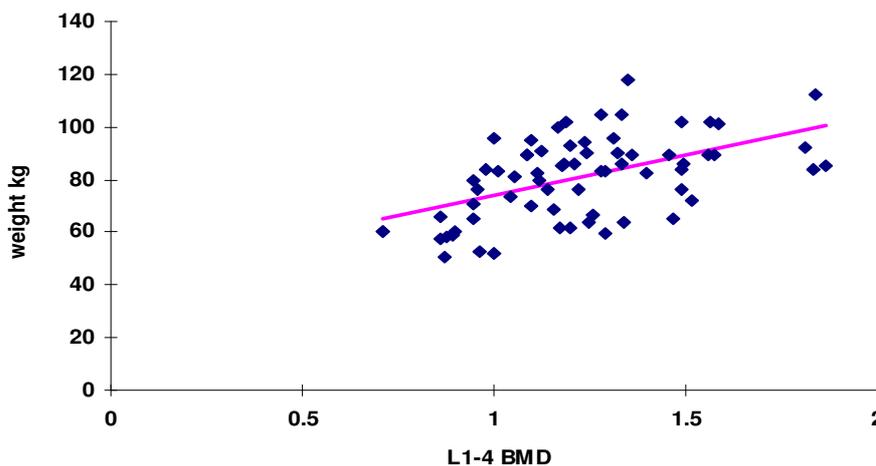


Figure 11-6. Correlation between weight and BMD

Shown with best fit linear regression line. ($r=0.51$, $p<0.001$)

This finding is in keeping with the findings of other studies that a higher BMI is associated with a higher BMD.

BODY MASS INDEX

Table 11.8 below shows the Body Mass Index (BMI) in each category of aseptic loosening . Data was normally distributed so parametric tests were used.

Table 11-8. Body Mass Index

	All	Stable	Loose		
			Mild	Severe	All *
Number	73	26	19	28	47
Mean	29.0	29.0	29.6	28.6	29.0
Median	29.0	29.2	30.1	28.0	28.7
St Dev	5.5	5.4	6.3	5.2	5.6

BMI for patients with varying degrees of loosening

*Patients with "all" loosening were a combination of the "mild" and "severe" groups

Analysis revealed that there was no difference in mean BMI between those with stable, mildly and severely loose arthroplasties (29, 30 and 29 respectively, $p=0.8$, ANOVA). This is shown in figure 11.7 below. Separate analysis comparing mean weight was not associated with loosening either (all groups mean weight 81 kg, $p=1$, ANOVA).

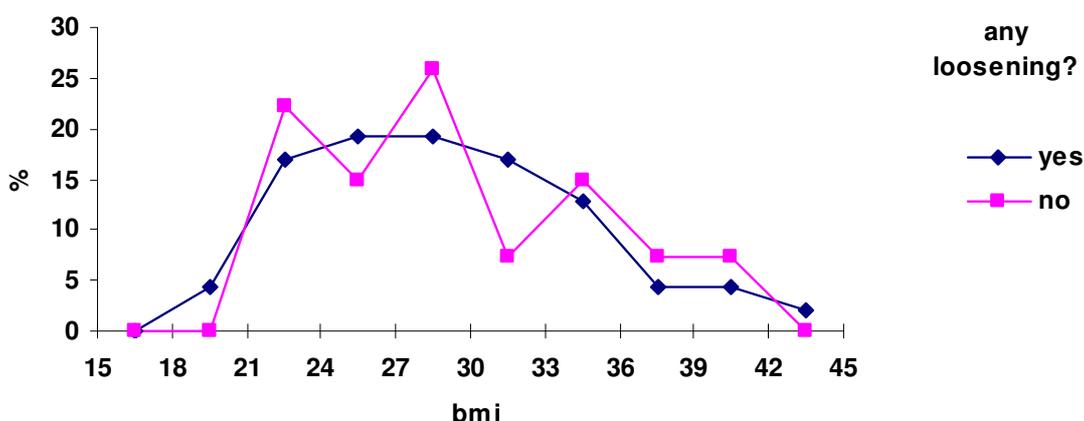


Figure 11-7. BMI and arthroplasty loosening

From this we conclude that BMI and weight are not significant risk factors for developing loosening.

MENOPAUSE

Table 11.9 below shows the age of menopause of the 53 post-menopausal women followed up in the study. Data was normally distributed so parametric tests were used.

Table 11-9. Age of menopause

	All	Stable	Loose		
			Mild	Severe	All *
Number	53	20	16	17	33
Mean	47.8	49.3	46.9	46.9	46.9
Median	50.0	50.0	49.0	50.0	50.0
St Dev	6.3	5.4	6.5	7.1	6.7

Age of menopause for patients with varying degrees of loosening

*Patients with "all" loosening were a combination of the "mild" and "severe" groups

Although there was a slightly higher age in the patients with stable arthroplasties, this did not reach statistical significance (mean ages 49.3, and 46.9 years for those with stable and loose arthroplasties respectively, p=0.1, t-test), Figure 11-8.

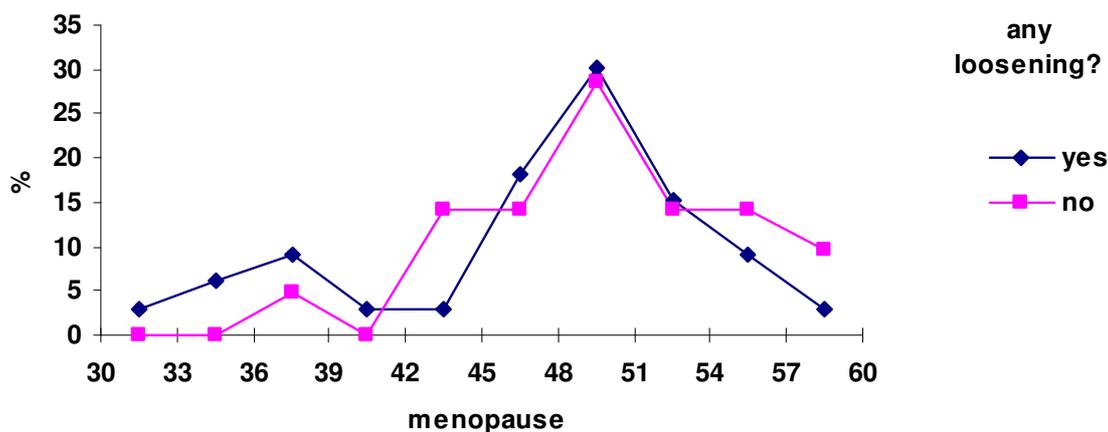


Figure 11-8. Age of menopause for patients with and without loosening

EARLY MENOPAUSE

Sub analysis of patients younger or older than 40 years old showed a similar trend. Only one of the 21 women under 40 (5%) had loosening, compared to 7 of the 33 women over 40 (21%). This also had a non significant trend (p=0.1, chi squared), see figure 11.9).

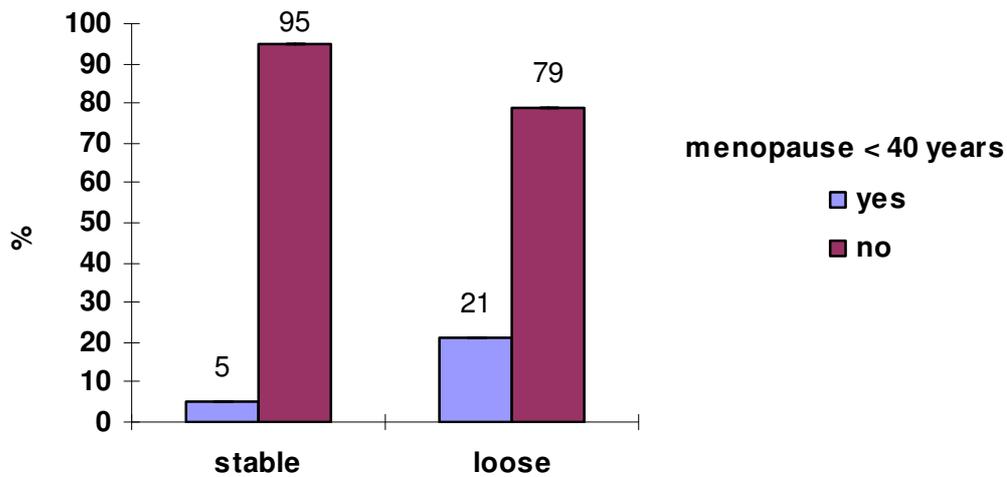


Figure 11.9. Early menopause for women with loose and stable arthroplasties

The conclusions from this part of the study are inconclusive. There appears to be a small trend for patients with early menopause to have a higher risk of loosening.

PAIN

95 patients gave information about the amount of pain they were experiencing, this is detailed in table 11.10 below. Because the data was non-parametric, median pain scores were compared using Kuskall-Wallis and Mann Whitney Tests.

Table 11-10. Pain and loosening

	All	Stable	Loose		
			Mild	Severe	All *
Number	95	35	29	31	60
Mean	2.5	1.5	2.2	3.8	3.0
Median	1.0	0.0	1.0	3.0	2.5
St Dev	2.8	2.5	2.8	2.8	2.9

Visual analogue pain score for patients with varying degrees of loosening
 Scores range from 0 (no pain) to 10 (worst pain).

Patients with loosening experienced more pain than those without. Patients with stable arthroplasties had a median pain score of 0, those with mild loosening had a median score of 1 and those with severe loosening had a median score of 3 (p=0.001, Kruskal-Wallis Test). This difference was significant for those with severe loosening (median pain scores 3 vs. 0, p=0.0003, Mann Whitney U, effect size=0.8), but not for those with mild loosening (median pain scores 1 vs. 0, p=0.3, Mann Whitney U, effect size =0.3). This is illustrated in figure 11.10 below.

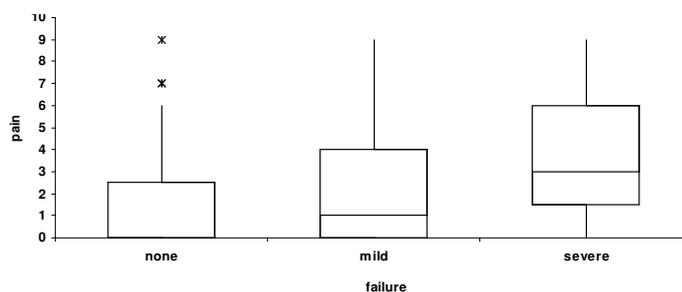


Figure 11-10. Pain Visual Analogues Score and arthroplasty loosening

Scores range from 0 (no pain) to 10 (worst pain).

From this we can conclude that patients with severe loosening have significantly higher pain scores, but not those with mild loosening.

Function

We used the 12 part Oxford Hip Score (OHS) questionnaire to assess function. The minimum score (12) represents optimal function and the maximum score (60) represents worst function. A complete questionnaire was available in 89 patients. The data was non-parametric, so the same tests as in the previous section were used, and are shown in table 11.11 below.

Table 11-11. Function

	All	Stable	Loose		
			Mild	Severe	All *
Number	95	35	29	31	60
Mean	22.4	20.4	21.8	25.5	23.8
Median	18.0	15.0	18.0	22.0	20.0
St Dev	11.0	9.9	10.7	12.2	11.6

Oxford Hip Score for patients with varying degrees of loosening
 Scores range from 12 (best function) to 60 (worst function).

There was less variation in OHS between the groups than the pain scores. Those with stable arthroplasties had the best function, with a median score of 15, those with mild loosening had a median score of 18 and those with severe loosening a score of 22 ($p=0.126$, Kuskall Wallis Test). This difference was significant between those with stable and severe loosening (15 vs. 22, $p=0.04$, Mann Whitney U Test, effect size 0.5), but not between those with stable and mild loosening (15 vs. 18, $p=0.4$, Mann Whitney U Test, effect size = 0.1). See figure 11.9.

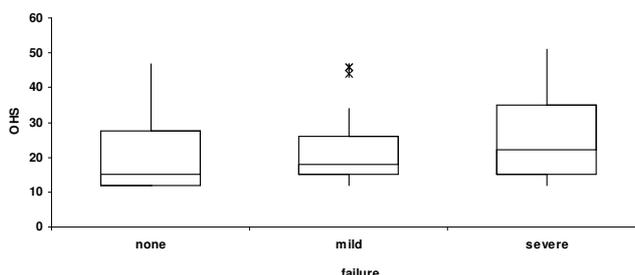


Figure 11-9. Oxford Hip Score for patients with varying degrees of loosening

From this we conclude that deterioration of function is only seen in advanced stages of loosening, and even then the effect size is very low.

USE OF A WALKING AID

Table 11.12 below shows the number of patients that required the use of walking aids in each group. Two patients were immobile for other reasons and so excluded. Chi-squared analyses were used.

Table 11-12. Walking stick

	All	Stable	Loose		
			Mild	Severe	All *
All	93	35	28	30	58
Yes	33	7	10	16	26
No	60	28	18	14	32

Number of patients requiring the use of a walking stick with varying degrees of loosening

*Patients with "all" loosening were a combination of the "mild" and "severe" groups

We found that those with a loose implant were more likely to need to use a stick (45% 26/58 vs. 22% 7/35), $p=0.03$, chi-square, odds ratio 2.8, 95% CI 1.1 to 7.2). This was more significant for those with severe loosening ($p=0.005$, chi square, OR 4.6 (1.6 to 13.2) than those with mild loosening ($p=0.2$, chi square, OR 2.2 (0.7 to 6.8), fig 11.10.

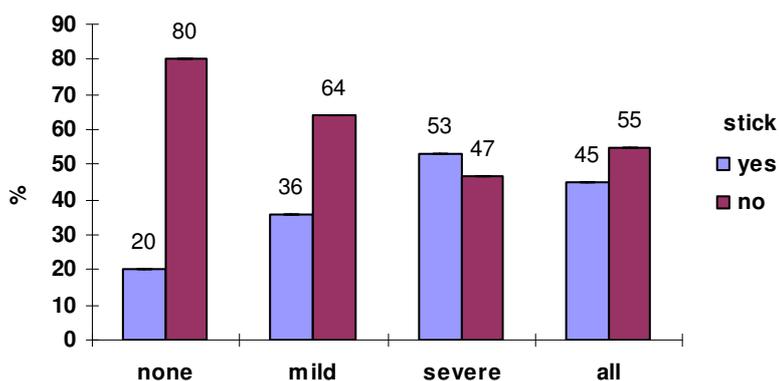


Figure 11-10. Use of a walking stick and loosening

From this we conclude that simply enquiring whether a patient uses a walking stick is as effective as the Oxford Hip Score at determining whether a patient has the degree of loss of function associated with arthroplasty loosening.

MULTIVARIATE ANALYSIS

CLINICAL RISK FACTORS

Backwards stepwise logistical regression analysis was performed using SPSS. With this technique, the least significant variable is removed after each cycle and the remaining variables re-analysed until only significant variables remain. A significance level of $p < 0.10$ was set for this analysis. In the first model, clinical risk factors for loosening were analysed. The variables assessed were history of a previous fracture, if they were an active smoker, and if they had a diagnosis of osteoarthritis or not. Age of menopause was excluded as there were insufficient numbers for this to be accurately analysed. The results are shown in the table below.

Table 11-13. Influence of clinical risk factors on loosening

Model	step	Unstandardised		Standardised		Signif.*
		B	Std. Error	Beta	t	
1	(Constant)	.542	.060		9.021	.000
	fracture	.338	.127	.270	2.667	.009
	smoking	.309	.166	.189	1.861	.066
	diagnosis	-.067	.138	-.050	-.487	.628
2	(Constant)	.532	.056		9.459	.000
	fracture	.331	.125	.264	2.642	.010
	smoking	.320	.164	.195	1.951	.054

* stepwise backward LR regression analysis with cyclical removal of the least significant variable before re-analysis

This confirms the univariate findings that a previous history of a fragility fracture has the highest significance ($p=0.01$), followed by being an active smoker ($p=0.05$). Underlying diagnosis was not significant ($p=0.63$). Note how in this case, removing the variable "diagnosis" alters the significance level of the other two variables.

PAIN AND FUNCTION

Similar analysis was performed to assess differences in pain or function in patients with a loose or stable arthroplasty. Variables measured were pain visual analogue score (from 0 (none) to 10 (maximal)), Oxford Hip Score over 20, and use of a stick. Results are shown in the following table.

Table 11-14. Influence of loosening on pain and function

Model	step	Unstandardised		Standardised		Signif.*
		B	Std. Error	Beta	t	
1	(Constant)	.464	.133		3.480	.001
	Pain	.015	.031	.083	.467	.642
	OHS	.003	.008	.070	.396	.693
	Stick	.089	.151	.086	.592	.556
2	(Constant)	.508	.070		7.230	.000
	Pain	.022	.025	.126	.910	.365
	Stick	.106	.144	.102	.739	.462
3	(Constant)	.516	.069		7.436	.000
	pain	.034	.019	.191	1.794	.076

* stepwise backward LR regression analysis with
cyclical removal of the least significant variable before re-analysis

This shows similar findings to the univariate analysis that pain is the best clinical sign of a loose arthroplasty, although the level of significance for this is not high ($p=0.076$).

12. RADIOGRAPHIC MARKERS OF LOOSENING

The first section analyses whether markers of cortical bone strength and the second section whether markers of cancellous bone strength affect the development of loosening. The third section assesses whether biological manifestation of osteoporosis affects development of loosening.

Of the 127 suitable study, 118 (93%) had their pre-operative radiograph available. The remaining patients' radiographs were either destroyed or unavailable. The high number of radiographs means that the findings have a high validity.

Summary of findings from radiographic study

- Patients with loosening have a significantly narrower femoral cortex.
- The Cortex ratio has a higher significance and better effect size
- The Singh Index was not a good tool for cancellous bone strength,
- Patients with atrophic OA were twice as likely to develop loosening.
- The cortex ratio was highly correlated to BMD at the hip, spine & radius

Box 12-1. Summary of radiological markers for loosening

CORTICAL BONE STRENGTH

CORTICAL THICKNESS

The Medial Cortex Thickness was the measured thickness of the cortex, as described in the methods section. Table 12.1 below breaks down the thickness (mm) for participants with different degrees of loosening. The data was normally distributed, but with a positive skew, so we therefore performed non-parametric tests. Results are given to the nearest 0.1mm, the accuracy of the digital calliper.

Table 12-1. Femoral Cortical thickness

	All	Stable	Loose		
			Mild	Severe	All *
Number	118	44	43	31	74
Mean	9.5	10.3	9.3	8.7	9.1
Median	9.1	9.7	8.9	7.9	8.7
St Dev	2.4	2.4	2.3	2.2	2.3

Femoral Cortical Thickness (in mm) for patients with varying degrees of loosening

* Patients with "all" loosening were a combination of the "mild" and "severe" groups

We found significant differences in the dimensions of the femoral canal between those with loose and stable arthroplasties. The median diameter of the medial femoral cortex in patients with stable arthroplasties was 9.7mm, compared to 8.9mm in those with mild loosening and 7.9 in those with severe loosening. Those with loosening had significantly narrower median femoral cortices than those with stable arthroplasties, with a moderate clinical effect size (8.7mm vs. 9.7mm, $p = 0.008$, Mann Whitney U Test, effect size = 0.4). Those with severe loosening had the greatest statistical and clinical differences (9.7mm vs. 7.9mm, $p=0.003$, Mann Whitney U Test, effect size = 0.8). The differences were less significance for patients with mild loosening (9.7mm vs. 8.9mm, $p=0.09$, Mann Whitney U Test, effect size = 0.3).

The following graphs (figure 12.1) represent the frequency of each cortical thickness for those with no, mild and severe loosening. Because the number of patients in each group varies, it is shown as a percentage rather than an absolute value (with each group totalling 100%).

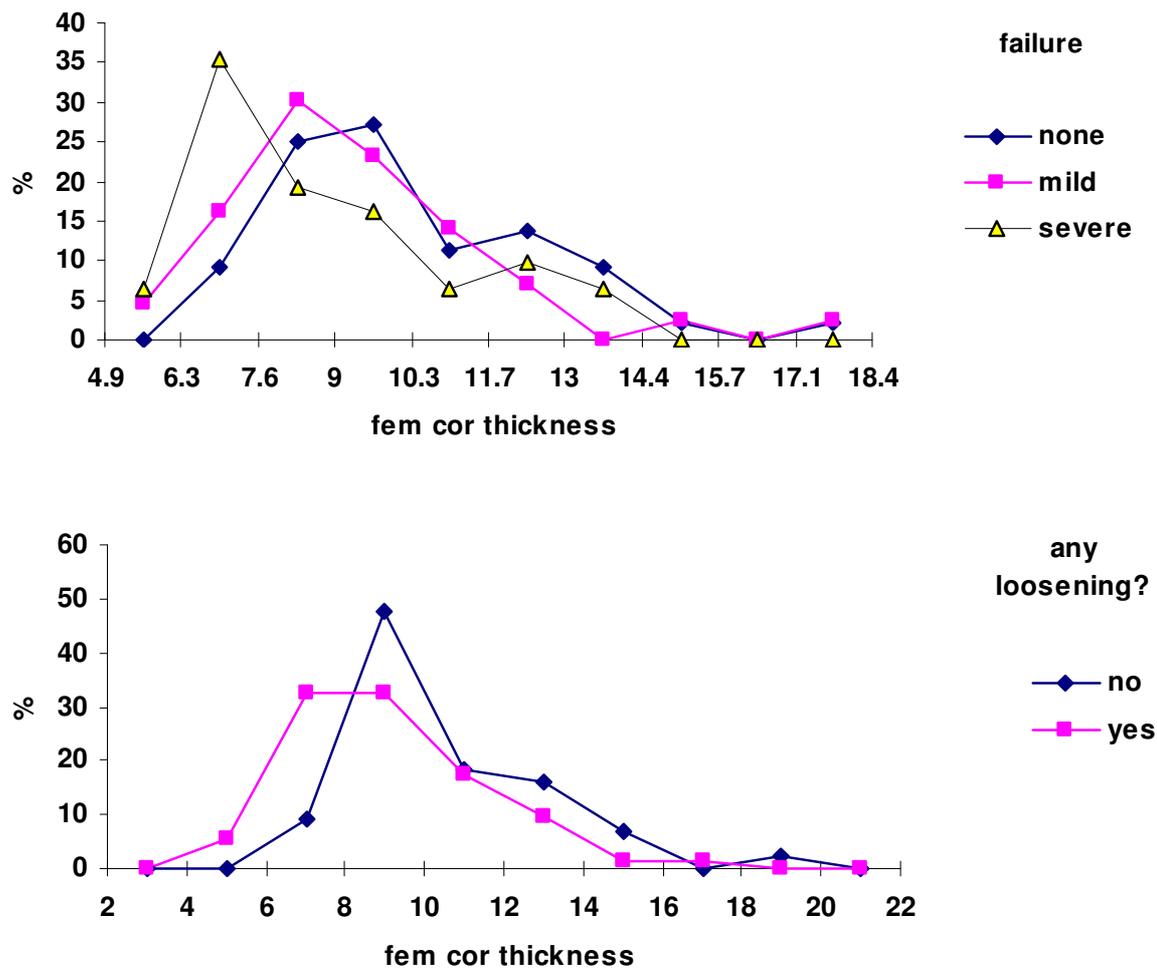


Figure 12-1. Femoral cortical thickness (mm).

(a) Comparing stable, mild and severe loosening (p=0.001, Kuskall Wallis Test);

(b) Stable vs. any degree of loosening (p=0.008, Mann Whitney U Test).

Shown as percentage due to variable numbers in each group

CORTEX RATIO

Table 12.2 below breaks down the cortical ratio for participants with different categories of loosening. As the data was normally distributed with little skew, parametric test were used. Figure 12-2 represents the frequency of each Cortex Ratio for those with no, mild and severe loosening. Because the number of patients in each group varies, it is shown as a percentage rather than an absolute value (with each group totalling 100%).

Table 12-2. The Cortex Ratio with varying degrees of loosening

	All	Stable	Loose		
			Mild	Severe	All *
Number	118	44	43	31	74
Mean	0.27	0.29	0.27	0.25	0.26
Median	0.27	0.29	0.27	0.24	0.27
St Dev	0.05	0.04	0.05	0.05	0.05

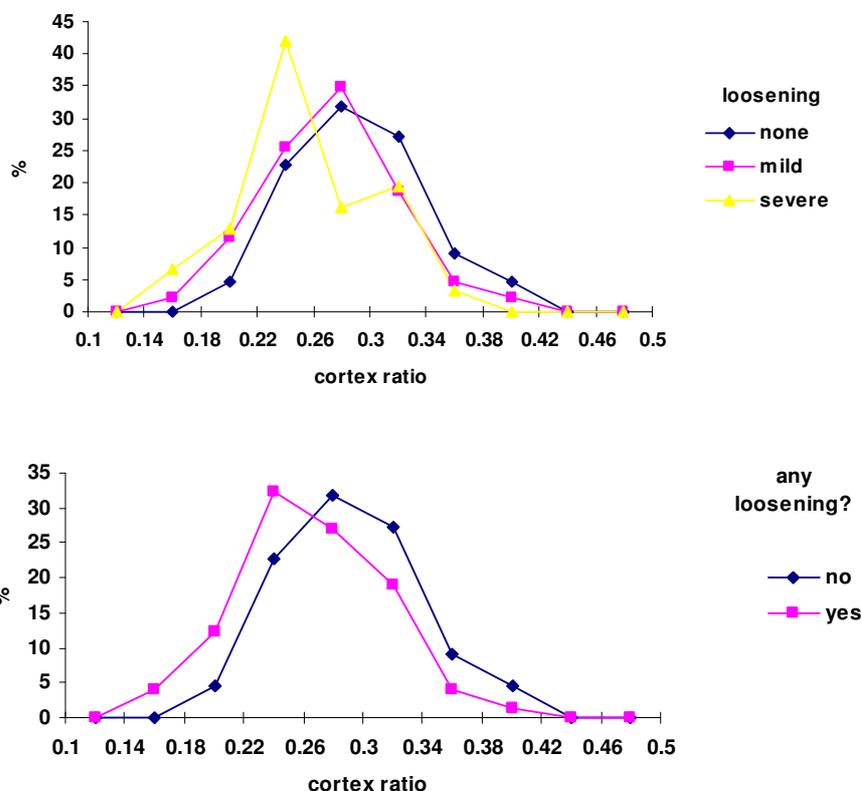


Figure 12-2. Cortex Ratio

(a) Comparing stable, mild and severe loosening (p=0.003, T test);

(b) Stable vs. any loosening (p=0.002, T test).

There was a significant difference in Cortex Ratio between those with loose and stable arthroplasties. The mean Cortex Ratio was 0.29 in those who had no loosening, 0.27 in those who had mild loosening and 0.25 in those with severe loosening ($p=0.003$, ANOVA). Those with any loosening had a mean Cortex Ratio of 0.26. When compared to patients with no loosening, those with any degree of loosening had a significantly lower Cortex Ratio ($p=0.002$, t test, effect size = 0.6), most pronounced amongst those with severe loosening (0.29 vs. 0.25, $p=0.001$, t test, effect size = 0.8). Patients with mild loosening also had a significantly lower Cortex Ratio, but this had a less clinically significant effect size (0.29 vs. 0.27, $p=0.05$, t test, effect size = 0.4).

The following figures 12.3 and 12.4 demonstrate typical cases of narrow and wide cortices progressing to having loose and stable prostheses respectively. The pre-op, immediate post op and most recent radiographs are shown.



Figure 12-3. Example of a THR in a narrow cortex developing loosening



Figure 12-4. Example of a stable prosthesis with a wide femoral cortex

CORRELATION BETWEEN CORTEX RATIO AND BONE MINERAL DENSITY

Femoral Cortex Ratio is not a standard method of assessing bone quality. By correlating it to the gold standard method of assessing BMD we aimed to determine if it was a reliable tool for future use. We found that there was a moderately strong ($r=0.45$), but highly significant ($p<0.0001$) correlation between the bone mineral density of the bone around the arthroplasty and the cortex ratio, as shown in Figure 12-5.

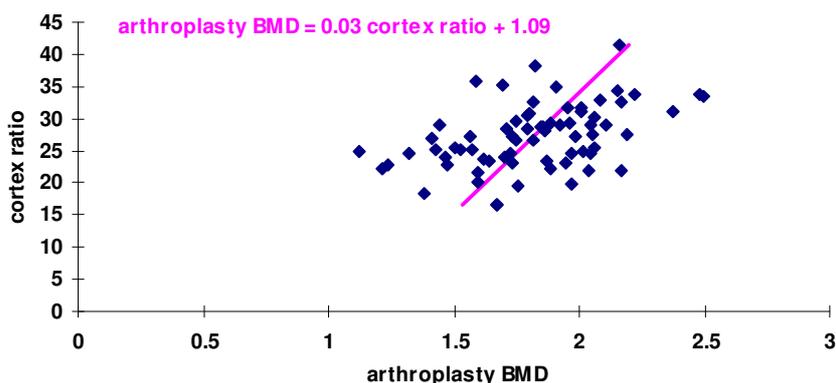


Figure 12-5. Correlation between the Cortex Ratio and the peri-prosthetic BMD.

Shown with best fit linear regression line and equation ($r=0.45$, $p<0.001$)

There were similar correlations between the cortex ratio and the BMD of the lumbar spine ($r=0.45$, $p<0.0001$) and the radius ($r= 0.49$, $p<0.0001$), as shown in Figure 12-6.

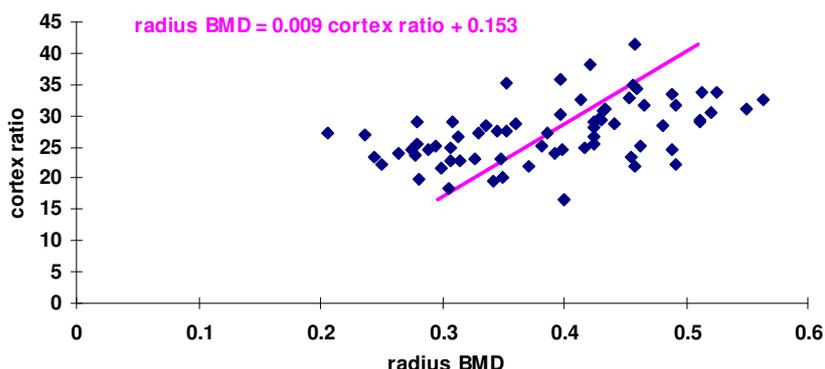


Figure 12-6. Correlation between the Cortex Ratio and the radius BMD.

Shown with best fit linear regression line and equation ($r=0.49$, $p<0.001$)

From this we can conclude that the Femoral Cortical measurements are a good tool for assessing regional and systemic BMD.

CANCELLOUS BONE STRENGTH

We did not find that the Singh Index was a useful tool to predict aseptic loosening. It should be noted however, that a significant proportion of patients had a total hip replacement (THR) on the contra-lateral side and it was thus difficult to make an accurate assessment as the numbers for analysis were reduced (as discussed in the methods section). Table 12.3 below shows the frequency of patients in each group.

Table 12-3. Singh Index for patients with loose and stable arthroplasties

	All	1	2	3	4	5	6	Exclusions *
All	107	0	0	0	1	45	40	21
loose	66	0	0	0	1	28	28	9
stable	41	0	0	0	0	17	12	12

Frequency of patients per group, measured on the contra-lateral side on the pre op radiograph

* patients excluded from analysis due to the presence of a hip arthroplasty

Of those who did have their Singh Index assessed, there was no difference in the proportion of patients in each group ($p=0.5$, chi square) or the mean Singh Index score (difference in means, $p=0.9$, ANOVA). As shown in Figure 12-7:

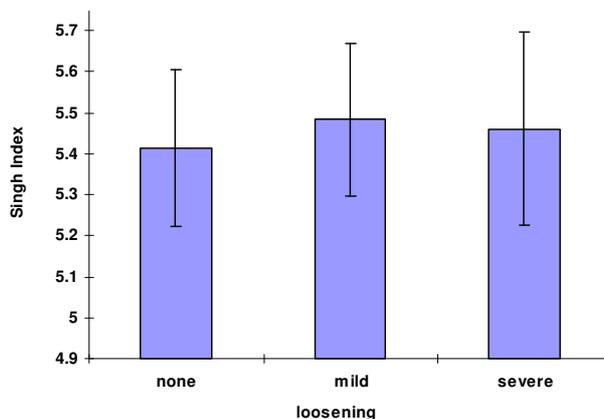


Figure 12-7. Mean Singh value, with 95%CI ($p=0.9$)

Because of the acknowledged difficulties measuring the Singh Index, it is difficult to assess whether the lack of differences observed were because of the study errors or due to a lack of clinical difference.

CLASSIFICATION OF OSTEOARTHRITIS

We found that the Bombelli classification of osteoarthritis was a significant predictor for the development of aseptic loosening. Overall, 28% (30/109) patients had atrophic, 59% (64/109) had normotrophic and (15/109) had 14% hypertrophic osteoarthritis. This is shown in table 12.4 below.

Table 12-4. Bombelli Classification of OA and development of loosening

	All	Stable	Loose		
			Mild	Severe	All *
All	109	40	40	29	69
Atrophic	30	6	9	15	24
Normotrophic	64	25	27	12	38
Hypertrophic	15	9	4	2	6

Numbers of patients by classification of OA and degree of arthroplasty loosening

Eighty percent of patients with atrophic OA had some evidence of loosening (24/30) compared to 40% (6/15) of patients with hypertrophic OA. This difference reached statistical significance (p=0.02, chi square, Figure 12-8). Fifty per cent of patients with atrophic OA progressed to severe loosening compared to 13% of those with hypertrophic OA (15/30 vs. 2/15, p=0.02, chi square). Conversely, 60% of those with hypertrophic OA had normal radiographs at follow up, compared to 20% of those with atrophic OA (9/15 vs. 6/30, p=0.007, chi square).

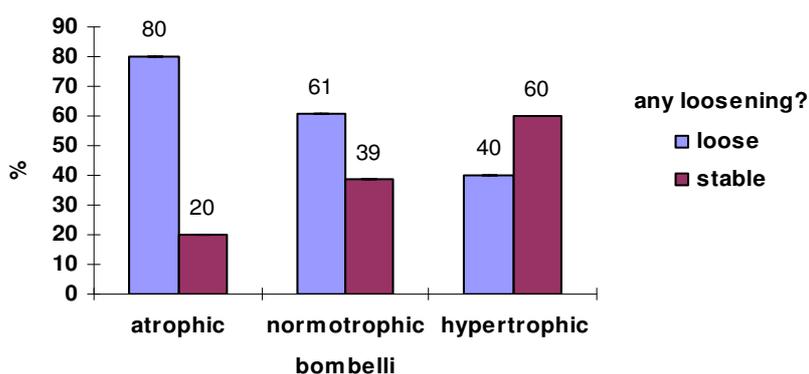


Figure 12-8. Classification of OA and the development of loosening

EXAMPLES

The following figure demonstrates a typical case of atrophic osteoarthritis progressing to having loosening around the acetabular component. The pre-op, immediate post-op and most recent radiographs are shown.



Figure 12-9. Example of a THR for atrophic OA developing loosening

The following figure demonstrates a typical case of hypertrophic osteoarthritis continuing to have a stable arthroplasty. The pre-op, immediate post-op and most recent radiographs are shown.



Figure 12-10. Example of a THR for hypertrophic OA maintaining stability

UNDERLYING DIAGNOSIS AND CLASSIFICATION OF OSTEOARTHRITIS

The classification of OA and the underlying diagnosis for each patient is given in table 12.5 below, with the relative proportions of each diagnosis given in the graph. Although the Bombelli classification was described for osteoarthritis, we have applied it here to the secondary osteoarthritic changes that develop. As the incidence of the each pathology other than osteoarthritis was low, we separated the underlying diagnosis into being OA or non-OA.

Table 12-5. Underlying diagnosis and type of OA

	All	Primary OA	All non-OA	RA	AVN	SCFE	DDH	Perthes
All	105	89	16	5	3	1	5	2
Atrophic	28	20	8	1	2	0	4	1
Normotrophic	62	54	8	4	1	1	1	1
Hypertrophic	15	15	0	0	0	0	0	0

Classification of OA and the underlying diagnosis prior to arthroplasty (frequency)

Patients with atrophic osteoarthritis were less likely to have a diagnosis of primary osteoarthritis (20/28 (71%), than those with normotrophic OA(54/62, 87%) or hypertrophic OA (15/15, 100%). This difference was statistically significant (p=0.02, chi-square, figure 12-11).

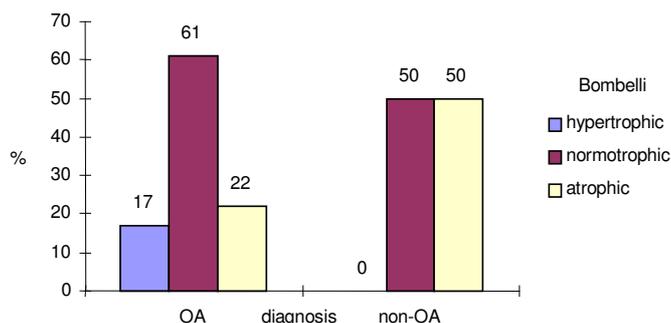


Figure 12-11. Underlying diagnosis and classification of OA

Despite the fact that a non-osteoarthritis diagnosis were more likely to have atrophic osteoarthritis (p=0.02), and atrophic OA was associated with developing loosening (as discussed in the section above, p=0.006) patients with non-OA diagnosis were not found to be have an increased incidence of loosening (p=0.9). The reason for this may be because the numbers are not large enough.

MULTIVARIATE ANALYSIS

Because a significant proportion of patients couldn't have their Singh Index assessed the analysis was performed with only the cortex ratio and Bombelli classification. 108 patients had full data for analysis. The results showed that both the Cortex Ratio ($p=0.002$) was a significant variable and that the Bombelli classification demonstrated a non-significant trend ($p=0.06$).

Table 12-6. Multi-variate analysis of radiographic markers on loosening

Variable	Model Log Likelihood	Change in -2 Log Likelihood	df	Sig. of Change *
Step 1 Cortex Ratio	-67.425	9.620	1	.002
Bombelli	-65.361	5.493	2	.064

Influence of Cortex Ratio and Bombelli classification on loosening

* stepwise backward LR regression analysis employed

This confirms the findings of the univariate analysis.

13. BONE MINERAL DENSITY AND LOOSENING

Seventy five of the potential 127 patients (59%) were able to attend for DEXA assessment. 35 (28%) refused to participate, 11 (9%) were lost to follow up and 6 (5%) were unable to attend for medical reasons. The main reason for refusal to participate was that the DEXA scan had to be performed at the Leicester Royal Infirmary, and many had concerns regarding parking. Despite many of these drop outs being unavoidable, it is acknowledged that the low participation rate may affect the validity of the findings presented here.

Analysis of the attenders and non-attenders revealed that there was no difference between those who attended for DEXA scan with regard to sex (percentage male: 25/82 vs. 15/50, $p=0.9$, chi-square), time since surgery (both mean 7.8 years, $p=0.8$ t-test) or patient age (mean years 67 vs. 68, $p=0.4$, t-test).

Summary of findings of BMD study

- Patients with loosening have a significantly lower prosthetic BMD.
- The greatest difference is greatest proximally and medially
- Patients with loosening have a generalised lower BMD
- BMD is not correlated to pain or function, and so unlikely to due to disuse osteoporosis.

Box 13-1. Summary BMD findings and loosening

ASSESSMENT AROUND THE HIP

PERI-PROSTHETIC BMD

The peri-prosthetic region was defined as the region made around the whole of the hip prosthesis (see Methods for details). We found that the development of aseptic loosening was significantly related to bone mineral density (BMD), when measured at this site. Table 13.1 below shows the mean, median and standard deviation peri-prosthetic region BMD for each group. As the data was normally distributed, parametric tests were used.

Table 13-1. Peri-prosthetic BMD (g/cm²) and aseptic loosening

	All	Stable	Loose		
			Mild	Severe	All*
Number	75	29	19	27	46
Mean	1.83	1.95	1.68	1.82	1.76
Median	1.85	1.98	1.75	1.87	1.79
St Dev	0.29	0.25	0.25	0.30	0.29

Patients with stable arthroplasties had a clinically and statistically higher BMD than those with loosening (1.95 vs. 1.76, $p=0.005$, T-test, effect size = 0.7). This difference was seen both in those with mild loosening (mean scores 1.95 vs. 1.67, $p=0.001$, T-test, effect size = 0.9) and severe loosening (1.95 vs. 1.82, $p=0.01$, T-test, effect size = 0.4). A histogram of the differences in relative frequency of BMD between those with loose and stable arthroplasties is shown in figure 13.1 below.

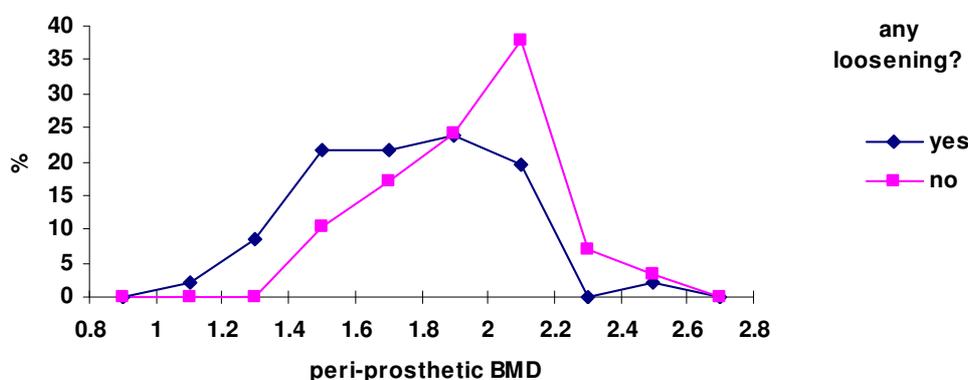


Figure 13-1. Peri-prosthetic BMD (g/cm²) and loosening.

BMD IN INDIVIDUAL GRUEN ZONES

As well as a mean value of all regions around the prosthesis, similar calculations were made for the BMD in each individual zone. The mean, standard deviation, t test and effect size are shown in table 13.2. There were significant differences in mean BMD at a number of Gruen zones, in particular zones 1 ($p=0.008$), 6 ($p=0.002$) and 7 ($p<0.001$). These correspond to the proximal and medial zones around the prosthesis. Figures 13.2 and 13.3 show the difference in value at each zone between those with loose and stable arthroplasties.

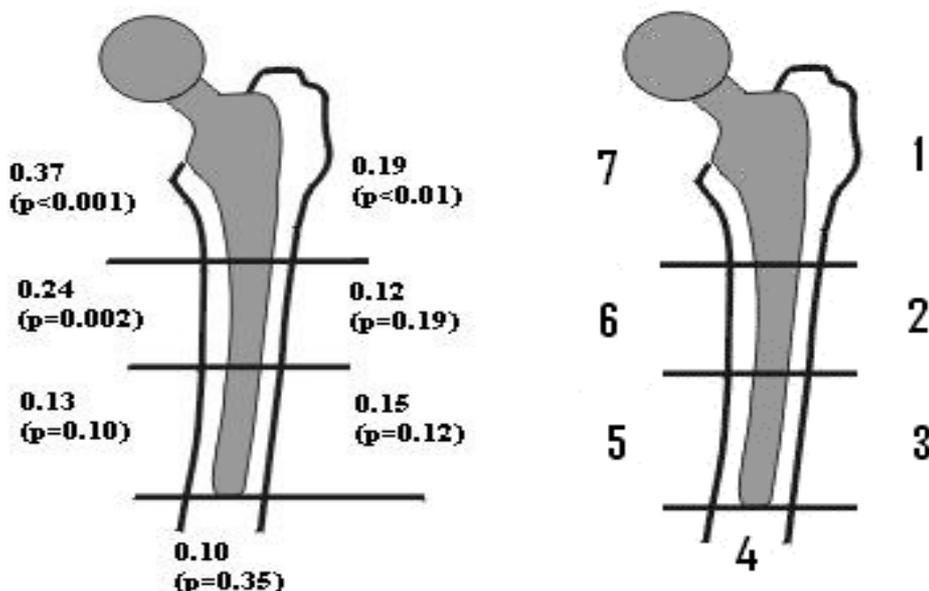


Figure 13-2. Differences in median BMD at 7 sites around the prosthesis

Shown with Gruen zones and with differences in means and p values for t tests

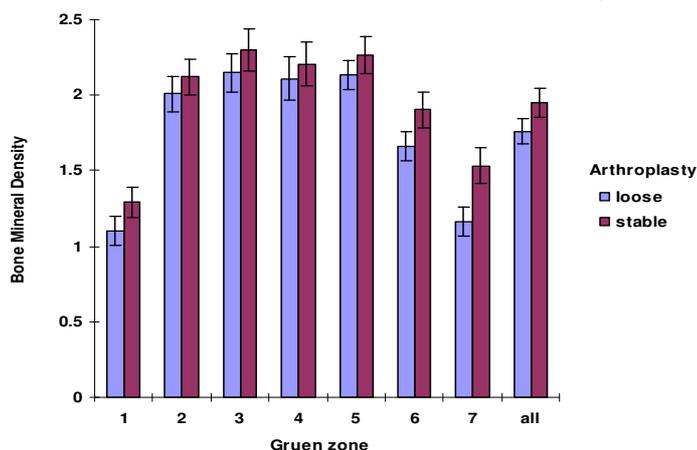


Figure 13-3. Bone mineral density at individual Gruen zones (with 95% CI)

Table 13-2. Bone mineral density in Gruen zones 1 to 3

Gruen Zone	BMD *		P**	Effect size	Figure
	Stable	Loose			
All	1.95 (0.25)	1.76 (0.29)	0.006	0.8	
1	1.29 (0.27)	1.10 (0.33)	0.008	0.7	
2	2.12 (0.31)	2.00 (0.41)	0.2	0.4	
3	2.29 (0.36)	2.14 (0.43)	0.1	0.4	

* Mean (and SD) BMD values given as g/cm²

There were 29 cases with Stable arthroplasties and 46 with Loose arthroplasties

**p values calculated with t test

Table 13-2b. Bone mineral density in Gruen zones 4 to 7

Gruen Zone	BMD		P**	Effect size	Figure
	Stable	Loose			
4	2.21 (0.39)	2.11 (0.49)	0.4	0.3	
5	2.26 (0.31)	2.14 (0.33)	0.09	0.4	
6	1.90 (0.33)	1.66 (0.32)	0.002	0.7	
7	1.31 (0.30)	1.16 (0.33)	<0.001	0.5	

From this we can conclude that the differences in BMD are localised to the regions most subjected to stress shielding (the proximal zones) and the regions normally subjected to compressive forces (the medial zones).

DISTANT ASSESSMENTS

LUMBAR BONE MINERAL DENSITY

We observed a strong link between Lumbar BMD and development of loosening. For each patient the Z and T score were calculated. The mean, median and SD for the Z score of each group is shown in table 13.3. Because the data was skewed, non-parametric tests are given (although statistically significant results were also obtained using parametric tests).

Table 13-3. Lumbar Z score at the lumbar spine and loosening

	All	Stable	Loose		
			Mild	Severe	All*
Number	75	29	19	27	46
Mean	1.1	1.8	0.0	1.1	0.6
Median	0.8	2.1	0.1	0.9	0.3
St Dev	1.7	1.5	1.1	1.9	1.7

* Patients with "all" were a combination of the "mild" and "severe" loosening groups

The median Z score was statistically lower in patients with loosening and this had a very significant effect size (0.3 vs. 2.1, p=0.001, Mann Whitney U Test, effect size = 1). This was seen both in patients with mild loosening (0.1 vs. 2.1, p=0.0002, Mann Whitney U Test, effect size = 1.2) and severe loosening (0.9 vs. 2.1, p=0.06, Mann Whitney U Test, effect size = 0.7). Figure 13.4 shows the Z score according to whether loosening was present or not.

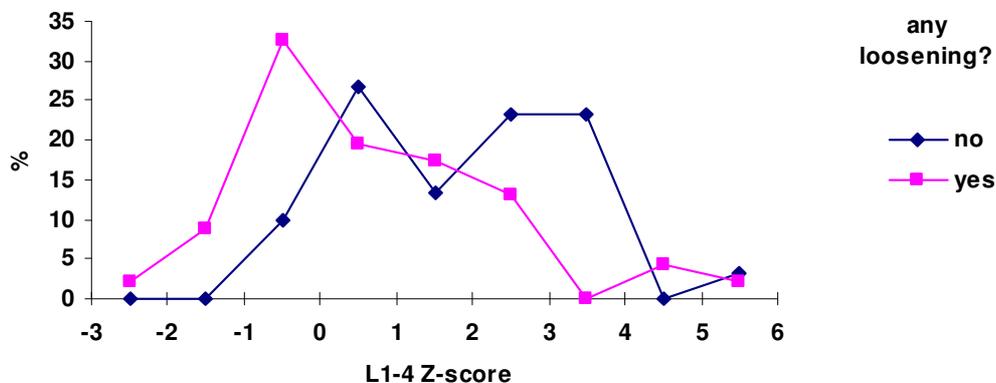


Figure 13-4. Lumbar Z score measurements according to presence of loosening

WHO CRITERIA FOR OSTEOPOROSIS

Analysis of the T score showed that 9 patients met the WHO criteria for osteoporosis (T score >-2.5). This was more likely in those with loose than stable arthroplasties, although not quite reaching statistical significance (8/46 (17%) vs. 1/30 (3%), $p=0.06$, χ^2 , Odds Ratio 6.1, 95% 0.9 to 41). This is shown in the figure 13.5.

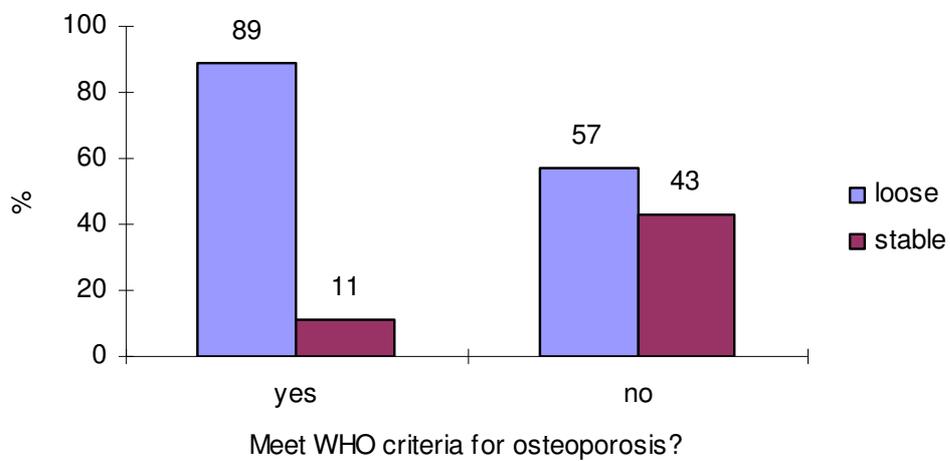


Figure 13-5. Loosening and meeting WHO criteria for osteoporosis

RADIUS BONE MINERAL DENSITY

At the ultra-distal radius there was a less strong link. The data was spread normally, so parametric tests were used. The mean, median and SD for the Z score of each group is shown in table 13.4. Data was parametric and so T tests were used.

Table 13-4. Distal radius Z score at the distal radius and loosening

	All	Stable	Loose		
			Mild	Severe	All*
Number	75	29	19	27	46
Mean	1.4	1.8	0.9	1.3	1.1
Median	1.2	1.6	0.6	1.3	1.0
St Dev	1.7	1.8	1.8	1.5	1.6

* Patients with "all" were a combination of the "mild" and "severe" loosening groups

Those with loosening had a lower mean Z score than those with a stable arthroplasty (1.1 vs. 1.8, $p=0.08$, T-test, effect size = 0.4). This was more marked in patients with mild loosening (0.9 vs. 1.8, $p=0.08$, t-test, effect size = 0.5) than patients with severe loosening (1.3 vs. 1.8, $p=0.2$, t-test, effect size = 0.3). The differences are shown in figure 13.6 below:

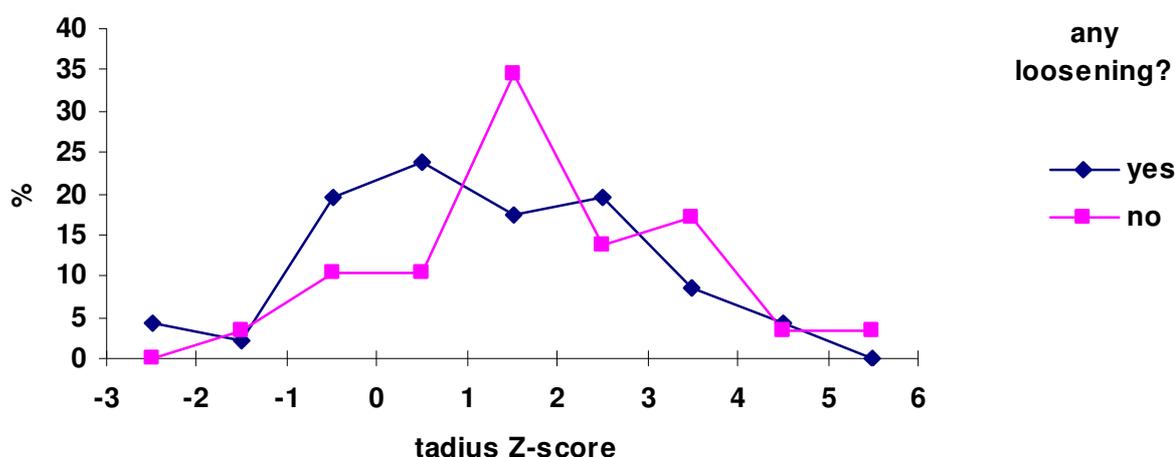


Figure 13-6. Distal radius Z score according to presence of loosening

CORRELATION BETWEEN PAIN AND FUNCTION AND BMD

We found no correlation between either pain or function and peri-prosthetic BMD (both $r=0.31$, $p=0.99$, Pearson’s correlation, figure 13.7). We also found that there was no correlation between pain or function and lumbar BMD ($r=-0.05$, $p=0.67$ and $r=-0.03$, $p=0.62$ respectively).

These findings suggest that disuse osteoporosis is not the cause of peri-prosthetic osteopenia

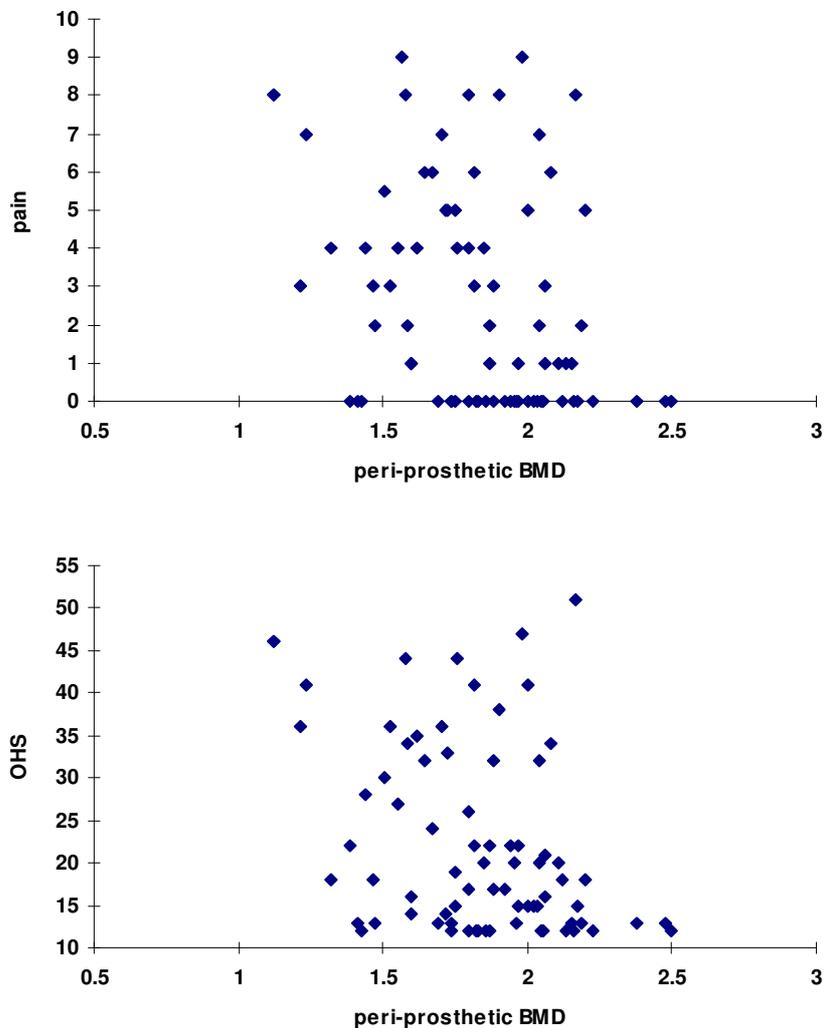


Figure 13-7. Correlation between peri-prosthetic BMD and pain or function

(a) pain visual analogue score. Range 0 (least) to 10 (most), $r=-0.31$, $p=0.997$

(b) function (Oxford Hip Score. Range 12 (best) to 60 (worst), $r=-0.31$, $p=0.99$

MULTIVARIATE ANALYSIS

Initially multivariate analysis was performed to assess the influence of the different regions around the hip. In addition to the separate 7 Gruen zones, the mean density of all zones was analysed. Analysis revealed that the only measurement that was significantly different between those with loose and stable arthroplasties, was the mean of all regions ($p=0.004$). This is shown in table 13-6 on the following page.

Next analysis was performed to assess the influence of different regions of the body. BMD at the lumbar spine, distal radius and the mean peri-prosthetic region were compared. Analysis revealed that only the BMD at the lumbar spine was significantly different between the two groups ($p=0.003$). This is shown below (table 13-5)

Table 13-5. Multivariate analysis of BMD at the spine, wrist and hip on loosening

Model	step	Unstandardised		Standardised		Signif.
		B	Std. Error	Beta	t	
1	(Constant)	1.321	.373		3.541	.001
	spine	-.062	.038	-.219	-1.637	.106
	radius	-.016	.035	-.057	-.464	.644
	Peri-prosthetic	-.336	.211	-.198	-1.594	.115
2	(Constant)	1.319	.371		3.555	.001
	Spine	-.068	.035	-.243	-1.974	.052
	Peri-prosthetic	-.344	.209	-.202	-1.641	.105
3	(Constant)	.719	.064		11.246	.000
	Spine	-.095	.031	-.336	-3.047	.003

Stepwise backward LR regression analysis with
cyclical removal of the least significant variable before re-analysis

Table 13-6. Multivariate analysis of Gruen zones and loosening

Model	step	Unstandardised		Standardised		Signif.
		B	Std. Error	Beta	t	
1	1	-.060	.288	-.040	-.207	.837
	2	-.132	.309	-.096	-.427	.672
	3	.003	.345	.002	.008	.994
	4	-.129	.240	-.117	-.536	.594
	5	.269	.339	.180	.794	.431
	6	-.021	.321	-.014	-.064	.949
	7	-.150	.324	-.112	-.462	.646
	Mean all	-.649	.255	-.368	-2.549	.014
2	1	-.060	.281	-.040	-.214	.831
	2	-.130	.247	-.095	-.527	.601
	4	-.128	.225	-.117	-.568	.572
	5	.270	.335	.180	.805	.425
	6	-.021	.313	-.015	-.067	.947
	7	-.149	.276	-.111	-.538	.593
		Mean all	-.649	.252	-.368	-2.580
3	1	-.067	.259	-.044	-.259	.797
	2	-.129	.243	-.094	-.528	.600
	4	-.126	.221	-.115	-.570	.571
	5	.264	.320	.176	.824	.414
	7	-.159	.226	-.118	-.705	.484
	Mean all	-.652	.246	-.370	-2.650	.011
4	2	-.145	.233	-.106	-.625	.535
	4	-.129	.218	-.117	-.590	.558
	5	.252	.314	.168	.803	.426
	7	-.175	.216	-.130	-.810	.422
	Mean all	-.665	.239	-.377	-2.787	.008
5	2	-.151	.231	-.111	-.656	.515
	5	.138	.246	.092	.562	.577
	7	-.195	.211	-.145	-.923	.360
	Mean all	-.632	.230	-.358	-2.742	.008
6	2	-.096	.207	-.070	-.463	.645
	7	-.160	.201	-.119	-.798	.429
	Mean all	-.647	.227	-.367	-2.849	.006
7	7	-.210	.168	-.156	-1.248	.217
	Mean all	-.668	.221	-.379	-3.025	.004
8	Mean all	-.669	.222	-.379	-3.011	.004

Stepwise backward LR regression analysis with
cyclical removal of the least significant variable before re-analysis

14. BIOCHEMICAL MARKERS OF LOOSENING

Eighty of the potential 127 patients (63%) gave a blood sample for analysis. 30 (28%) refused to participate, 11 (9%) were lost to follow up and 6 (5%) were unable to attend for medical reasons.

VITAMIN D

Of the 110 patients still alive and not lost to follow up, 80 (72%) gave a blood sample. The vitamin D levels were measured in mmol/l and sub-categorised into normal (>50mmol/l), deficient (<25 mmol/l) and insufficient (<50 mmol/l). Table 14.1 shows the values for each group. Because data was not normally distributed, non-parametric tests were used. Categorical tests were used to analyse the subcategories.

Table 14-1. Vitamin D level and aseptic loosening

	All	Stable	Loose		
			Mild	Severe	All*
Number	80	31	19	30	49
Mean	51.4	47.7	54.4	53.4	53.8
Median	41.3	36.8	43.3	50.1	44.3
St Dev	33.8	35.0	37.4	31.0	33.2

Vitamin D level (mmol/l) for patients with varying degrees of loosening
 *Patients with “all” were a combination of the “mild” and “severe” groups

The incidence of vitamin D deficiency or insufficiency within the group as a whole was very high, with the median level being only 41.3 mmol/l. Overall, only 32 (40%) of patients had a normal serum vitamin D, with 33 (41%) having insufficiency and 15 (19%) being deficient (figure 14.1).

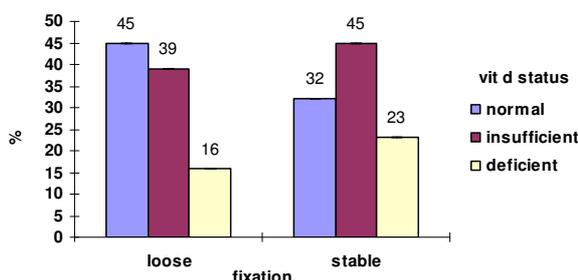


Figure 14-1. Incidence of vitamin D deficiency and insufficiency

Despite this high prevalence of vitamin D insufficiency/deficiency, there was no difference in either absolute level between those with loose and stable arthroplasties (median level 44 vs. 37, p=0.3, Mann Whitney U Test) or sub-category (p=0.3, chi sq).

PARATHYROID HORMONE

Parathyroid Hormone (PTH) levels were also measured in pmol/l, with a normal range between 0.8 and 8.0 pmol/l. Table 14.2 shows the values according to the degree of loosening, because the data was not normally distributed, non-parametric tests were used.

Table 14-2. Serum Parathyroid hormone levels and loosening

	All	Stable	Loose		
			Mild	Severe	All*
Number	80	31	19	30	49
Mean	3.3	3.6	2.9	3.4	3.2
Median	3.0	2.5	2.8	3.2	3.2
St Dev	2.0	2.6	1.2	1.6	1.5

Serum PTH level (pmol/l) for patients with loose and stable arthroplasties

*Patients with “all” were a combination of the “mild” and “severe” loosening groups

Although patients with loosening had slightly higher PTH levels than patients with stable arthroplasties, this did not reach clinical significance (median levels 3.18 and 2.54 respectively, $p=0.71$, Mann Whitney U Test). This is illustrated in figure 14.2 below.

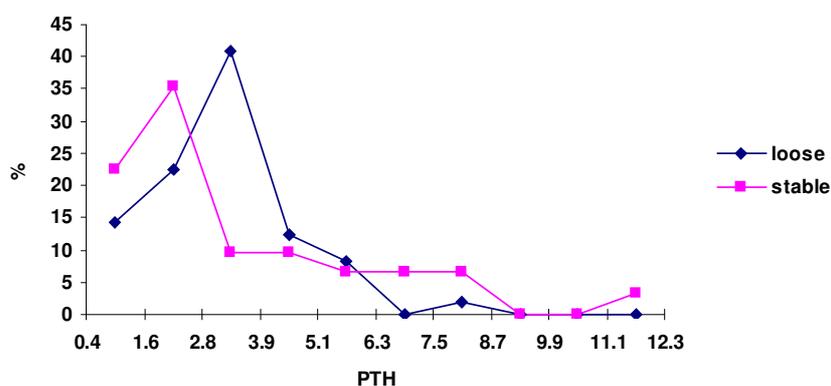


Figure 14-2. Parathyroid hormone levels (PTH) and loosening

3/80 patients (4%) had hyperparathyroidism (serum value >8pmol/l), in keeping with previous reported frequencies (Glowacki et al., 1985). Again, there was no difference between the 2 groups ($p=0.3$, chi sq).

ALKALINE PHOSPHATASE

Alkaline Phosphatase (ALP) levels were measured in international units per litre (IUL), with a normal range of 30 to 300 IUL. Table 14.3 shows the values according to the degree of loosening, because the data was not normally distributed, non-parametric tests were used.

Table 14-3. Serum Alkaline Phosphatase levels and loosening

	All	Stable	Loose		
			Mild	Severe	All*
Number	75	28	18	29	47
Mean	89.1	88.2	94.9	86.4	89.7
Median	80	81.5	72.5	79.0	78.0
St Dev	36.6	24.1	60.7	26.7	42.3

Serum ALP levels (IUL) for patients with loose and stable arthroplasties

*Patients with “all” were a combination of the “mild” and “severe” loosening groups

There was no difference in serum alkaline phosphatase levels between those with loose and stable arthroplasties. The median value for loose arthroplasties was 78 IUL compared to 81.5 IUL for those with stable arthroplasties (p=0.40, Mann Whitney U Test). This is shown in figure 14.3 below.

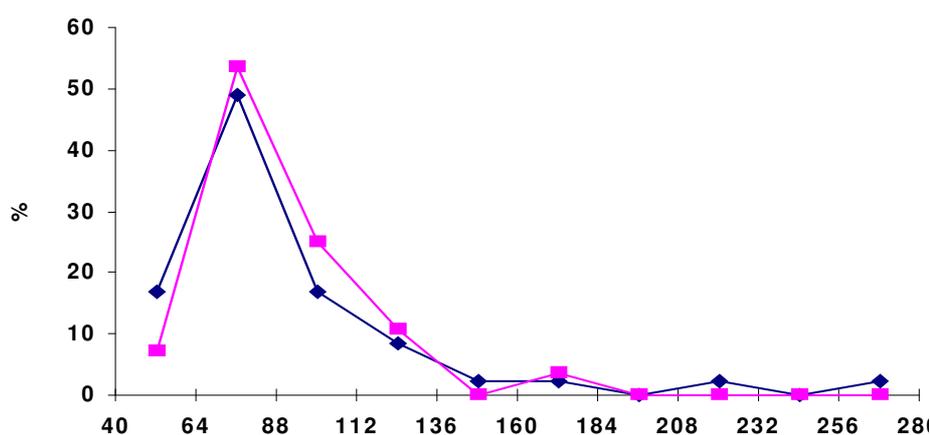


Figure 14-3. Alkaline phosphatase levels in those with loose and stable arthroplasties

Difference in medians, p=0.40, Mann Whitney U Test

ADJUSTED CALCIUM

Adjusted calcium (Ca) levels were measured in mmol/l, with a normal range of 2.1 to 2.6 mmol/l. Table 14.4 shows the values according to the degree of loosening, because the data was normally distributed, parametric tests were used.

Table 14-4. Serum Calcium levels and loosening

	All	Stable	Loose		
			Mild	Severe	All*
Number	74	28	18	28	46
Mean	2.3	2.3	2.4	2.3	2.3
Median	2.3	2.3	2.3	2.3	2.3
St Dev	0.1	0.1	0.1	0.1	0.1

Serum calcium levels (mmol/l) for patients with loose and stable arthroplasties

*Patients with “all” were a combination of the “mild” and “severe” loosening groups

There was no difference in adjusted calcium levels between those with loose and stable arthroplasties (difference in means 2.34 vs. 2.35, $p=0.65$, t test), figure 14.4.

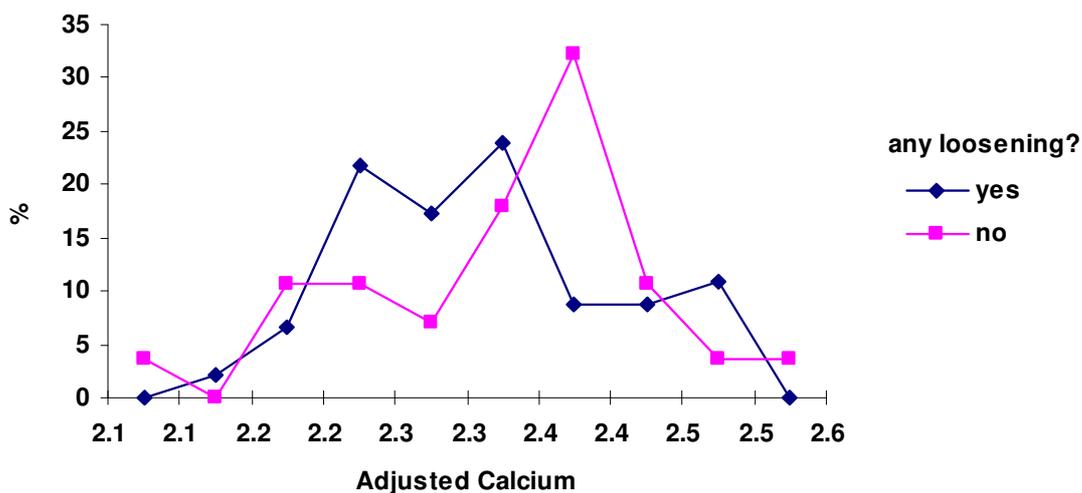


Figure 14-4. Serum calcium levels in those with loose and stable arthroplasties

SERUM PHOSPHATE

Serum Phosphate levels were measured in mmol/l, with a normal range between 0.8 and 1.5 mmol/l. Table 14.5 shows the values according to the degree of loosening, because the data was normally distributed, parametric tests were used.

Table 14-5. Serum Phosphate levels and loosening

	All	Stable	Loose		
			Mild	Severe	All*
Number	74	28	18	28	46
Mean	1.2	1.1	1.2	1.2	1.2
Median	1.2	1.2	1.2	1.2	1.2
St Dev	0.1	0.2	0.1	0.1	0.1

Serum phosphate levels (mmol/l) for patients with loose and stable arthroplasties

*Patients with “all” were a combination of the “mild” and “severe” loosening groups

There was no difference in serum phosphate levels between those with loose and stable arthroplasties (difference in means 1.19 vs. 1.14, $p=0.23$, t test), figure 14.5.

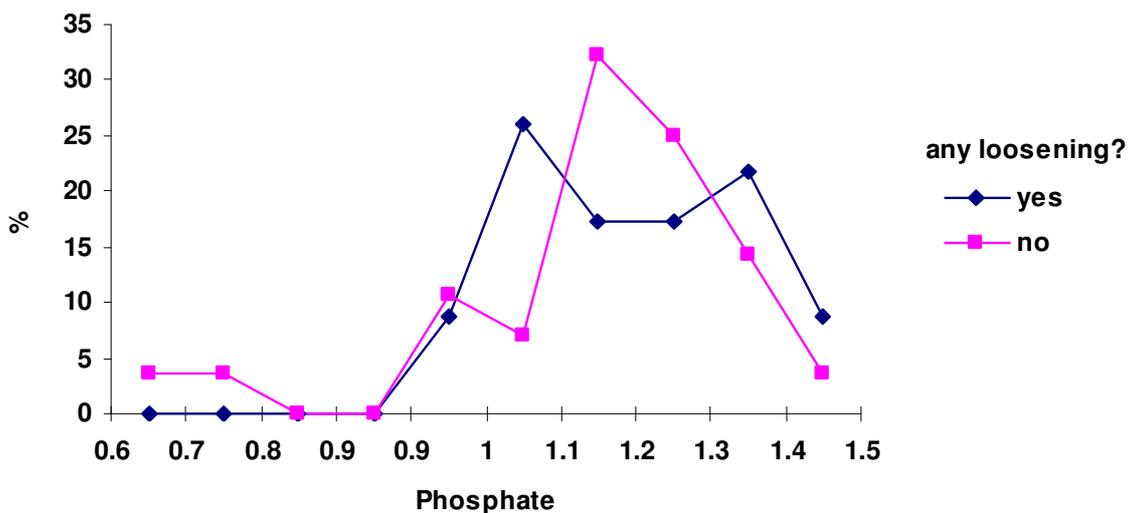


Figure 14-5. Serum phosphate levels in those with loose and stable arthroplasties

MULTIVARIATE ANALYSIS

Multivariate analysis was performed on calcium, phosphate, alkaline phosphatase, PTH and vitamin D serum levels to assess their influence on loosening. Stepwise backwards analysis revealed that none had any significant effect, in keeping with the univariate analysis findings.

Table 14-6. Multivariate analysis of serum calcium, phosphate, alkaline phosphatase and vitamin D on loosening

Model	step	Unstandardised		Standardised		Signif.
		B	Std. Error	Beta	t	
1	(Constant)	.728	1.619		.450	.654
	calcium	-.373	.654	-.069	-.571	.570
	phosphate	.556	.412	.166	1.348	.182
	Alkaline Phosphatase	.001	.002	.085	.662	.510
	Parathyroid hormone	-.018	.030	-.073	-.600	.551
	Vitamin D	.001	.002	.102	.790	.432
2	(Constant)	-.130	.597		-.218	.828
	phosphate	.555	.410	.166	1.352	.181
	Alkaline Phosphatase	.001	.002	.074	.582	.562
	Parathyroid hormone	-.017	.029	-.071	-.583	.562
	Vitamin D	.001	.002	.098	.766	.446
3	(Constant)	.040	.518		.077	.939
	phosphate	.505	.400	.151	1.264	.210
	Parathyroid hormone	-.019	.029	-.078	-.652	.517
	Vitamin D	.001	.002	.073	.608	.545
4	(Constant)	.145	.487		.298	.766
	phosphate	.471	.394	.141	1.195	.236
	Parathyroid hormone	-.022	.028	-.092	-.779	.439
5	(Constant)	.026	.461		.057	.955
	phosphate	.508	.390	.152	1.303	.197
6	(Constant)	.622	.057		10.951	.000

DISCUSSION

15. SUMMARY OF CURRENT KNOWLEDGE

A. CLINICAL RISK FACTORS

Although a significant amount of work has examined the clinical risk factors for osteoporosis and subsequent fracture risk, much less has studied similar risk factors' influence on developing arthroplasty loosening. This is largely due to the fact that arthroplasty surgery is a relatively new, and rapidly evolving branch of medicine, with a very heterogeneous mix of techniques.

In addition, although the fundamental hypothesis of this study is that as well as predisposing to fractures, osteoporosis also increases the risk of loosening, there are a number of paradoxical influences. For example although increasing age is a clear risk factor for osteoporotic fractures, its influence on loosening is confounded by the fact that older people have less wear of their prosthesis, a factor that is associated with increased arthroplasty survival. Similarly, women are more likely to have osteoporotic fractures, but men have a higher rate of implant loosening, again probably due to increased wear rates.

Many studies have shown that a previous fragility fracture roughly doubles the risk of subsequent fractures, but no similar studies have looked for an association between fracture history and loosening. Smoking increases fracture risk by 25%, and may also increase arthroplasty loosening, although the evidence base is very patchy. There is conflicting data regarding the body weight. Although some studies have shown that it increases BMD and decreases fracture risk, but an increase proportion of body fat actually increases fracture risk. Again, there is no conclusive data regarding BMI and arthroplasty loosening.

The lifetime variation in bone mass is well known, in particular the influence of the menopause on bone remodelling, and the subsequent reduction in BMD and increased fracture risk. Despite arthroplasty being commonly performed on post-menopausal women, there are no studies examining the impact of the menopause on aseptic loosening.

Finally, although many studies have sought to help predict whether an implant is loose radiographically or biochemically, very little work has correlated the level of pain or dysfunction to the degree of loosening.

B. RADIOGRAPHIC MARKERS

A number of measurements have previously been made to determine bone strength based on bone morphology, cortical thickness and trabecular pattern. The cortex contributes to over half the strength of bone and femoral cortical thickness measurements are correlated to BMD and fracture risk, but there is little evidence suggesting they predict arthroplasty loosening. The Singh Index classifies the trabecular pattern of cancellous bone in osteoporotic bone. Although there is good correlation between the Singh Index and BMD and biomechanical strength, there is little prospective evidence that it predicts fracture risk. There are very few studies examining the influence of the Singh Index on arthroplasty loosening. The Bombelli classification of osteoarthritis is based on the number of osteophytes around an arthritic joint and has since been shown to be dependent on the concentration of osteoblasts within them. There is conflicting evidence whether this classification is important in the development of arthroplasty loosening.

C. BONE MINERAL DENSITY

DEXA is the gold standard for bone mineral density assessment and is a good predictor for both biomechanical strength and fracture risk. Significant changes occur to the peri-prosthetic BMD after hip arthroplasty, with up to a 50% reduction in BMD, mainly in the 1st year post surgery and greatest in the medial calcar region. This is probably due to stress shielding and depends on the type of prosthesis, but may also be due to disuse and post-traumatic osteoporosis that are associated with generalised bone loss.

D. BIOCHEMICAL MARKERS

The mineralisation of bone is sacrificed at the expense of maintaining serum calcium levels for important cellular pathways. Vitamin D is activated by hepatic and then renal hydroxylation. It then increases intestinal calcium absorption as well as stimulating bone formation and having other systemic effects, including aiding muscle contraction. Vitamin D deficiency is common, particularly in certain population groups. However there is conflicting evidence whether supplements reduce the incidence of fractures, and very little evidence whether it affects the outcome of arthroplasty.

Parathyroid hormone (PTH) increases serum calcium by stimulating osteoclastic bone resorption, decreasing renal calcium excretion and activating vitamin D-mediated intestinal absorption. Although PTH levels are high in patients who have suffered a fragility fracture, there is very little evidence that PTH level predicts fracture risk, and there is no evidence examining its effect on arthroplasty loosening.

16. SUMMARY OF FINDINGS IN THIS STUDY

A. CLINICAL RISK FACTORS

This study has provided answers and stimulated further questioning in equal measure. One of the key findings is that patients with loosening are nearly four times more likely to have suffered a fragility fracture in the past. This hasn't been investigated or shown in other studies. There were a number of other less significant, but nonetheless interesting trends that future studies will examine in more detail. For example, patients with loosening tended to be active smokers and have had an earlier menopause. Although Body Mass Index and weight were correlated with peri-prosthetic BMD, they did not appear to influence development of loosening. These weak associations are backed by strong theoretical links between BMI/menopause/smoking and bone health, with high-level evidence demonstrating these risk factors increase fracture risk.

With regards to clinical detection of loosening, only patients with advanced loosening complained of significantly higher levels of pain or had a worse level of function. In addition, simply asking whether a patient uses a walking aid is as good as the Oxford Hip Score at determining those with significantly reduced function.

B. RADIOGRAPHIC MARKERS

This study has shown a number of markers are useful in predicting loosening. Patients with loosening, particularly when severe, have a significantly narrower medial femoral cortex. Because of the relatively broad distribution in thickness, the effect size was only moderate. Similar results, but with higher significance and better effect sizes were observed when the cortex ratio was measured (effect size 0.8 for patients with severe loosening). There was also a highly significant correlation between the cortex ratio and the bone mineral density at the hip, spine and distal radius.

We did not find the Singh Index to be a good tool for predicting cancellous bone strength in osteoarthritic patients, and little information can be obtained from the results of the findings of this section of the study.

Patients with atrophic OA were twice as likely to develop loosening as those with hypertrophic OA.

C. BONE MINERAL DENSITY

Patients with loosening have a significantly lower BMD around their prosthesis. This difference was greatest in the zones around the proximal and medial parts of the prosthesis (Gruen zones 1, 6 and 7). However because the assessments were made after the loosening had already developed, it is difficult to differentiate whether the lower BMD is a cause or a consequence of arthroplasty loosening.

There are several potential explanations for patients with loosening having a lower BMD around the hip. Our study hypothesis is that patients with a lower BMD have poorer bone micro-architecture, with less trabecular support for the prosthesis. However, a second explanation is that patients with loosening have discomfort from their prosthesis and develop disuse osteoporosis. A third possible explanation is that the process of osteolysis causes bone resorption, cavitation and consequently a lower BMD.

We attempted to exclude the possibility of disuse osteoporosis by showing there was no correlation between peri-prosthetic BMD and pain or function. Because of the retrospective nature of this study, it is difficult to categorically exclude the third explanation – that the lower BMD is a consequence, rather than a cause of loosening. We addressed this issue by showing that the BMD was also lower at multiple sites distant to the prosthesis. Because these regions are less likely to be effected by surgery, it makes it more likely that the low BMD around the hip is a cause rather than a consequence of loosening.

D. BIOCHEMICAL MARKERS

There were a very high percentage of patients with abnormal vitamin D levels (60%). This is likely, in part, to represent seasonal variation, as the samples were taken during the winter months. We did not demonstrate a difference in levels between patients with loose and stable arthroplasties.

Serum levels of PTH, ALP, calcium and phosphate were no different between patients with loose and stable arthroplasties. This is likely to relate to the fact that these are kept at tight levels under negative feedback control.

17. STRENGTHS AND WEAKNESSES OF THIS STUDY

GENERAL STRENGTHS AND WEAKNESSES

OVERALL DESIGN

The study is a compromise. The original intention being to conduct an interventional study to assess whether established loosening can be reversed pharmacologically. It soon became apparent that suitable patients were relatively rare, and highly heterogeneous in terms of timing and method of presentation (asymptomatic, symptomatic or periprosthetic fracture) and the type and longevity of prosthesis. Many patients were operated on rapidly, whereas others were kept on long-term review. With these issues in mind, a prophylactic preventative study was considered, of which several similar studies had already been conducted. It was decided that the time frame (realistically at least 15 years) and number of patients (power analysis suggested 500) required would make such a study expensive and too long to conduct for a study of this type.

Several compromises were accepted to design a workable project. One of the general strengths of this study is that it was a well-conducted and ethically-approved study. In addition the principal investigator was involved at all steps, from design and funding, to implementation and analysis. To reduce patient numbers, established loosening in a high-risk group was used as a model. To reduce the time frame a lot of the study was done retrospectively (although much of the radiographic study was prospective and adjustments were made to address this flaw in the other studies).

PROSTHESIS USED

On the whole, a reasonable number of patients were recruited, in what is the largest study of its kind, with all patients having the same ElitePlus femoral stem. Furthermore the time span that the prostheses were followed up is very narrow (all 127 participants had their original surgery within 5 years of each other). With such a variety of prostheses available on the market, these factors are definite strengths. There was, however, some variation in type of acetabular cup and bearing surface used. All patients had a cemented femoral stem, but there was a mixture of fixation techniques for the acetabulum. These factors would effect the type and size of wear particles produced and so be a potentially confounding factor.

A further key fault of the study is tendency for the ElitePlus prosthesis to fail. It is acknowledged that the study hypothesis investigates biological risk factors for loosening (ie osteoporosis), and that the principal cause of failure in the ElitePlus is mechanical. We anticipated that osteoporotic patients would be more susceptible to the biomechanical stresses, but acknowledge that there is some discrepancy here.

PATIENT NUMBERS

A reasonable number of patients were recruited to the study. More patients would improve certain aspects of the study, particularly the clinical study where there was a number of findings that did not quite reach statistical significance, and this will be addressed in future work. However, for a study of this type it would have been very difficult to increase the numbers without affecting the homogeneity of the group. Using a broader time frame for follow up after surgery, including different prosthesis types, recruiting patients operated on in other regions and not matching patients by age/sex were all options that were considered during the development of the protocol and rejected as they would have adversely affected the validity of the results obtained.

We also did our best to track down as many patients as possible. A 11% lost to follow up and 5% death/illness at a mean of 9 years is acceptable for a retrospective study of this nature. A surprising problem was that so many patients (20%) refused to come to the Leicester Royal Infirmary, having been initially seen and recruited at the Glenfield hospital. They cited fears of parking, difficulty with the lifts and a general dislike of the place as reasons not to attend, even though the clinics were to be held out of office hours on a Saturday. It was contemplated to bring the DEXA scanner to the Glenfield, but this was not practical. Perhaps future studies in Leicester could utilise handheld calcaneal ultrasound as a method of assessing BMD instead. Regardless of this, the lack of available participants could have affected the results, particularly for the BMD and biochemical parts of the study.

It is also acknowledged that there was a significant cross over between 2001 and 2006, of the loose and stable groups. An alternative method would have been to invite all patients from the original cohort to have a radiograph, and then re-perform the matching. This would have been more costly and harder to justify ethically. The principal aim of the matching scheme was to keep relatively even numbers of patients in each group that were well matched for age, sex and time since surgery. As this aim was achieved, I am happy with this part of the study.

WEAKNESSES OF EACH PROJECT

A. CLINICAL RISK FACTORS

One potential source of error came from determining whether a fracture was low energy or not. This is difficult retrospectively, and to address this, a detailed history of event was taken by the principal investigator. An alternative methodology utilised in similar studies (such as the Fracture Index by Black et al.), is to include all adult fractures or to only include classical fragility fractures (proximal hip, distal radius or vertebral compression fractures). These too have their errors, but may be more applicable for a questionnaire completed by an unsupervised patient in future studies.

This study did not specifically look at postmenopausal women, and this part of the study was under powered. Of note, many patients had difficulties recalling when their menopause was, and no attempt was made to determine the age of menarche, the number of lifetime pregnancies or the age of first pregnancy – all important factors in determining lifetime oestrogen exposure. In addition to this, it would be ideal to calculate the peak bone mass, although as this was often 40 years or more prior to their surgery it would not be practical in a study like this. Smoking history was confined to being an active, ex or non-smoker. A more detailed history, for example to determine the number of pack years may be useful for future studies, as would the type of cigarettes smoked.

Body Mass Index is an easy to measure clinical assessment of a patient's morphology, however it is not good at determining the difference between fat and muscle. This is important because of the influence of body fat on circulating oestrogen, and the influence of these on bone health. Future studies may benefit from measuring abdominal girth and subcutaneous fat measurements. A second error is that the measurement only provides a snapshot of a patient's BMI. A more accurate assessment could be made by taking serial measurements.

Errors may have arisen when determining the level of pain or disability in participants who had reduced function due to pathologies other than from the hip. For example, some patients reported having difficulty getting in and out of a car due to contra-lateral hip problems, back problems or generalised weakness such as polio. All patients were assisted in the completion of the Oxford Hip Score to attempt to focus solely on the pain or disability from the hip. Although the overall function of the hip was estimated using the Oxford Hip Score, a more detailed history regarding the level of use of the hip could be made to help calculate the degree of wear. In future studies this could be supplemented by calculating the amount of polyethylene wear on weight-bearing radiographs.

B. RADIOGRAPHIC MARKERS

A high proportion of patients had pre-op radiographs available for this part of the study (93%), and these were interpreted prospectively.

Although pre-operative films were reviewed without knowing which group patients were in, it is possible there could be some bias due to the fact that patients with loosening (who may subsequently have further surgery) are likely to have thicker x-ray packets. Future studies could avoid this by having an independent investigator collating only the relevant x-rays, and storing them electronically after removing identifiable markings (such as the patient name and hospital). They could then be reviewed at random.

Care was taken to make cortical thickness measurements in a standardised fashion using a digital calliper and reproducibility tests revealed high levels of precision. Improvements could be made by magnifying the radiographs prior to measurement. Expression of the cortical thickness as a ratio rather than an absolute value eliminated errors derived from variations in image magnification and body size.

Previous studies have shown a reasonable inter and intra-observer correlation of the Singh Index (kappa values of 0.6). Despite this there were significant errors assessing the Singh Index due to difficulty interpreting radiographs in the presence of osteoarthritis or contra-lateral osteoarthritis. Future studies wishing to assess the cancellous bone strength in similar studies would be better using either high definition 3D CT of the femoral neck or performing biomechanical strength tests on histological specimens. This would be relatively easy to do as the femoral head and neck are removed (and usually discarded) at the time of arthroplasty surgery.

Attempts were made to make assessment of the Bombelli classification as uniform as possible. The degree of osteophyte production is a continuous rather than discrete variable and so this is a source of error. We tried to account for this by comparing the atrophic and hypertrophic groups, disregarding the grey area normotrophic group. Improvements for future studies could be made by expressing the classification as a continuous volumetric measurement of the amount of osteophytes. This would be difficult to do fully on a two-dimensional radiograph, but may be possible if discreet sections of the radiograph are measured (such as the lateral lip of the superior acetabular wall). An alternative method would be to use volumetric CT scanning or measurements of surgical specimens.

C. BONE MINERAL DENSITY

A significant proportion of patients attended for a DEXA scan. All scans were done by a single radiographer in a standardised, blinded fashion. Multiple assessments were made around the prosthesis and at distant sites. All patients had the same cemented ElitePlus prosthesis. This made the BMD assessments in the 7 Gruen zones more reproducible. In contrast, a number of different acetabular prosthesis types and fixation methods were used, and so it was not possible to generate reproducible measurements in the 3 DeLee zones.

The reproducibility of the Lunar Prodigy Advance scanner used in this study has been well studied. Shepherd et al. (2006) compared the Lunar Prodigy Advance with the Hologic Delphi scanner, looking at various anatomical sites. Subjects were scanned by a single radiographer at 3 separate hospitals using the standardised techniques as employed by the radiographer in our study. Standard deviations and coefficient of variation measurements were made. The results showed that the Lunar Prodigy Advance scanner generated the most precise measurements with a pooled Coefficient of Variance of 1% at the spine and 0.9% at the hip. These variations should be taken into consideration when interpreting our findings.

Assessment at the wrist and lumbar spine allowed for assessment of generalised osteoporosis, and correlating BMD with pain and function scores allowed us to account for disuse osteoporosis. Care was taken to standardise results by accounting for osseous factors (such as sclerosis and lumbar scoliosis), non-osseous factors (such as metal zips and patient positioning) and prosthesis factors (such as prosthesis subsidence, cementation and prosthesis type).

D. BIOCHEMICAL MARKERS

A reasonable proportion of potential participants gave a blood sample for analysis. Serum samples were carefully taken, processed, stored and transported in a uniform manner to prevent sample degradation to ensure results were as accurate as possible. Despite these precautions, it is acknowledged that levels of PTH in particular are very labile, with a high rate of degradation. It is therefore possible that despite the efforts to process the samples correctly, there is chance that the results are inaccurate. All vitamin D and PTH samples were analysed in one batch to minimise processing variability, as the enzymes used in ELISA are subject to biological variations. Careful calibration tests were done to ensure reproducibility.

18. CLINICAL IMPLICATIONS AND FUTURE WORK

Many patients after arthroplasty have many years of trouble free use, with the implant out-surviving the patient. This is particularly true with the development of better implants. However with arthroplasty being used on younger and more active patients, this is balanced with an increased rate of wear and failure. The identification of patients at high risk of developing loosening would help direct surveillance efficiently.

A. CLINICAL RISK FACTORS

This study has shown that a number of clinical risk factors predict development of aseptic loosening, and several others that may be also important. I think this is an important area that has the potential several future studies. There is the potential to assess in detail each of the clinical risk factors (such as smoking history and details about the menopause). These are already well established risk factors for fractures, with multiple large scale studies and meta-analyses.

Further studies could also utilise fracture prediction scores to predict arthroplasty loosening. Several fracture risk scoring systems are already available. The fraX scoring system would be easily adaptable, as it asks questions regarding:

- Age
- Sex
- Weight
- Height
- Previous fracture in adult life occurring after minor trauma
- Previous of parental hip fracture
- Current smoking status
- Use of glucocorticoids
- History of rheumatoid arthritis
- Causes of secondary osteoporosis (e.g. osteogenesis imperfecta, diabetes, hyperthyroidism, chronic liver disease, premature menopause)
- Drinking more than 3 units of alcohol per day
- Femoral neck BMD

B. RADIOGRAPHIC MARKERS

This study has demonstrated that easily measurable assessments of the pre-operative radiograph identify patients likely to develop arthroplasty loosening. These markers are especially useful as they are based on investigations that are routinely used on all patients undergoing arthroplasty, and so could easily be incorporated into a pre-operative index to predict loosening. Further prospective work should be done to evaluate the predictive nature of the cortex index.

Further work needs to evaluate in more detail the use of markers of cancellous bone quality. As this is the tissue primarily responsible for supporting a prosthesis in cancellous bone, it is disappointing that the Singh Index did not prove to be a useful tool. It may be that alternative methods of assessment such as DEXA or CT provide a better marker of cancellous bone in osteoarthritic patients, and this could be used in future studies. Surgical specimens obtained at the time of surgery could be used for biomechanical analysis of cancellous bone strength, and this too could be correlated to arthroplasty survival.

Another avenue for future studies could use surgical specimens to assess the histological osteoblastic response to OA. Does the histological nature of the tissue (e.g. concentration of osteoblasts) predict the outcome of surgery? Why do some patients produce less osteophytes and can this be controlled? It is possible that bone growth stimulating factors such as BMP may influence the survival of implants. Surgical specimens could also be used to allow precise volumetric quantification of number of osteophytes.

C. BONE MINERAL DENSITY

This work provides further evidence that aseptic loosening is associated with regional and systemic osteoporosis. Accurately quantifying arthroplasty loosening is difficult and subject to inter and intra observer variability (as demonstrated by the differences in classification for the assessments done in 2001 and 2006). Serial measurements of BMD using DEXA may be a useful tool for monitoring progression of loosening and helping to predict timely intervention to prevent catastrophic events such as peri-prosthetic fractures.

Further work needs to investigate the long term pattern of bone loss after arthroplasty, with similar prospective studies. Other important work will investigate how peri-prosthetic BMD is influenced by different prosthesis designs. Prosthesis shape, material, thickness and fixation probably all influence BMD.

Other studies will assess how the pattern of bone loss can be modulated pharmacologically. Early studies (such as the work done in Sheffield by Wilkinson et al) suggest that bisphosphonates do limit peri-prosthetic bone loss after arthroplasty, although the long term consequences are not known (for example the effect on loosening or revision).

If such interventions are beneficial, the optimal mode of delivery also needs to be investigated. Regular oral or intravenous administration is likely to be the best method, but is expensive and requires regular surveillance for side effects. The work by Wilkinson utilised a single dose given peri-operatively; a further potential method would be to impregnate cement with a bisphosphonate. Again, long term randomised control studies need to investigate the true clinical benefit for such interventions.

D. BIOCHEMICAL MARKERS

The high incidence of vitamin D deficiency in this study reflects the high incidence in the general population. It is likely that the time of year increased the incidence. It is also possible that the population group as a whole tend to be less mobile and so are more likely to have lower exposure to sunlight.

There was no significant difference between any of the biochemical markers and whether patients had developed arthroplasty loosening or not. This either means that they are not an important factor or that the measured levels do not reflect the levels in the time since their surgery.

Lack of funding meant that only a few biochemical markers could be measured. Serum and early morning urine samples have been stored for these patients and these could be used for future studies to assess the level of NTX and osteocalcin amongst others in our population group.

Turnover markers are commonly used markers of response to osteoporosis treatment, and give a picture of the entire body's response to pharmaceutical agents. If similar agents are used to be used for treatment of aseptic loosening, more specific markers need to be developed. These will need to be sensitive to the region of interest, and may involve the use of isotope imaging to determine where the active turnover is occurring.

An alternative method of measuring peri-prosthetic bone turnover would be to label the bone around the prosthesis and measure the rate that this is released into the serum. A potential method for doing this would be to locally introduce labelled bone substrate around the prosthesis at the time of surgery. This could be done after the final wash before introduction of the prosthesis. Potential markers could be, for example, radiolabelled strontium or even a bisphosphonate, both of which would be taken up and absorbed into the bone matrix at the time of early remodelling after surgery. As the bone continues to be remodelled the marker would be gradually released into the serum and could be measured. It would be anticipated that patients developing loosening would have a higher rate of release.

Rather than measuring the absolute value of each marker, it would be better to take serial measurements and calculate the area under the curve to give a better idea of overall levels.

19. CONCLUSIONS

With regard to the original aims, the following conclusions can be made.

A : Do clinical risk factors for osteoporosis predict loosening?

- A prior history of fracture has been shown to be a significant risk factor for, and smoking and age of menopause may also be important, but future work needs to be done to quantify the risks.
- Pain is not a good marker for detection of early loosening, and is only slightly worse in patients with advanced loosening. Patients with loosening rarely have significantly worse function.
- Future studies should examine these factors in more detail in bigger groups

B : Do pre-operative radiographic markers predict loosening?

- Simple pre-operative measurements of the cortical dimensions and the degree of osteophyte formation appear to predict patients at risk of developing loosening. The cortex ratio correlates well to DEXA, and may be simple marker for future assessment of BMD.
- The Singh Index is hard to measure in arthritic patients and so is not a good predictor.
- Future studies should assess whether the biomechanical strength or histological nature of bone harvested at the time of surgery influences the development of loosening.

C : Do patients with loosening have a lower Bone Mineral Density?

- Patients with loosening have a lower BMD around their femoral prosthesis, particularly proximally and medially.
- They also have generalised osteoporosis at the wrist and spine. The similar level of pain and function suggests that this is not due to disuse osteoporosis.
- Longitudinal prospective studies have been started elsewhere to assess whether this can be influenced pharmacologically.

D : Do biochemical markers predict loosening?

- Although Vitamin D deficiency is common amongst the patients measured, there was no difference in this or any of the biochemical markers measured between those with loose and stable arthroplasties.
- Future studies should assess whether bone turnover markers are a useful tool to detect and monitor loosening.

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