Hip Fracture and Osteoporosis

A comparison of the demographic profile, risk factors, outcomes and health care costs in geriatric patients with and without osteoporotic hip fractures in the public health sector in the eThekwini area.

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Declaration

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Abstract

Introduction: With the worldwide demographic change of increased longevity, the prevalence of osteoporosis is set to rise exponentially, particularly in developing countries. Hip fractures, perhaps the most serious complication of osteoporosis, are associated with significant morbidity, mortality and health care costs. There is a wide geographic and ethnic variation in the burden of osteoporosis and hip fractures. Data on the incidence of osteoporotic hip fractures, their risk factors and outcomes have been well documented in developed countries and used to inform screening, diagnosis and treatment protocols. Scant data exists for Africa including South Africa (SA), however it is predicted that the number of hip fractures will increase exponentially with increasing longevity.

Methodology: In a prospective case control study in the public sector hospitals of eThekwini, 277 consecutive subjects aged 60 years and over and admitted with minimal trauma hip fractures, 230 of which were documented in a one year period (1 August 2010 - 31 July 2011), were enrolled. Two hundred (200) subjects with hip fractures consented to participate in a longitudinal one year study and further 200 age, gender and ethnic matched controls were recruited.

The crude incidence, age, gender and ethnic adjusted incidence rates were calculated using the population of eThekwini and SA, as determined by Statistics SA 2007 Census, as the denominator and the number of fractures in one year as the numerator.

A questionnaire, clinical examination and biochemical investigations were undertaken in the 200 hip fracture and control subjects to evaluate the demographic characteristics, risk factors and functional activity levels between hip fracture and matched control subjects, male and female hip fracture subjects and Indian and African hip fracture subjects. The Student's t - test and Chi-square test was used to compare means and categorical data, respectively. In the case control study, matched conditional logistic regression was used to determine association between outcome and risk factors. All significant variables ($p < 0.05$) were entered into a multiple regression analysis model to determine significance.

Hip fracture subjects were followed up for one year to determine mortality and morbidity and predictors for mortality were determined by comparing survivors to subjects who had died using logistic regression analysis.

Health care costs for acute hip fracture management were calculated using the bottom up method and compared to normative costs. The duration of hospital stay, number of days before surgery, anaesthetic and surgical procedure used and medication prescribed were recorded for each subject. Costing was calculated using the 2010 KwaZulu-Natal Department of Health billing and tariff guides and appropriate fee structures.

Results

Demographic characteristics: The mean age of the 277 hip fracture subjects was 75.9 ± 9.2 years with a female to male ratio of 2.8:1. Men were significantly younger than women; (72.2 ± 9.3 years vs. 77.2 ± 8.6 years; $p < 0.0001$). The majority of subjects were Indians (51.3%), followed by Africans (32.1%), Whites (14.1%) and least were Coloureds (2.5%).

Incidence rates: The crude incidence rate in persons over 60 year olds for eThekwini was 97.4 per 100 000 persons. The age adjusted incidence rate for South Africa in persons over 60 year olds was 109 per 100 000 persons. Incidence rates increased with age and the highest rate was seen in the 80 - 84 year age group at 346.8 per 100 000 persons. The rate was higher in women than men (133 per 100 000 vs 68.5 per 100 000). The highest rate in the different population groups was observed in Indian subjects at 201.1 per 100 000 persons while African subjects had a lower rate at 63.7 per 100 000 persons. The rate in the White (women only) and Coloured population group was 91.6 per 100 000 and 77.4 per 100 000 persons respectively. This lower rate is probably due to differences in utilisation of health care facilities for the former and small total percentage of Coloureds in the eThekwini area for the latter.

Risk factors: In the 200 subjects enrolled in the case control study, hip fracture subjects were less likely to have had formal education (37% vs. 12.5 %; $p < 0.0001$; OR 11.560, 95%CI 4.38-30.49) but were more likely to be smokers (18% vs. 10.5%; $p = 0.04$; OR 1.784, 95%CI 1.0-3.2) and to use alcohol (15.5% vs. 4%; $p < 0.0001$;

OR 11.0, 95%CI 2.59-46.78). Hip fracture subjects were also more likely to have a lower body weight (54.7 ± 13.7 kg vs. 72 ± 16.2 kg; $p < 0.0001$; OR 0.906, 95%CI 0.87-0.94), lower BMI (22.7 ± 5.6 kg/cm^2 vs. 29.2 ± 6.1 kg/cm^2; $p < 0.0001$; OR 0.786, 95%CI 0.71-0.87), higher frequency of prior fragility fractures (27.5% vs. 8.5%; $p < 0.0001$; OR 4.083, 95%CI 2.27-7.34), a sideways fall (31.5% vs. 21%; $p = 0.016$; OR 3.5, 95%CI 1.15-10.6), poor memory (39% vs. 22.5%; $p = 0.001$; OR 2.000, 95%CI 1.29-3.1) and better self-reported activity levels (37.5% vs. 12%; $p < 0.0001$; OR 5.118, 95%CI 2.42-10.85). Morphometric vertebral fractures were significantly more commonly seen in subjects with hip fractures (32.7% vs. 20.3%; $p < 0.0001$).

The mean vitamin D level was lower in hip fracture subjects (38.9 ± 22.4 nmol/L vs.51.4 ± 24.2 nmol/L; $p < 0.0001$) as was the bone mineral density (BMD) at femoral neck and spine (0.518 ± 0.106 g/cm^2 vs. 0.713 ± 0.127 g/cm^2; $p < 0.0001$ and 0.701 ± 0.173 g/cm^2 vs. 0.848 ± 0.183 g/cm^2; $p < 0.0001$) respectively. There was a significant negative correlation between hip BMD and age ($p < 0.0001$), weight ($p < 0.0001$) and BMI ($p < 0.0001$) in the hip fracture group.

There was no difference in number of falls, caffeine use, self-reported sunlight exposure and dietary calcium intake.

The age of menarche (13.7 ± 1.6 years vs. 14.0 ± 1.8 years; $p = 0.290$) and menopause (47.9 ± 6.2 years vs. 47.3 ± 6.8 years; $p = 0.992$) was not significantly different but hormone replacement therapy was a significant protective factor in control subjects (14.6% vs. 4.9%; $p = 0.001$; OR 0.201, 95%CI 0.08-0.49).

Hip fracture subjects reported a significantly greater difficulty with physical self-maintenance prior to the fracture with lower total mean scores (13.4 ± 1.9 vs. 13.8 ± 1.1; p = 0.001), instrumental activities of daily living (IADL) (22.1 ± 4.8 vs. 25.2 ± 3.7; p < 0.0001), poorer quality of life (QoL) with higher scores (6.3 ± 1.7 vs. 5.9 ± 1.2; p = 0.003).

In the multiple regression model significant risk factors for hip fracture were low BMI (p < 0.0001), lower education level (p < 0.0001), history of a prior fracture (p = 0.001), higher self-reported activity level (p = 0.002), impaired IADL (p = 0.002) and QoL score (p = 0.038). In addition hip fractures subjects had a significantly lower haemoglobin (p = 0.011) and albumin (p < 0.0001) and significantly higher white cell count (p < 0.0001) and C-reactive protein (CRP) (p = 0.005) respectively.

Outcomes: The majority of subjects were treated surgically (86.5%) and the mean length of hospital stay was 21.9 days with a mean delay before admission of 4.2 days. The mean number of days before surgery was 11.3 days. The mortality rate at one year was 36.4%; subjects who died were significantly older (76.2 ± 9.7 years vs. 73.4 ± 8.2 years; p = 0.048). Mortality was higher in men than women (41.1% vs. 30.6%; p = 0.34), but this was not significant. In the multiple regression model predictors of mortality were African ethnicity (p = 0.031), low body weight (p = 0.004), low BMI (p = 0.023), higher educational level (p = 0.003), impaired mobility (p = 0.007), inability to cook, (p = 0.004) take medication (p = 0.006), and manage finances (p = 0.006) prior to the hip fracture, low serum albumin levels (p = 0.008), high CRP (p = 0.003) and a longer length of hospital stay (p = 0.012).

In survivors there was a significant deterioration in the ability to perform daily activities from pre-fracture in the first three months which persisted to one year later with decrease in the mean Physical Self-Maintenance score (13.5 ± 1.6 vs. 11.5 ± 3.6; $p < 0.0001$) and IADL (22.5 ± 4.6 vs. 16.8 ± 5.1; $p < 0.0001$). The scores for the QoL (6.2 ± 1.7 vs. 8.7 ± 2.6; $p < 0.0001$), Oswestry Disability Index (ODI) (29.7 ± 14.4 vs. .55 ± 18.1; $p < 0.0001$) and Visual Analogue Score (VAS) for pain (1.4 ± 1.3 vs. 4 ± 2; $p < 0.0001$) were all significantly increased at one year in keeping with deterioration in functional ability.

Health care costs: The actual costing of acute hip fracture treatment was almost one third higher than the normative costing as calculated using National Osteoporosis Foundation of South Africa (NOFSA) hip fracture guidelines (R62 891.65 vs. R39 895).

Conclusions: This study is the first to report hip fractures in all ethnic groups in SA and to examine risk factors and outcomes. Compared to developed countries, the mean age of hip fracture subjects was lower. In addition, men were significantly younger than women in keeping with findings from other developing countries. The female to male ratio, however was similar to developed countries.

Despite the fact the study was only undertaken in the public sector; important trends in incidence rates can be inferred, especially for the Indian and African groups. Hip fractures are more common than previously reported in the South African population and fracture rates increase exponentially with age as described in the literature.

Specifically, the rate in Africans was significantly higher compared to the historic study by Solomon in 1968 (5.2 per 100 000 African persons).

In this first report of hip fractures in Indians in SA, the data suggests that Indians may be at a higher risk than other ethnic groups. The low incidence rate in Whites is probably an underestimation and reflects their lower utilisation of the public sector hospitals compared to the other ethnic groups.

The risk factors identified in our subjects are similar to the published literature and support the use of clinical risk factors for the identification of persons at risk for hip fractures, especially since bone densitometry may not be readily available in the public sector. This study also confirms the high prevalence of morphometric vertebral fractures in both the hip fracture and control groups as previously reported in SA.

A significant mortality rate of 36.4% which is comparable to other developing countries was seen. The significant delay in admission and surgery with a prolonged hospital stay is not within the current international and national management recommendations and needs urgent attention. Contributing factors to mortality were an older age, low body weight, poor pre-fracture functioning, and low serum albumin and raised CRP. In addition, the significant deterioration in function seen at three months in survivors, persisted to one year.

This study was only able to calculate the costs of the acute management of hip fractures and the calculated expenditure was a one third greater than normative cost most likely due to prolonged hospital stay and delays in surgery.

Study Limitations: A limitation of the study is the disproportionate representation of the different ethnic groups due to differences in utilization of public sector hospitals. Whites are under-represented and their incidence rate underestimated. Furthermore Coloureds make up a very small percentage of the population in the eThekwini region and no conclusions can be made in this group.

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Dedication

To my husband, boys, parents and family for their unwavering love.

Research Presentations

- Epidemiology of osteoporotic hip fractures in the elderly in the eThekwini area. South African Geriatrics Society Forum, 2011. Bloemfontein, SA
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- Risk factors and outcomes of osteoporotic hip fractures in older persons in the eThekwini region of South Africa. 1st IAGG; Africa regional conference, October 2012. Cape Town, SA
- Osteoporotic hip fractures in a South African population group: risk factors and outcomes at one year; UKZN Faculty of Health Science Research Day, 2012
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Publications

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Published Abstracts

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% cv	*Percentage coefficient variant*
1, 25 $(OH)_2$ D_3	*1, 25 dihydroxy vitamin D_3*
1, 25 $(OH)_2$ D	*1, 25 - dihydroxyvitamin D*
ADD	*Addington Hospital*
ADL	*Activities of daily living*
ALT	*Alanine transaminase*
AOS	*Asian Osteoporosis Study*
AP	*Antero-posterior*
ASA	*American Surgical Association*
ASR	*Age specific rate*
BMAD	*Bone mineral apparent density*
BMC	*Bone mineral content*
BMD	*Bone mineral density*
BMI	*Body mass index*
BPF	*Best practice framework*
BRAZOS	*Brazilian Osteoporosis Study*
BREC	*Biomedical research ethics committee*
BSU	*Bone structural unit*
BUA	*Broadband ultrasound attenuation*
BW	*Bone width*
cAMP	*cyclic adenosine monophosphate*
CaMos	*Canadian Multicentre Osteoporosis Study*
cm	*Centimetre*
COLIA1	*Collagen 1α-1 gene*
CRF	*Clinical risk factor*
CRP	*C - Reactive protein*
DALY	*Disability adjusted life years*
DOES	*Dubbo Osteoporosis Epidemiology Study*
DOH	*Provincial Department of Health*

DM	*Diabetes mellitus*
DXA	*Dual energy x-ray absorptiometry*
EPIDOS	*European Incidence of Osteoporosis Study*
EPOS:	*European Prospective Osteoporosis Study*
ER	*Oestrogen receptor*
ESR	*Erythrocyte sedimentation rate*
EVOS	*European Vertebral Osteoporosis Study*
FISCIT	*Frailty and Injuries: Cooperative studies of Intervention Techniques*
FIXED%	*Fixed percentage reduction*
FLS	*Fracture liaison service*
FRAX®	*Fracture Risk Assessment Tool*
GC	*Glucocorticoid*
GDP	*Gross domestic product*
GGT	*Gamma glutamyl transferase*
GH	*Growth hormone*
HAL	*Hip axis length*
HIV	*Human immunodeficiency virus*
HRT	*Hormone replacement therapy*
IADL	*Instrumental Activities of Daily Living*
IALCH	*Inkosi Albert Luthuli Central Hospital*
ICD	*International Classification of Diseases*
IF-γ	*Interferon gamma*
IGF	*Insulin growth factor*
IL 6	*Interleukin 6*
IL1	*Interleukin 1*
IOF	*International Osteoporosis Foundation*
ISCD	*International Society of Clinical Densitometry*
KEH VIII	*King Edward VIII*
Kg	*Kilogram*
KZN	*KwaZulu Natal*

LASA	*Longitudinal Aging Study Amsterdam*
LAVOS	*Latin American Vertebral Osteoporosis Study*
LE	*Life expectancy*
LVA	*Lateral vertebral assessment*
m-CSF	*Macrophage - colony stimulating factor*
MGH	*Mahatma Gandhi Memorial Hospital*
MONICA	*WHO Monitoring Trends and Determinants in Cardiovascular Disease Scale*
MR	*Mortality rate*
NA	*North America*
NCD	*Non communicable disease*
NHANES III	*Third National Health and Nutrition Survey*
NHLS	*National Health Laboratory Service*
NIH	*National Institute of Health*
NO	*Nitric oxide*
NOFSA	*National Osteoporosis Foundation of South Africa*
NORA	*National Osteoporosis Risk Assessment*
ODI	*Oswestry disability index*
OPG	*Osteoprotegrin*
OR	*Odds ratio*
PBM	*Peak bone mass*
PMB	*Primary medical benefit*
PMMH	*Prince Mshiyeni Memorial Hospital*
PSMS	*Physical self-maintenance scale*
PTH	*Parathyroid hormone*
QCT	*Quantitative computed tomography*
QoL	*Quality of life*
QUS	*Quantitative ultrasound*
RA	*Rheumatoid arthritis*
RANK	*Receptor activator of nuclear factor-κβ*
RANKL	*Receptor activator of nuclear factor-κβ ligand*

RECORD	*Randomized Evaluation of Calcium Or Vitamin D*
RKK	*RK Khan*
SA	*South Africa*
SD	*Standard deviation*
SES	*Socio-economic status*
SF-36	*Short Form Health survey*
SOF	*Study of Osteoporotic Fractures*
SOS	*Speed of sound*
Sost	*Sclerostin*
SPA	*Single photon absorptiometry*
TB	*Tuberculosis*
TGF-β	*Transforming growth factor beta*
TNF - α	*Tumour necrosis factor - alpha*
UCR	*Ultrasound critical angle reflectometry*
UK	*United Kingdom*
UKZN	*University of KwaZulu-Natal*
USA	*United States of America*
USD	*United States dollars*
UVB	*Ultra violet light B*
VAS	*Visual Analogue Scale*
VDR	*Vitamin D receptor*
VF	*Vertebral fracture*
WHI	*Women's Health Initiative*

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Chapter 1 Background to the study

1.1 Introduction

Osteoporosis, with its consequence of fragility fractures, is a common and serious public health problem in older persons. In the United States of America (USA) it is estimated that one in three women and one in five men over the age of 50 years will experience an osteoporotic fracture during their lifetime [1, 2]. Osteoporotic fractures account for 0.83% of global burden of non-communicable diseases (NCD), increasing to 1.75% in Europe [3].

With the worldwide demographic change of increased longevity, the prevalence of osteoporosis and osteoporotic fractures is projected to rise in both developed and developing countries. Worldwide estimates predict that the number of hip fractures will increase from 1.26 million in 1990 to 2.6 million in year 2015 and almost double to 4.5 million by the year 2050 [4].

Common sites for fragility fractures include the wrist, spine and hip [1, 2]. Wrist fractures after minor trauma, usually occur at an earlier age, are associated with an increased risk of hip fractures in later life and are therefore important clinical indicators of osteoporosis. However, only a small number of patients are investigated for osteoporosis at the time of the wrist fracture [5]. Vertebral fractures (VF) occur in about 25% of women aged 50 years and over with the prevalence increasing with age. The fractures may be spontaneous or occur after minimal trauma. Although associated with pain and progressive spinal deformities, these

fractures are often missed, either because radiographs are not taken or because the deformity is not identified [6, 7]. Even when a radiographic deformity has been reported, the majority of subjects are not treated for osteoporosis [8]. Vertebral fractures (VF) are a strong indicator for subsequent VF [9] and hip fractures [10] and are associated with a significant mortality and morbidity [11, 12].

Unlike wrist and VF, the presentation of a hip fracture is usually a dramatic event preceded by a fall, often in an older individual with multiple comorbidities. The majority of patients will seek immediate attention and require hospitalization and surgery. Hip fractures are associated with a significant mortality, morbidity and health care costs. Estimates of mortality rate vary from 20 to 30% depending on access to health care and available resources. A higher mortality rate is associated with older age, male gender, multiple co-existing illnesses and a poor level of functioning prior to the fracture [13-17]. The risk of death although highest in the first six months, persists for at least a year in women and even longer in men. Following a fracture, the majority of patients experience a marked decline in function with up to 40% not being able to live independently and up to 60% requiring assistance a year later [18, 19].

Osteoporotic fractures contribute significantly to health care costs. Hip fractures are the most expensive to treat and are estimated to cost three times more than treating a patient without a hip fracture. In the USA, the cost of treating a hip fracture has been estimated to be between 8 358 and 32 195 US dollars (USD). Costs are greatest in the first six months post fracture and hospitalization accounts for up to 72% of the total costs [20-22]. Independent of the type of surgical procedure, major

factors influencing costs are patient's age, functional status and duration of hospital stay [23]. Rehabilitation costs, during hospital admission and up to a year later contribute significantly to direct and indirect costs [24].

With the increasing incidence of hip fractures, the economic burden of osteoporosis has risen proportionately. The annual health care cost attributed to osteoporotic fractures in the USA was between 5 - 10 billion USD in 1995 [25] and doubled to 20 billion USD by 2002 [26]. Between 1990 - 2011 the medical and hospital cost of treating patients post fracture was 1.6 - 6.2 fold and 2.2 - 3.5 fold greater respectively, than treating matched controls [21]. With population ageing, a further doubling or tripling of the cost by 2040 is projected [27].

The acute cost of treating a hip fracture in South Africa (SA) is estimated to be R170 000 (24 000 USD), with an average hospital stay of 7 - 9 days, in the private sector [28]. There is no recent data on the cost of the acute management of hip fractures in the public sector, nor is there data on long term and indirect costs. In a country with an increasing number of older persons and limited health resources the cost of treating osteoporosis becomes of extreme importance, as prevention of fractures will result in significant health savings.

Despite the serious consequences of osteoporosis, this condition often remains undiagnosed, and unfortunately even in patient's presenting with fragility fractures, is often untreated. In a systematic review the majority of patients sustaining fragility fractures were not treated for osteoporosis, even though 7 - 67% reported prior

fractures [29]. Approximately 5 - 10% of patients will experience a second hip fracture usually within 3.3 years [30].

To develop appropriate strategies for the prevention, screening and treatment of osteoporosis and the prevention and treatment of osteoporotic fractures, an understanding of the epidemiology of and risk factors for osteoporotic fractures is vital. Internationally, several initiatives have been adopted to increase the identification of individuals at high risk for fractures, to develop country specific intervention thresholds and start to fracture registries [31].

1.2 Epidemiology of osteoporotic hip fractures

There is a wide geographic, ethnic and gender variation in the incidence of hip fractures. While the incidence of hip fractures has been extensively reported in developed countries, data from developing countries are limited. The highest rates of osteoporotic hip fractures are seen in Norway, Sweden and the USA [32-34]. There is a north to south gradient with latitude with decreasing incidence southwards. Intermediate rates have been reported in Latin America [4] and Asia [35, 36], and the lowest rates in Africa [37-40] and the Middle East [28]. In Europe and America the prevalence of fractures is greater in women, with the lifetime risk for sustaining a hip fracture for a women being 15% and for men 5% [41]. In contrast, in the developing world the prevalence of hip fractures is similar for both men and women with fractures occurring at a lower rate [42].

Varying hip fracture rates have been reported in Asia. In a recent study from India the crude hip fracture incidence rate in over 50 year olds was 129 per 100 000 persons and rates of 105 per 100 000 and 159 per 100 000 in men and women respectively, were reported [43]. The rate increased exponentially with age to reach 962 per 100 000 in the 90 - 94 year age group. Despite a lower incidence, osteoporotic fractures occur 10 - 20 years earlier in Indians as compared to Caucasians [44]. While the above rates are similar to those from South East Asia, they are lower than that seen in more developed Asian countries such as Japan or Singapore and that in northern Europe and North America (NA) [36, 42].

1.2.1 Hip fractures in Africa

There are few published studies from Africa and early studies failed to document a significant hip fracture incidence. The first study from rural Gambia found that African women had lower bone mineral density (BMD) compared to United Kingdom (UK) women but no hip fractures were noted [45]. A further study confirmed the lower rate of hip and forearm fractures in Nigeria compared to the USA [40]. Possible reasons postulated for the lower incidence include reduced longevity in developing nations and a possible under-reporting [40, 46-48].

Recent studies show that incidence rates have increased nine-fold for women and five fold for men with age specific incidence rates increasing exponentially. The rates however remain lower than in Europe [49]. In contrast to Europe and USA the mean age of fracture is lower and male to female ratio fairly similar.

The first study to report a change in hip fracture trends in Africa was a study from Morocco in 2002, in which the rate of hip fractures was 52.1 per 100 000 persons [50]. Although higher than previously reported this was still not comparable to the USA (80.5 per 100 000 persons). A subsequent retrospective hip fracture study from Nigeria (2002 - 2008) found the mean age of fracture remained younger compared to developed countries. The female to male incidence rate had also changed to 1.7:1 unlike earlier studies which showed a similar incidence rate in men and women in Africa [37, 40, 51].

The only longitudinal hip fracture study in Africa from Rabat, Morocco (2006 – 2009) reported that age and sex specific hip fracture incidence trends were stable, but projected that a doubling would occur in the period between 2010 and 2030 [47]. In keeping with previous studies from Cameroon men were significantly younger (73.3 ± 11.0 years vs. 75.0 ± 10.7 years; $p = 0.014$) and hip fracture rates increased with age.

1.2.2 Osteoporotic hip fractures in South Africa

In SA although studies have looked at risk factors and prevalence of osteoporosis in the different ethnic groups, few studies have documented incidence rates or risk factors for hip fractures. In the landmark study by Solomon, published over forty years ago, an extremely low prevalence of hip fractures in Africans (5.2 per 100 000 persons) was seen [39]. The reason for this was not well understood, as a subsequent study showed no significance difference in BMD between Africans and

Whites [52]. Schnaid et al., in 2000 reported a higher rate of hip fractures in Nelspruit, but this study had several limitations as it excluded subjects with osteoporosis and was limited to small geographic area [39, 52, 53].

However, a recent study showed a similar prevalence of VF's in African and White subjects suggests that the pattern of osteoporosis may be changing [54].

In keeping with the worldwide demographic change, the older population of SA is expected to increase exponentially despite population growth remaining static. The number of elderly will increase from the present 8 million (16%) aged 50 years and over and 1.6 million (3%) aged 70 years and over to 13.6 million (28%) and 4 million (8%) respectively by the year 2050 [28]. In addition there is significant urbanization and change in dietary and lifestyle factors. It is therefore expected that there will be a commensurate increase in osteoporotic fracture rates.

The effects of urbanization on osteoporosis are well documented. In Asia, urbanization has had a marked increase in the rate of hip fractures [55]. A high protein diet is associated with a negative calcium balance and there is strong correlation between animal protein intake and hip fracture rates [49, 50]. In post-apartheid SA, there has been a massive shift from rural to urban areas with associated lifestyle and dietary changes. Whilst the intake of calcium has decreased there has been an associated increase in the intake of animal protein. This combined with a decrease in physical exercise may contribute to a decrease in bone mass. Whether the effects of the increased body mass found in the African

population and the inherent genetic predisposition can counteract the urbanization effects needs further study [56].

1.3 BMD and clinical risk factors for osteoporosis

Central to the concept of osteoporosis is a decrease in bone strength as reflected by a decrease in bone mass and quality. Bone mass or BMD is currently the only readily measurable skeletal risk factor and the relationship of BMD to bone strength has been extensively studied. BMD is able to predict 75 - 90% of variance seen in bone strength; a 10% loss of vertebral bone mass is associated with a doubling of the risk of a spinal fracture while a 10% bone loss in the hip will result in a 2.5 fold increase in hip fracture risk [57].

In 1994, the World Health Organization (WHO) defined osteoporosis in White post-menopausal women as a BMD, measured by dual energy x-ray absorptiometry (DXA), which is 2.5 standard deviations (SD) or more below that of a young adult (T - score of less than - 2.5), while severe osteoporosis is a T - score of less than - 2.5 with the presence of one or more fractures usually at the wrist, hip or spine [58]. Based on epidemiological study data obtained from the Third National Health and Nutritional Study (NHANESIII), a reference range for BMD has been established [59].

While there is a relationship between BMD and fracture risk, there are several limitations. The relationship is continuous and there is no absolute value below which fracture risk is increased. When used as a single risk factor, BMD lacks

sensitivity and significant proportions of subjects who fracture have either a normal or low bone mass and do not fulfil the diagnostic criteria for osteoporosis [32, 58, 60]. Other limitations include the fact that the WHO criteria do not consider changes in bone quality and other risk factors for osteoporosis [51]. Furthermore these criteria are not applicable to pre-menopausal women, men and different ethnic populations.

1.3.1 Ethnic differences in BMD

In the last decade, a number of studies have tried to explain the observed ethnic differences in BMD. Studies in the USA, show that African Americans have higher BMD independent of weight, and a lower rates of hip fractures than Whites Americans [61]. Postulated reasons for these differences include lower bone turnover rates, lower rates of bone loss in early menopause [62], shorter vertebra and wider, longer bones with shorter hip axis length (HAL) in African Americans [63]. Additionally the higher prevalence of obesity in African-Americans is thought to increase skeletal loading during walking and provide an endogenous oestrogen source post menopause, which may be protective factors [64].

In contrast, although Asian woman have a high rate of metabolic bone disease and a 15% lower bone mass [44], their incidence of hip fractures is lower compared to Whites. This difference in BMD is also seen in Asian women residing in America [44, 63, 65]. In a further study, although Indo-Asian women had a lower BMD and shorter HAL, bone mineral apparent density (BMAD) was similar to Whites [44, 66]. The authors propose that the BMD values in Asians may be a size related artefact,

as the actual depth is not considered in areal BMD measurements and further longitudinal studies may be required [44, 66].

In SA, in an attempt to understand and explain the differences in fracture rates, several studies have compared bone mass and geometry in SA Africans and Whites. After adjusting for differences in body size, higher femoral neck and proximal femur BMD but a lower BMD at the lumbar spine has been reported in African women compared to White women [67, 68]. In addition, vertebral bone size was paradoxically smaller and HAL shorter in Africans compared to Whites [69]. Histomorphometric analysis of iliac cortical crest, showing thicker trabeculae, better osteoid seam thickness, greater endocortical mineral apposition rates and better bone formation in Africans, suggests stronger bone microarchitecture in Africans [70].

There is only one study on BMD measurement in the Indian population in SA and Indians had a lower BMD than Africans [71]. It therefore may be postulated that if international trends are followed, SA Indians may have a lower bone mass and fracture rates than Whites, similar to Indo-Asians and Indians living in the UK and US [44, 65].

1.3.2 Clinical risk factors for osteoporotic fractures

Apart from a low BMD there are multiple well established risk factors for osteoporotic hip fractures, including body composition (weight, height, and bone mass), underlying comorbid illness, family history of osteoporosis or hip fractures, smoking, alcohol, prior fractures, diet, level of physical activity, dietary calcium intake, sunlight exposure, seasonal, genetics and fall risk [33, 72-77]. Several large epidemiological studies have established the relationship between these clinical risk factors (CRF) and fracture risk in much of NA, Europe, Australia, and parts of Asia and the Middle East [78-82].

Similar risk factors, including a premature menopause, low calcium intake, smoking, physical inactivity, low levels of female sex hormones, eating disorders, diabetes mellitus, steroid use and low levels of vitamin D have been previously documented in SA [68, 83, 84]. In addition the association between excessive alcohol and osteoporosis has also been documented [85]. African men who consumed high levels of alcohol have been shown to have increased erosions, femoral neck fractures at younger age and severe osteoporosis as compared to Whites [53].

The combination of CRF and BMD vastly improves the quantification of fracture risk. A major advance for risk assessment is the introduction of the Fracture Risk Assessment Tool (FRAX®) which uses CRF with or without BMD to compute a 10 year probability of a major and hip fracture. This information is then employed to develop intervention thresholds for the management of osteoporosis. The FRAX®

tool is however country specific and depends on local incidence, mortality rates and health economics [31, 86].

In SA, while national guidelines for the diagnosis and management of osteoporosis and for the acute management of hip fractures have been developed [87, 88], osteoporosis is not a primary medical benefit (PMB), and therefore does not need to be reimbursed for by medical insurance companies. This limits access to both screening and diagnosis and appropriate therapy.

1.4 Problem statement

From historical studies the prevalence of hip fractures documented in the African South African population is thought to be extremely low. The exact reasons for this low rate are not well understood and may have been due to a constellation of factors. However, more recent studies suggest that this may no longer hold true. While international studies also suggest a lower incidence of hip fractures in Indians compared to Whites, there is no data in SA.

As the country emerges from 20 years of democracy; the effects of urbanization, decreasing physical activity and dietary changes have led to the rapid increase of non-communicable diseases [89], particularly as the life expectancy increases.

It is therefore postulated that the previous findings no longer hold true and the rate of osteoporosis and hip fractures may have risen in Africans in SA, and that hip fractures occur in all ethnic groups.

1.5 Hypothesis

The risk factors and outcomes of osteoporotic hip fractures are similar in the different ethnic groups.

The cost of treatment for osteoporotic hip fractures is underestimated in South Africa and screening will be an effective intervention tool.

1.6 Objectives

1. To document and compare the demographic profile and risk factors in subjects with minimal trauma hip fractures in the different ethnic groups.
2. To determine the incidence rate of hip fractures in the public sector in the eThekwini Metropolitan area.
3. To determine the prevalence of silent vertebral fractures in subjects presenting with hip fractures and control subjects.
4. To determine the mortality and morbidity of hip fracture subjects at three months, six months and one year.
5. To determine the direct costs of acute hip fracture treatment in the public sector.

1.7 Methodology

A descriptive study, documenting the incidence and demographic characteristics (age, gender and ethnicity) of hip fracture subjects older than 60 years old presenting with minimal trauma hip fractures in the public health sector of eThekwini area, SA was undertaken. Two hundred hip fractures subjects and 200 control subjects who consented to participate in the study were enrolled in a one year prospective case control study to determine risk factors and outcomes post hip fracture. Using a bottom up approach the health care costs associated with acute hip fracture management were determined.

Study data was collected using a standard data form, standardized clinical examination and haematological and biochemical investigations. The Student's t test and Chi-square test was used to compare means and categorical data, respectively. In the case control study, matched conditional logistic regression was used to determine association between outcome and risk factors. All significant variables ($p < 0.05$) were entered into a multiple regression analysis model to determine significance.

1.8 Significance of study

- There is limited data on hip fractures from Africa and this is the first study since 1968 to describe the profile of subjects presenting with hip fractures to the public sector hospitals in eThekwini, South Africa.
- The study will be able to provide important epidemiological insights into the burden posed by osteoporotic hip fractures, risk factors, outcomes post hip fracture and associated costs in SA.
- The acute management of hip fractures, including cost, is documented and can be compared to national and international guidelines.
- The health care gaps in the management of osteoporosis will be identified and will inform future health care policies. This will include review of current screening and treatment guidelines for osteoporosis, referral pathways, staffing needs, access to operating theatres and rehabilitation facilities for hip fracture subjects.
- The study will result in increased knowledge and awareness of osteoporosis and the impact of osteoporotic fractures in the elderly in the community.

1.9 Outline of the study

Chapter 2 Reviews the literature relating to the epidemiology, risk factors and outcomes and health care costs of osteoporotic hip fractures. The review highlights the burden posed by osteoporotic hip fractures in developing countries and the associated excessive mortality and morbidity post hip fracture.

Chapter 3 Presents the methodological framework of the overall study, and outlines the study sample, inclusion and exclusion criteria, data collection, management and analysis methods, as well as reliability, validity and ethical considerations of the study.

Chapter 4 The results are presented in the subsections as demographic characteristics, incidence, risk factors for osteoporotic fractures in hip fracture and matched control subjects (stratified into gender and ethnic groups), outcomes in hip fracture subjects (mortality and one year functional outcome) and health care costs associated with the acute management of hip fractures.

Chapter 5 Discusses the results and comparison is made to international and local literature. Similarities and differences are highlighted allowing for recommendations for the SA population and for future research.

Chapter 6 Concludes this thesis and presents the key findings, conclusions and study limitations. Possible areas for future research are identified and proposals recommended for increasing the awareness of osteoporotic fractures in the community, medical fraternity and to policy makers.

Chapter 2 Literature review

2.1 Background

Hip fractures are the most devastating consequence of osteoporosis and are associated with significant morbidity, mortality and health care costs [90]. With advances in the understanding of the pathogenesis and epidemiology of osteoporosis and the risk factors for fractures, integrated screening tools [31] and treatment guidelines [91-93] for osteoporosis have been generated for much of the developed world. Despite this, treatment is not always instituted even in patients at highest risk, namely those with a previous fragility fracture. This prompted the International Osteoporosis Foundation (IOF) to launch the global "Capture the Fracture Campaign" which targets this high risk group of patients and aims to increase awareness of osteoporotic fractures, improve the acute management of hip fractures and ensure appropriate screening and treatment post fracture [94].

Little is known of the incidence, risk factors and outcomes of hip fractures in developing countries, especially in Africa. In a review of the worldwide incidence of hip fractures, the lowest incidence is reported in Nigeria and SA. In the case of the latter this is based on a single study undertaken more than 40 years ago [36].

Developing countries, including SA, are faced with the challenges of coping with a quadruple burden of disease, (communicable and NCD, perinatal and maternal and injury related conditions) [89], and limited resources. It is not entirely surprising then, that not much emphasis is placed on a condition perceived to be uncommon and perhaps affecting only the privileged.

2.2 Structure of bone

Bone as a metabolically active tissue, has the ability to adapt to variations in load and to repair damage, in order to carry out its functions of supporting body weight, acting as a site for the attachment of muscles and as a metabolic reservoir for minerals. Specialized bone cells, osteoblasts, osteoclasts and osteocytes, are embedded in an organic matrix of type 1 collagen fibres and proteins, strengthened by calcium, phosphate and carbonate in the form of hydroxyapatite crystals [95]. Of the two types of bone cortical bone found predominantly in the shaft of long bones and flat bones, provides strength and resistance to bending and torsion [96, 97]. In contrast, trabecular or cancellous bone found mainly in the axial skeleton and arranged as interconnecting plates and rods, provides flexibility and plays an important role in the metabolic functions of bone [98].

2.3 Bone growth, modeling and remodeling

Bone undergoes longitudinal and radial growth and modeling during adolescence and young adulthood until skeletal maturity is reached. Bone modeling, in which bone formation and resorption are not tightly coupled, results in a change in bone shape and size. Bone remodeling in contrast, is a continuous ongoing renewal process, in which trabecular micro-damage is repaired. Discrete units of old bone are removed and replaced by new bone in a closely interrelated cycle [95] in a bone structural unit (BSU). The cycle has 5 steps (Figure 2.1) and takes approximately 3 -

6 months to complete and is regulated by cytokines, growth factors and mechanical stimuli [95].

Activation of the cycle occurs when monocytes are attracted to resting bone by stimuli including hormones and cytokines. Matrix metalloproteinases digest the thin collagenous membrane. Thereafter osteoclasts are recruited, bone is resorbed forming a cavity known as the “Howship lacunae” and calcium is released into blood. This process occurs takes approximately 2 - 4 weeks [99]. In the reversal phase unknown cells repair the erosion by lining it with a thin layer of cement. Subsequently osteoblasts lay down a new matrix which is then mineralized. In the resting phase, remodeling is complete and osteoblasts trapped in the BSU change to osteocytes.

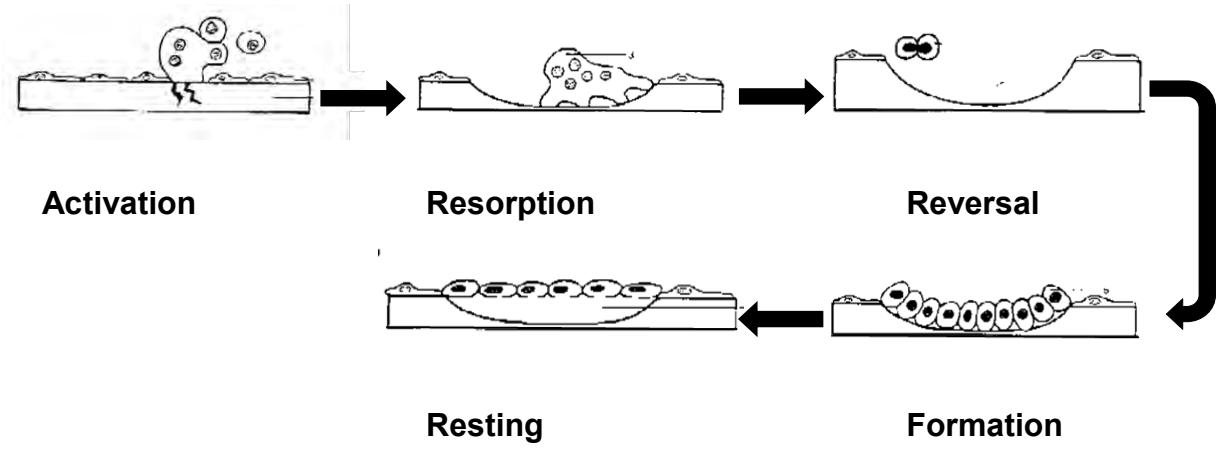

Figure 2.1 Diagrammatic summary of the 5 cycles in bone remodeling

Adapted from Arden 2006 [95]

2.3.1 Regulation of bone growth, modeling and remodeling

Cells involved in bone modeling and remodeling

Osteoblasts, derived from pluripotent stromal stem cells, are the bone lining cells responsible for the synthesis and secretion of the organic bone matrix and bone mineralization. Their growth and functioning is controlled by core binding factor A1 and Indian hedgehog [95, 100], which regulate the expression of osteoblast specific genes including osteocalcin, osteopontin, bone sialoprotein, and receptor activator of nuclear factor-κβ ligand (RANKL). Osteoblasts express receptors for parathyroid hormone (PTH) and 1, 25 - dihydroxyvitamin D (1, 25 $(OH)_2$ D) which play an important role in calcium homeostasis [99].

Osteocytes act as mechanosensors and initiate the remodeling process via nitric oxide (NO), insulin like growth factor (IGF) and glucose-6-dehydrogenase [101]. They also respond to changes in PTH and calcitonin levels, and therefore play a role in maintaining body calcium levels [95].

Osteoclasts are large multinucleated cells derived from the monocyte/macrophage lineage cells and are responsible for bone resorption [95, 102, 103]. Their development and growth is regulated by macrophage colony stimulating factor (m-CSF) and RANKL found on osteoblast progenitor cells and stromal fibroblasts. The binding of RANKL to its receptor activator of nuclear factor-κβ (RANK), expressed by osteoclasts, initiates and stimulates osteoclast differentiation. In contrast, when RANKL binds to osteoprotegerin (OPG), a soluble decoy receptor secreted by osteoblasts, osteoclast differentiation is inhibited [103-105]. The ratio of

OPG/RANKL is critical in determining bone mass and lower levels of OPG are associated with decreased bone mass. Osteoprotegerin levels decrease with age, at menopause and in glucocorticoid induced osteoporosis. Osteoclast apoptosis is inhibited by PTH, 1, 25 $(OH)_2$ D, interleukin 1(IL1), interleukin 6 (IL6), m-CSF, tumour necrosis factor alpha (TNF-α) and RANKL while transforming growth factor beta (TGF-β) and OPG stimulate osteoclast apoptosis [106].

Physical stimuli and muscle action both influence bone remodeling and according to Wolff's law, "bone accommodates the load placed on it by altering its mass and distribution of mass" [107]. There is a positive linear relationship between physical activity and bone mass, namely chronically increased mechanical load on bone increases bone mass, while a decreased load results in bone loss.

Vitamin D is important for homeostasis and bone metabolism. It maintains extracellular calcium concentrations by controlling absorption of calcium and by direct effects on bone and on PTH secretion. Parathyroid hormone acts directly and indirectly on the osteoclasts to increase bone resorption and skeletal calcium mobilization [108]. In the kidney it decreases calcium excretion and increases the formation of 1, 25 $(OH)_2$ D_3 which in turn, increases intestinal calcium absorption. Continuous administration of PTH leads to bone loss but intermittent administration has an anabolic effect [95].

Calcitonin directly inhibits bone resorption by its action on both precursor and mature osteoclasts by decreasing the ruffled borders of osteoclasts and increasing cyclic adenosine monophosphate (cAMP) [95, 103].

Sex hormones

Oestrogen inhibits bone resorption by acting directly on receptors found on osteoclasts to enhance osteoclast apoptosis and indirectly by blocking pro-inflammatory cytokines. It also acts directly on osteoblasts to increase OPG [101, 109, 110] and indirectly on osteocytes, bone marrow megakaryocytes and mononuclear cells [111]. Oestrogen actions on bone include decreasing the pro-resorptive cytokines, RANKL and TNF-α, increasing antagonists IL1, TGF- β and OPG, and increasing serum calcium by increasing intestinal calcium absorption and decreasing renal calcium excretion. Oestrogen deficiency results in rapid bone loss especially after menopause due to an increase in the rate of bone remodeling with an imbalance between resorption and formation of BSU, leading to formation of unfilled bone cavities [112].

Testosterone acts directly on bone via androgen receptors found on osteoblasts and is responsible for the increase skeletal growth seen at puberty in boys. In males oestrogens derived from androgen are important for normal bone development similar to oestrogen in women. The importance of oestrogen for normal skeletal growth in males is supported by the failure to achieve normal skeletal growth in males with oestrogen receptor (ER) resistance despite normal testosterone levels [95]. Oestrogen is also important in the maintenance of normal bone mass in older men [113].

Glucocorticoids (GC) have direct and indirect effects on bone via GC receptors. They inhibit osteoblast activity and generation whilst increasing osteoclast activity

and decreasing osteoclast apoptosis. This results in an increase in RANKL and decrease in OPG levels [95, 114, 115].

Other systemic hormones which influence bone metabolism include growth hormone (GH), thyroid hormone and leptin. Growth hormone acts primarily via IGF to increase bone turnover and bone mass [95]. Excess thyroid hormone levels stimulate bone resorption, hypercalcaemia and decrease PTH and vitamin D levels [95]. While leptin, an adipocyte derived hormone, increases osteoblast differentiation and inhibits osteoclasts, its relevance in humans has not been proven [116-118].

2.4 Changes in bone mass with ageing

The rapid and linear bone growth in childhood bone stops in the second decade of life, whilst appositional bone growth continues till peak bone mass (PBM) is attained by the age of 18-25 years. Peak bone mass is largely determined by genetic factors (75-80%) [119], with a smaller contribution by environmental factors and is higher in males than females. This difference is most likely due to differences in gonadal hormones rather than genetic factors as shown in male-female twin studies [120, 121]. Bone mass remains fairly stable thereafter until age associated bone loss of approximately 0.7 - 1% per annum commences during the fourth decade of life (Figure 2.2) [122]. In women accelerated bone loss of approximately 2 - 5% per annum occurs in the first five years after menopause, slowing thereafter to the same rate as age-related loss [95].

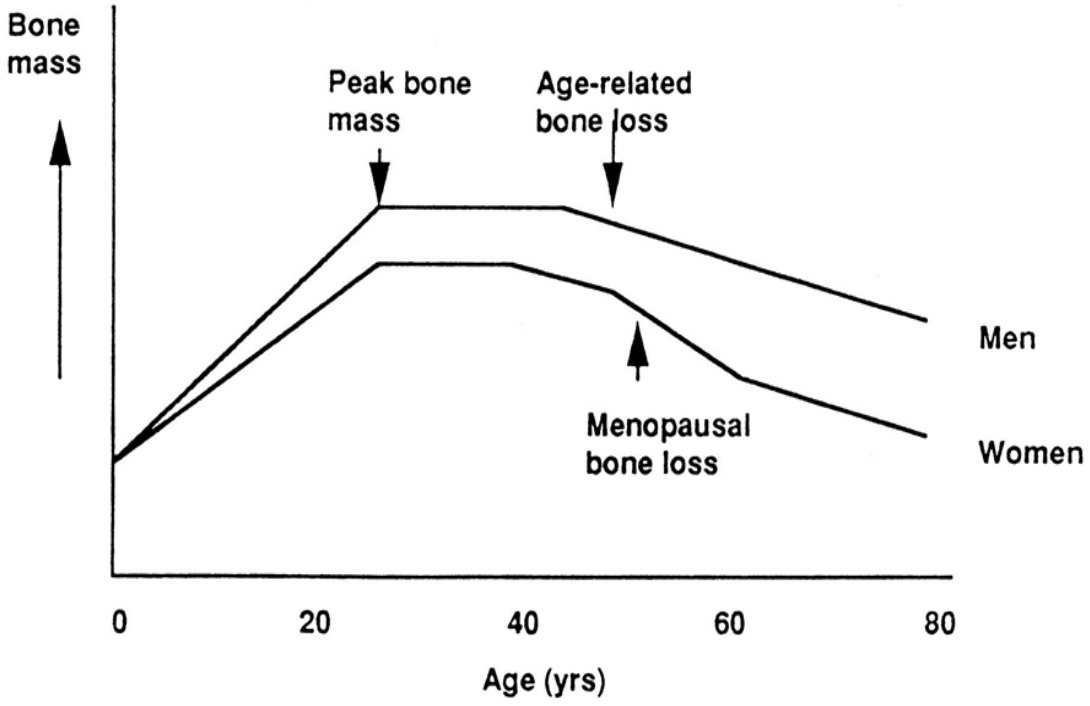

Figure 2.2 Changes in bone mass with age in men and women.

Adapted from Compston JE, Physiological Reviews [122]

2.5 Definition of osteoporosis

Although historically the term “osteoporosis” was first used in 19th century to describe the porous quality of aged bone [123], Sir Astley Cooper had earlier described fractures secondary to a decreased bone mass with ageing occurring more commonly in women and at sites of increased trabecular bone mass [104]. Later, Albright defined osteoporosis as “vertebral fracture syndrome in women 20 years within menopause” [124]. However this definition excluded men and persons with low bone mass who were yet to sustain a fracture [123].

It was only in 1991 that the WHO defined osteoporosis as a “systemic skeletal disease, characterized by low bone mass and micro architectural deterioration of bone tissue with a resultant increase in bone fragility and susceptibility to fracture” [125]. This definition was further modified by the National Institute of Health (NIH) in 2000 to a “skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture”. This now addressed both bone mass and quality allowing for the earlier identification of persons at high risk for fractures [126].

2.6 Pathogenesis of osteoporosis

The main mechanisms for low bone mass is either a failure to achieve PBM or increased bone loss. Causes of bone loss include increased bone turnover and or a remodeling imbalance in which bone resorption is greater than formation [95].

Failure to attain genetic bone potential is often multifactorial and due to inter-dependent environmental factors, such as low calcium intake, inadequate exercise and physical activity [127]. Ethnic and gender differences also exist. African men have the heaviest skeleton, followed by White men and African women with White women having the lightest skeleton [128]. Fracture trends follow a similar pattern [61]. While an increase of 10% in PBM decreases fracture risk by 50%, a low PBM increases fracture risk once age related bone loss commences [129].

Bone loss occurs due to either a remodeling imbalance or increased turnover. In remodeling imbalance, there is an uncoupling of bone formation and resorption. Bone formation within a BSU is decreased compared to resorption resulting in an increase in the erosion depth and/or a reduction in the amount of bone formed. The latter is due to a failure of osteoblast attraction. This type of bone loss is irreversible [95, 130].

In increased bone turnover states the activation frequency of bone remodeling is greater i.e. there is an increase in the number of sites (BSUs), at which bone resorption followed by formation occurs. The net deficit of bone that occurs during remodeling, due to under-filled cavities, increases as the number of BSUs increase. The higher resorption rate and deeper resorption cavities can potentially erode into

trabecular plates. In addition there are larger amounts of immature and incompletely mineralized bone than normal. Increased bone turnover in seen in postmenopausal osteoporosis, hyperparathyroidism and with prolonged immobilization [130].

2.7 Classification of osteoporosis

Osteoporosis is classified as primary, which is either age-related postmenopausal, or secondary.

2.7.1 Age related bone loss

Age is one of the most important determinants of bone mass. While men attain a higher PBM than women and bone mass is usually 15% lower in women than men in all life stages and all sites [103], a similar degree of age related bone mass occurs in both men and women independent of disease after the fourth decade [131]. The bone loss which starts in trabecular bone and affects cortical bone 5 - 10 years later is gradual, at approximately 0.7 - 1% per year. Due to the higher bone turnover rate larger losses occur in trabecular bone. Age related bone loss is estimated to account for 25% of bone loss seen in both cortical and trabecular bone.

The main mechanism for this age related bone loss is a remodeling imbalance due to the ageing osteoblast [132, 133]. Resorption cavities are of normal or even decreased depth but osteoblasts fail to fill these cavities resulting in thinning of trabeculae, however trabecular connectivity is maintained. The decreased functioning of osteoblast is not fully explained by senescence as fracture healing still

occurs; rather it is probably due to impaired regulation of osteoblastic activity by systemic or local growth factors, including IGF-1 and GH, which are decreased by almost 50% with ageing.

The second factor potentially causing age related bone loss is the decreased calcium absorption and transport which occurs, especially after the age of 70 years possibly due to decreased 1, 25 $(OH)_2$ D levels. With aging there is a decreased absorption and dermal synthesis of vitamin D and a decreased renal conversion of 25 (OH) D to 1, 25$(OH)_2$ D_3. The net effect is secondary hyperparathyroidism which increases the bone turnover rate and bone loss [98, 132].

2.7.2 Postmenopausal bone loss

Bone loss associated with menopause was first proposed by Albright et al., [124] and is due to both increased turnover and a remodeling imbalance [134]. Oestrogen affects bone metabolism directly through receptors expressed on osteoblasts, osteocytes and osteoclasts, and indirectly through cytokines and growth factors [135]. Oestrogen enhances osteoclast apoptosis via increased production of TGF-β. When oestrogen deficiency occurs at menopause, there is an increase in IL1 and IL6 production by osteoblasts, which stimulate the recruitment and differentiation, and survival of osteoclasts. In addition, osteoblast differentiation and activity is inhibited and there is increased apoptosis of osteoblasts through cytokines such as IL-7 [136]. Finally, oestrogen deficiency sensitizes bone to the effects of PTH [137].

Bone loss is sequential; the rate is highest within the first few years after menopause with a 3 - 10% loss in trabecular bone, and decreases thereafter to the rate seen with ageing [131]. During menopause, women will lose up to 25% of trabecular, 10% of cortical and up to 15% of spinal bone mass [95]. With combined age-related and postmenopausal bone loss, women between the ages of 30 and 80 years lose approximately 35% of cortical mass and 50% of trabecular bone mass [138] compared to men, who lose 15 - 20% of their cortical bone and 25 - 30% of trabecular bone [139].

While the rate of menopausal bone loss in Indian [140] and African American women has been reported to be similar to Caucasian women in the early postmenopausal period in some studies, [141, 142], [143] other studies have reported a slower decline in BMD with ageing [69, 144, 145] in African American and SA African women compared to Whites. Bone loss is however slower in obese women who have higher circulating levels of oestrogen from increased peripheral conversion of androstenedione in fat [103].

Hormone replacement therapy (HRT) significantly decreases the rate of peri and post-menopausal bone loss and if used for more than five years, decreases fracture risk [146].

2.7.3 Secondary osteoporosis

Secondary osteoporosis refers to osteoporosis not due to merely ageing or menopausal bone loss. A specific pathological mechanism is identified for the failure to achieve PBM or increase bone loss. The causes are often multifactorial and significant overlap often exists between primary and secondary causes of osteoporosis [147]. It is important however to screen for these conditions especially in young subjects or men presenting with osteoporosis.

The most common conditions usually are glucocorticoid use, hypogonadism, malignancy and autoimmune diseases. Table 2.1 highlights diseases frequently associated with osteoporosis.

Table 2.1 Secondary causes of osteoporosis

Endocrine diseases	Hyperthyroidism	Hyperparathyroidism
	Diabetes mellitus	Acromegaly
	Addison disease	Cushing disease
	Ovarian agenesis	Prolactinoma
Hypogonadism	Premature menopause	Delayed puberty
	Anorexia nervosa	Bulimia
	Athlete's amenorrhoea	Turner's syndrome
	Klinefelter's syndrome	Kallman syndrome
Gastrointestinal Diseases	Inflammatory bowel disease	Chronic liver disease
	Pancreatic disease	Gastric bypass
	Coeliac disease	Gastrectomy
Bone marrow disorders	Multiple myeloma	Leukaemia
	Lymphoma	Thalassemia
	Haemophilia	Sickle cell disease
	Systemic mastocytosis	
Connective tissue diseases and autoimmune disorders	Rheumatoid arthritis	
	Psoriasis	
	Systemic lupus erythematosus	
	Ankylosing spondylitis	
Drugs	Corticosteroids	Anticonvulsants
	Lithium	Heparin
Miscellaneous	Alcoholism	Malignancy
	Sarcoidosis	Parental nutrition
	Organ failure	Amyloidosis
	Post-transplant bone disease	
	Pregnancy associated osteoporosis	
	Prolonged immobilization	
	Chronic obstructive pulmonary diseases	

2.8 Consequences of osteoporosis

The most devastating consequence of osteoporosis is a fragility fracture, defined as a “fracture caused by an injury that would be insufficient to fracture normal bone: the result of reduced compressive and / or torsional strength of bone” [148], or clinically as a fracture resulting from minimal trauma e.g. a fall from standing height [149]. The most common sites for osteoporotic fractures are the hip, distal forearm and spine [18, 150].

In the USA, 1.5 million fractures occur annually with the majority being VFs (650 000), followed by hip fractures (250 000) and distal forearm fractures (200 000). A 50 year old white woman in the USA has a life time risk of 17% for hip fracture, 16% for wrist, and 15.6% for clinically evident VF and 39.7% for combination of all three sites, whilst these risks are halved in African and Asian women [2]. It is estimated that one in two women above the age of 50 years will experience a VF and one in three women will experience a hip fracture in their lifetime. These projections are based on a stable age adjusted rate and may over or under estimate the health impact of osteoporotic fractures [151].

Wrist fractures are more common in women than men with a ratio of 4:1 and usually occur in the early postmenopausal period and plateau thereafter (Figure 2.3). In contrast wrist fractures rates in men are fairly stable between the ages of 20 - 80 years. Compared to hip and VF, wrist fractures are usually easily treatable and do not impact significantly on long term quality of life or functioning or mortality [96]. The most common cause of wrist fractures is a fall on an outstretched hand [152].

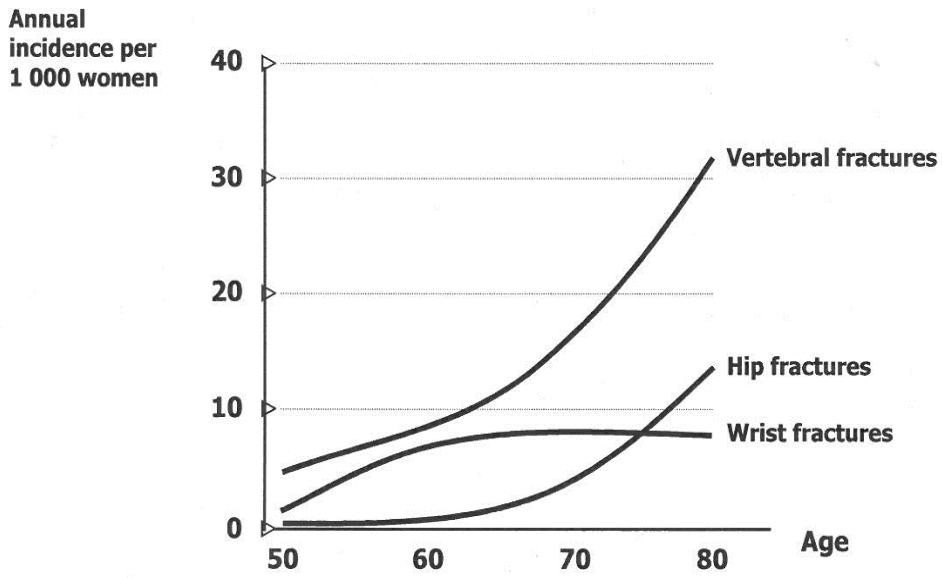

Figure 2.3: Annual incidence of osteoporotic fractures in women

Adapted from Wasnich RD et al. Osteoporosis Int. [153]

The majority of VFs (75%), unlike other fragility fractures, occur without any associated trauma and are due to daily activities e.g. lifting or bending, and often remain undetected clinically. In a multi-national study, 68% of postmenopausal women with osteoporosis had undiagnosed VFs [3]. The usual sites for VFs are the mid thoracic or thoraco-lumbar transition zone with most fractures occurring between the eleventh thoracic to first lumbar vertebrae [154]. Especially if multiple, VFs can result in chronic pain, deformities and cardiorespiratory limitations and increased mortality. The increased risk of death with VFs varies widely from between 20 - 90% [12, 155, 156].

Hip fracture incidence increases exponentially with age (Fig 2.3). A white woman has a 15% lifetime risk at age of 60 years for a hip fracture, which equals the combined risk of breast, endometrial and ovarian cancer. Similarly in men the 5% risk equates to risk of prostate cancer [41]. Several well established risk factors for hip fractures exist [76] and include age, ethnicity, gender, genetic, family history [157], prior fractures, smoking [158] and alcohol [85, 147]. Post fracture individuals have significant loss of function in multiple domains [159]. The higher mortality persists for over a year post fracture and is greater in older persons, males and in non-White individuals [13, 61, 160-162].

Several longitudinal studies suggest that osteoporosis per se increases mortality by 1.5 times for each SD decrease in BMD. More importantly, compared to the general population, mortality is significantly higher with any osteoporotic fracture and highest in subjects with hip fractures (Figure. 2.4) [162-165].

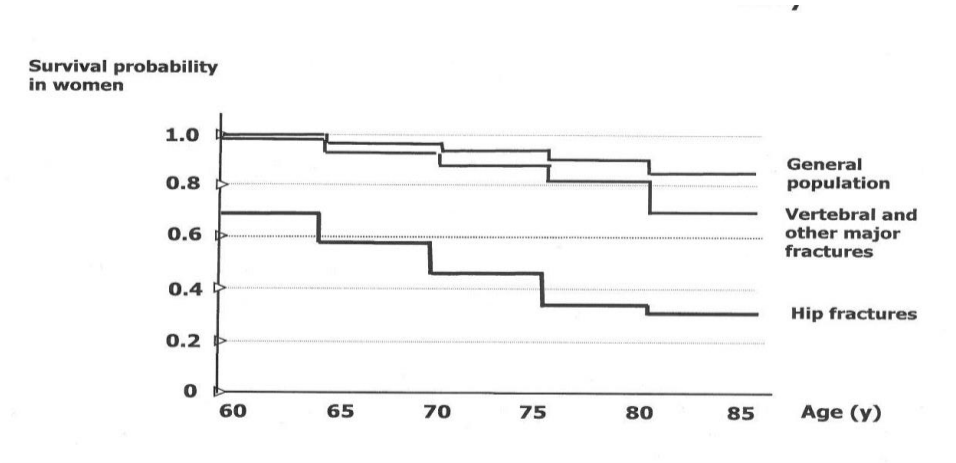

Figure 2.4 Mortality rates in major osteoporotic and hip fractures compared to the general population.

Adapted from Center JR et al. [166]

2.9 Diagnosis of osteoporosis

Traditionally the diagnosis of osteoporosis was based on the presence of a fragility fracture. This definition however, did not take into account the underlying cause of the fracture, namely the decreased bone mass. With advances in the measurement of bone mass, especially with the development of DXA, diagnostic criteria for osteoporosis based on BMD were introduced.

2.9.1 WHO diagnostic criteria for osteoporosis

It is well accepted that fracture risk increases as BMD decreases [58], and with increasing age [33, 86, 167]. Bone mineral density in the population follows a normal or Gaussian distribution. Epidemiological studies have determined that the "fracture threshold", beyond which the risk of fractures increases, is 1.0g/cm^2. This level represents the lower limit of the normal distribution of BMD, namely that it is two standard deviations (SD) below the mean of a young normal individual [25].

In 1994, the expert panel of the WHO, introduced diagnostic criteria for osteoporosis, based on the BMD as measured by DXA [168]. The updated version (2008) recommends a diagnostic threshold of BMD or bone mineral content (BMC) more than 2.5 SD below the mean value of young gender matched individual at the hip be used to define osteoporosis i.e. a T - score of -2.5 (Table 2.2) [169]. This would identify 15 - 20% of postmenopausal women as having osteoporosis. If DXA measurements were made at the hip, spine and radius, these criteria would then

identify 30% of postmenopausal women as having osteoporosis, approximating the lifetime risk of fractures.

Table 2.2 World Health organization diagnostic criteria for the diagnosis of osteoporosis, based on bone mineral density, measured by dual energy x-ray absorptiometry

Definition	Criteria
Normal	BMD or BMC value (measured with DXA at either the spine, total hip or femur neck) within 1 SD of the young adult reference mean (T - score at or above -1.0)
Low Bone Mass	BMD or BMC value more than 1 SD, but less than 2.5 SD below the young adult mean (T - score between -1.0 and -2.5)
Osteoporosis	BMD or BMC value is 2.5 SD or more below the young adult mean

World Health organization [168]168]

Although widely used, these criteria have several limitations. Used as a single criterion, BMD has a low sensitivity to predict fractures [170]. While the rate of fractures increases as the BMD decreases, the majority of fractures occur at a BMD which is in the normal or osteopaenic range [171].

The criteria are based solely on BMD and do not consider other risk factors for osteoporotic fractures such as fall risk, secondary causes and bone quality. Furthermore the criteria were developed for post-menopausal White women and may not be applicable to men and other ethnic groups.

2.10 Measurement of bone mineral density

The gold standard for the measurement of BMD is with DXA. The older method such as single photon absorptiometry (SPA), used to measure changes in the rates of bone loss in the 1980's, is seldom used today as it does not measure appendicular skeleton bone mass [62]. Conventional radiography [172], quantitative computed tomography (QCT) [173, 174] and quantitative ultrasound (QUS) [2] have specific advantages, but are not recommended for the diagnosis of osteoporosis. Biochemical markers of bone turnover have several limitations [175], and have no value in the diagnosis of osteoporosis, and bone biopsy has very limited indications [176].

2.10.1 Dual energy x-ray absorptiometry (DXA)

This technique measures the attenuation of transmission of x-rays of two different energy levels through the body, one of which measures soft tissue density and the other both soft tissue and bone. This allows for bone mineral (hydroxyapatite) to be compared to soft tissue and a two dimensional view is obtained. The BMC of area is

measured and expressed as BMD in grams of mineral per unit projected area of bone (areal bone density) [177]. Dual energy x-ray absorptiometry can be performed for the entire skeleton or at specific sites which have been identified as high risk for fracture e.g. hip and wrist.

Dual energy x-ray absorptiometry is the most widely validated instrument in measuring bone mass and interpretation has been standardized with development of a standard international reference range. It is one of the least invasive and most accurate devices available presently. The radiation dose is less than one tenth compared to a standard radiograph, and the procedure fairly short. Dual energy x-ray absorptiometry is fairly accurate and has greater than 90% accuracy at measuring bone mass at the hip. The precision error with DXA for spine, proximal femur and forearm is about 1 - 2% [178].

Potential error sources include osteoarthritis, soft tissue calcification, osteomalacia, previous fracture, scoliosis, extreme obesity, contrast use, overlying metal objects and untrained operators. Dual energy x-ray absorptiometry is the gold standard for BMD for the diagnosis of osteoporosis, monitoring the natural history of the disease and treatment response and predicting fracture risk [174, 179].

The main disadvantage of DXA is that as the relationship between volume and area is non-linear, the BMD calculated by DXA only provides a two dimensional areal measurement. The normal distribution of BMD, allows for it to be expressed in relation to a reference population in SD units. The T - score is areal BMD expressed in grams per centimetre (g/cm^2), compared to a young normal adult of same sex

while the Z - score compares BMD of the individual to that of age and gender matched adults [174]. The reference range recommended by the IOF is the NHANES III database III [80].

Lateral vertebral assessment (LVA) from DXA scans also provide detailed analysis from T 7 – L4 [180]. It has significant advantages over lateral thoracic and lumbar radiographs, as it uses both digital x-rays and parallel beam geometry, and is therefore able to measure vertebral height and detect VFs [181]. The dose of radiation is lower and the procedure can be combined with conventional DXA scan avoiding the need for two imaging procedures. The main limitations are that a narrower view is obtained than radiographs, other potential pathologies may be missed, upper thoracic vertebrae are excluded and the spatial resolution is inferior to plain radiographs [182].

2.10.2 Conventional radiology

Although inexpensive and simple to perform, plain radiographs are an insensitive method for detecting osteoporosis [172]. Approximately 30 - 40% bone needs to be lost before it can be detected on plain radiographs. Furthermore up to 25% of individuals diagnosed with osteopenia on radiographs will have a normal BMD on further testing.

Lateral radiographs of the spine however, are of value in the older individual, particularly in the presence of loss of height, to detect clinically silent VF and deformities [183]. Compression fractures by definition require 20% height loss and

can be classified as wedge, biconcave or crush [184]. A number of methods have been used to classify VFs [185]. These include quantitative measures [186, 187], semi-quantitative [188], or an algorithm based qualitative method [154, 189]. The Genant's semi-quantitative method of staging is most widely used and has been validated and has good intra-and inter-rater reliability and predictability [185].

2.10.3 Quantitative ultrasound (QUS)

Ultrasound variables, broadband ultrasound attenuation (BUA), speed of sound (SOS) and ultrasound critical angle reflectometry have also been used to measure skeletal status [95]. The SOS measures the time taken for a sound wave to travel through bone and is proportionate to bone mass. The BUA determines the amount of sound absorbed in bone and increases with solidity of bone. While QUS is a relatively inexpensive method, free from radiation, can be used at various sites and may provide information on bone quality, there are limitations to its use. The main disadvantage is that the correlation between fracture risk and QUS values are not well established and clinical studies have shown a poor relationship between therapy and QUS response [2].

2.10.4 Quantitative computed tomography (QCT)

Quantitative computed tomography measures BMD at the appendicular skeleton and the spine. Its greatest value is the ability to measure true volumetric density. Results are also unaffected by degenerative disease. However, there is limited data

on the ability of QCT to predict fracture risk. Additional disadvantages include the high dose of radiation, higher costs and a higher precision error (2 - 5%) due to marrow fat [174, 177].

2.10.5 Bone markers

During the remodelling process, osteoblasts synthetize and release bone specific alkaline phosphatase, procollagen 1 carboxyterminal propeptide, and osteocalcin. Osteoclasts release degradation products including collagen type 1 cross linked N-telopeptide, C-telopeptide, pyridinoline and hydroxyproline. These bone markers are not useful in the diagnosis of osteoporosis but may assist in identifying subjects with accelerated bone loss [190]. Although resorptive markers help predict fracture risk, there is limited data [191]. The use of bone markers is further limited by inter-assay differences and lack of reproducibility. The IOF recommends that the use of bone markers should be limited to subjects in whom clinical or BMD data is insufficient to make a diagnosis or to monitor treatment responses after short periods in selected individuals [175].

2.10.6 Bone biopsy

Biopsy of the iliac bone crest allows for the examination of trabecular bone including cells, rate of bone resorption and formation. The use of bone biopsy is limited to an individual case basis and for research purposes [176]

2.11 Fracture risk assessment

2.11.1 Bone mineral density and fracture risk

The role of BMD in determining fracture risk is well recognised; as the BMD decreases, fracture risk increases. A 10% loss of bone mass at the spine doubles the risk of a VF, while a 10% loss of bone mass at the hip can results in a 2.5 fold increase in the risk of a hip fracture [57]. While some studies, including the Canadian Multicentre Osteoporosis Study (CaMos), suggest that that femoral neck BMD correlates best with fracture risk [192], in other studies, predominantly in peri-menopausal and early postmenopausal women, both femoral neck and spine BMD correlated with fracture risk [72]. Although spine BMD may be of predictive value in younger women, in older women spinal BMD may be spuriously increased due to osteophytes from degenerative disease, vascular calcification and vertebral deformities and not be as useful [193]. Hip BMD has the highest predictive value for hip fracture and there is a 2 - 3 fold increase in the relative risk of a hip fracture with each SD decrease in hip BMD [58, 126].

A low BMD however is not the only predictor of fracture risk and only explains 60 - 85% of the variation in fracture risk [194]. In the National Osteoporosis Risk Assessment (NORA) study, while the fracture rate increased as the BMD decreased, the majority of fractures occurred in subjects with low bone mass and osteopaenia rather than a normal BMD [195] (Figure 2.5). Similarly, in the Study of Osteoporotic Fractures (SOF), 54% of the women who sustained a hip fracture during the five year follow up, had a normal bone mass [171]. These women were more likely to be

older, have a sedentary lifestyle, reduced visual contrast sensitivity, a prevalent VF, and falls in last year compared to women with a low BMD and fracture [171].

These findings support the notion that other risk factors, such as bone turnover, bone geometry and CRF, increase fracture risk independently of BMD.

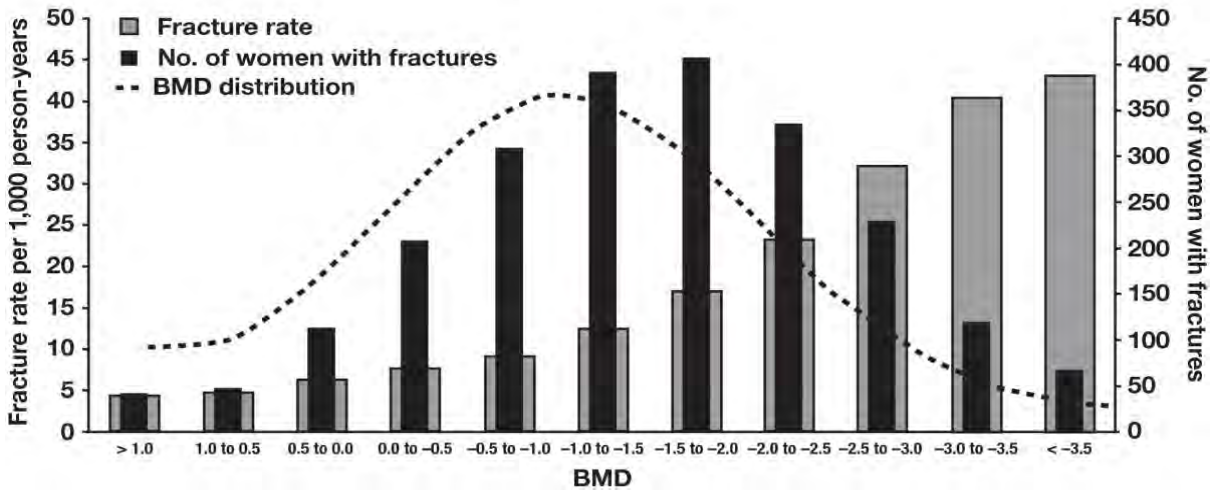

Figure 2.5 Relationship between bone mineral density and hip fractures. Adapted from Siris ES, et al. [171]

2.11.2 Bone geometry

Bone microarchitecture and bone geometry contribute to bone strength and play a critical role in the pathogenesis of osteoporotic fractures. Hip axis length, calculated as the distance from the greater trochanter to inner pelvic brim, width of femoral neck

and the angle between the femoral neck and shaft all determine fracture risk [33, 196-199]. In elderly women, a longer HAL was associated with an increased fracture risk, independent of age and BMD [200]. Each SD increase in HAL increased fracture risk by almost two fold. Decreased thickness of the femoral neck and wider intertrochanteric area also increase fracture risk [200, 201]. In hip fracture subjects, trabeculae are more likely to be orientated along the loading axis with decreased cross bracing elements and a subsequent increased buckling risk [202]. Increased cortical porosity also increases fracture risk [202].

2.12 Risk factors for osteoporosis and osteoporotic fractures

The risk factors for hip fractures can be divided in to those which predispose to increased skeletal fragility and those that increase fall risk [33] or as modifiable and non-modifiable.

Modifiable risk factors include oestrogen deficiency, low body weight, alcohol use, smoking, sedentary lifestyle, medication use and chronic diseases. While White race, older age, female gender, poor health status, prior fragility fracture, family history of fragility fracture and dementia are not modifiable.

2.12.1 Genetic factors

Genetic factors play an important role in the attainment of PBM in early life and twin and family studies confirm the hereditary pattern of bone mass, with a hereditability

that is higher at the appendicular skeleton (70 - 85%) and lower at the wrist (50 - 60%) [95, 203, 204]. Despite the clear association, the exact genes responsible remain unknown. Several candidate genes have been proposed to affect BMD, bone architecture and bone size, and include the vitamin D receptor (VDR), collagen 1α-1 gene (COLIA1) [193], TGFβ-1 gene, TNF receptor 2, sclerostin (Sost), IGF-1 and ER gene [205].

The VDR has been associated with variations in BMD in White, African American, Australian, Mexican and Japanese premenopausal women [206-208]. The effect seems greatest in young adulthood and declines with age. A recent prospective study [209] suggests that only the CdX2 polymorphism is associated with vertebral fractures and not the other previously studied polymorphisms (ApaI, BsmI, TaqI and FokI) [210].

The COLIA 1 Sp 1 polymorphism is associated with a decreased BMD and increased vertebral fracture risk independent of BMD [211]. The mutation is found more commonly in Whites than the African and Asian populations and may be an important independent marker of fractures in the future [212, 213].

Two other genes involved in bone formation via the Wnt pathway are low density lipoprotein receptor related protein and Sost [214]. Both gene mutations are associated with increased bone formation.

Twin studies in postmenopausal women have also shown a moderate association between quantitative ultrasound of the calcaneus and HAL. This suggests that bone strength, independent of BMD, may also be influenced by genetic factors [215].

Lastly, conclusive evidence exists that a maternal or family history of osteoporosis or fractures increases fracture risk. A maternal history of fracture before the age of 80 years doubles the fracture risk [147]. Several large prospective studies have confirmed that a parental hip fracture doubles the risk of fracture independent of BMD, in both men and women, suggesting that factors other than bone mass are involved [80, 174].

2.12.2 Age and gender

Two of the strongest independent predictors for fractures are age and gender. Fractures have a typical bimodal curve with trauma accounting for first peak (10 - 20 years) and low bone mass the second peak (> 50 year old) [6, 95]. The SOF reported a 40% increase in fracture incidence with every 5 year increase in age after adjusting for age and prior fracture risk [147]. The risk of comorbid diseases and propensity for falls increases with age and further increases the fracture risk.

Globally women live longer than men, and this in part explains why 75% of hip fractures occur in women. The female to male ratio of hip fractures in developed countries is 2:1 [26] and the lifetime risk for a hip fracture in White women from age 50 years is 17% compared to 6% in men [216]. Other reasons for the lower fracture rate in White men include a higher PBM, slower rate of age related bone loss [217], decreased risk of hypogonadism and a lower fall rate. Gender differences in fracture rates in other ethnic groups is less marked [218].

2.12.3 Ethnicity

Several studies have reported ethnic differences in bone mass, geometry and fracture rates. In the USA, African Americans have a higher bone mass, thicker bone cortices and greater vertebral density than do Whites, Japanese or Indians [103, 145, 219]. Ethnic differences in skeletal structure, bone turnover rates, calcium homeostasis and vitamin D levels also contribute to differences in fracture rates [82, 220-222].

2.12.4 Role of hormonal factors

The age of menarche and menopause, as measures of oestrogen exposure, are important determinants of subsequent bone mass. A later menarche and earlier menopause are associated with lower bone mass [76, 174, 223]. Primary or secondary hypogonadism results in bone loss in both women and men irrespective of the aetiology. Common causes in men include hypopituitarism, hyperprolactinaemia, castration from any cause and genetic causes e.g. Klinefelter's syndrome. Common secondary causes in women are a premature menopause (spontaneous or secondary to drugs, radiation or surgery), exercise induced amenorrhoea, eating disorders (anorexia nervosa) and chronic illness [174]. Sex hormone levels are also potentially influenced by lifestyle factors, such as smoking and alcohol use, which can affect skeletal growth independently.

In addition, HRT has been shown to increase BMD and decrease fracture risk [73]. The benefit of HRT however decreases once HRT is stopped and 5 years post HRT exposure the risk of fracture is equivalent to women who have never used HRT [224]. While the hormonal changes in pregnancy are well documented, the effect of pregnancies on BMD remains controversial. Pregnancy induced osteoporosis has been reported with an increase in BMD post-delivery [223]. Most authors however, conclude that the number of pregnancies is not an independent risk factor for osteoporosis [225, 226].

2.12.5 Early environmental influence

Early environmental factors affect the attainment of PBM independent of genetic factors [227]. Weight at one year has been shown to correlate with BMC in adulthood, independent of BMI, diet and lifestyle [103]. The most likely mechanism for this is changes to the endocrine set points in utero involving GH - IGF1 axis, the hypothalamic - pituitary - adrenal axis and the PTH - vitamin D axis. Maternal factors e.g. smoking and body built also affect foetal nutrition and skeletal growth.

2.12.6 Socio-economic status (SES) and education levels

The positive correlation between a low level of education (less than 12 years) and increased risk of osteoporosis is postulated to be due to the indirect association

between lower education levels and poor economic and nutritional status during childhood and decreased access to health care [140].

In contrast, a more common theory is that increasing SES and urbanization are associated with an increase in hip fracture risk, despite the better access to health care and nutrition [75].

2.12.7 Seasonal variation and latitude

The majority of hip fractures, in temperate countries, occur during winter despite the fact that the majority of falls occur inside the home and therefore are not thought to be related to weather. The increase fracture rate is thought to be due to an increase in neuromuscular dysfunction secondary to the cold temperature and vitamin D deficiency secondary to a decreased sunlight exposure [95]. The latter is supported by the 0.3% and 0.8% increase in fracture risk in men and women respectively for every 10° change in latitude from the equator [75].

2.12.8 Influence of weight, height and body mass index

Almost 50% of the variance in bone mass may be accounted for by weight differences in the population. The exact role weight plays however, is not clearly defined and extends beyond the concept that weight loading itself increases bone mass as lean body mass is a better indicator of bone mass than total body fat mass or total body weight [127, 228, 229]. The protective effect of a higher body weight

may be due to higher levels of circulating oestrogen from the peripheral conversion of androstenedione to active oestrogen in fat tissue, the potential for fat pads over the hip area to act as hip protectors and decrease the force of a fall, and the postulate that the increase in mechanical strain on the joint due to increased body weight may also promote bone remodeling.

Low body weight is an independent risk factor for fractures. Elderly individuals whose body weight was lower compared to their weight at the age of 25 years have been shown to double their hip fracture risk [33], while the fracture rate decreased by 40% in those whose weight increased by 20% [147]. A low body weight may also be due to other underlying diseases which increase osteoporosis risk independently [147].

Although initially only a low body weight was considered as an important risk factor [230], further studies have indicated [231] that both height and low body mass index (BMI) are independent risk factors in all ethnic groups [140]. Taller persons with a longer HAL also have a higher fracture risk [33, 147].

An increase in age adjusted hip fracture risk has been reported with a lower BMI, independent of age and sex, but dependent on BMD [76, 232]. A non-linear relationship between BMI and fracture risk has been noted, with a lower BMI increasing the relative risk by a higher degree, namely a BMI of 20 kg/cm^2 was associated with an almost doubling of the risk, whilst a BMI of 25 kg/cm^2 compared to 30 kg/cm^2 decreased the fracture risk by only 17% [219]. Further in non-African women followed up over a 5.3 year period, women with a smaller body size were

found to have a lower hip BMD and increased fracture risk [229]. In contrast, in a review of several other epidemiological data bases, weight or height were better at predicting BMD at all three measured sites compared to BMI [233]. The consensus is however that all three anthropometric measures are useful in predicting fracture risk.

2.12.9 Calcium and vitamin D

An adequate calcium intake (recommended as least 1500 mg per day) and vitamin D levels are important for bone metabolism [88]. An average daily intake of vitamin D of 800 - 1000 IU and a serum 25 $(OH)_2$ vitamin D level of greater than 75 nmol/L or 30 mg/ml is recommended to prevent osteoporotic fractures [234]. In older persons, poor calcium intake and decreased calcium absorption due to low vitamin D levels or a relative resistance to 1, 25 $(OH)_2$ vitamin D cause secondary hyperparathyroidism and increase fracture risk [235]. Low vitamin D levels also result in muscle weakness, gait instability and falls which all play an important independent role in the causing hip fractures [236].

Paradoxically, although calcium intake is much lower in developing countries, so is the fracture rate. This paradox may be explained by more efficient absorption and utilization of calcium, a protective effect of the associated low protein diet found in developing countries [103], or maybe due to other unrelated bone protective factors including skeletal geometry and bone turnover rates [141, 220, 222].

In a review of vitamin D levels in osteoporotic women from 18 countries across Europe, Latin America, Pacific Rim and Asia, low 25 $(OH)_2$ vitamin D levels were universal with no single region having a mean level of >30ng/ml. This may however be an under-representation and may not reflect the true deficiency in a normal population, as all the study participants had osteoporosis and were probably more likely to be aware of the importance of vitamin D [235, 237]. The levels varied independent of latitude and lower levels were associated with obesity, Asian race, lack of vitamin D supplements, lower education levels, latitude of enrolment country, decreased sunlight exposure, lack of travel to sunny climate and poor communication with health care provider. Low vitamin D levels have also been documented in other large epidemiological studies including the Brazilian Osteoporosis Study (BRAZOS) [238].

The association of obesity and low vitamin D levels may be due to a combination of decreased sun exposure and lower bioavailability of vitamin D due to excessive fat storage, resulting in a decreased conversion of vitamin D to its active form. This possibility is supported by the inverse relationship between body fat and vitamin D levels, and a positive association between body fat and PTH levels in the Longitudinal Aging Study in Amsterdam (LASA) [239].

Despite the fact that Africa lies between latitudes of 35° South to 37° North and has a sunny climate for most of the year, the few population studies conducted mainly in Gambia, Nigeria and SA have also reported vitamin D deficiency, most likely on the basis of poor intake and possibly darker skin colour [240]. In SA, only one third of women had low vitamin D levels [241]. However, no studies have looked at

cutaneous vitamin D synthesis in Africans [242]. The geographic gradient seen with vitamin D levels is present in Africa as well with lower levels noted in northern and southern Africa [241]. The vitamin D results from Africa however need to be interpreted with caution as multiple methods were used in assays and only three studies used quality assurance methods. Nonetheless, results show vitamin D levels are usually greater than 25 nmol/l with 5 - 20% of the continent having lower values as seen in northern Africa and SA in individuals with rickets, tuberculosis, pneumonia and in veiled women [28, 240, 243]. The studies from SA have mainly been conducted in children and a seasonal variation in ultra violet light B (UVB) exposure has been reported in Cape Town but not Johannesburg [244]. Indian persons under 60 years old from Gauteng have also been shown to have a lower vitamin D level than Africans [71]. Early studies in the elderly in SA found no seasonal variation in vitamin D and femoral neck fracture [245].

The secondary hyperparathyroidism from the calcium and vitamin D deficiency reverses with calcium and vitamin D supplementation with a subsequent increase in BMD and reduction in fracture risk [246]. The effects of calcium supplementation are however contentious. In the NHANES Follow Up Study the rate of BMD loss decreased after the first year of calcium supplementation and remain sustained thereafter [247]. In addition BMD increases of between 4 - 6% have been observed at the lumbar spine, femoral neck and hip after calcium supplementation [248]. Furthermore, in a large meta-analysis combined supplementation of calcium and vitamin D decreased hip fracture risk by 25% compared to vitamin D alone [249].

However, other observational studies and the Randomized Evaluation of Calcium Or Vitamin D (RECORD), study failed to show any benefit of calcium supplementation [250]. Possible explanations for the difference in outcomes are the smaller number of subjects in the RECORD study who were younger and had a lower compliance rate of < 60% with trial medication [249]**.** Adequate calcium and vitamin D supplementation is however recommended for all osteoporotic patients [88].

2.12.10 Glucocorticoid and other medication use

The association between excess endogenous or exogenous GC and osteoporosis is well established. Glucocorticoid use is one of the commonest causes for secondary osteoporosis, estimated to account for up to 25% of the osteoporosis burden in the UK [251]. The pathogenesis of GC induced osteoporosis is multifactorial and is due to both decreased bone formation and increased bone resorption [252, 253]. Long term use of moderate to high doses of GC results in trabecular bone loss which is greatest in the first year with an associated increased fracture risk in the first few months of use. The fracture risk is dose dependent and increases proportionately with higher doses, but a dose as low as 2.5 mg per day is associated with increased risk of VF [254]. The risk however decreases rapidly once steroids are stopped [103].

Other medications associated with accelerated bone loss include excessive thyroid medication, aluminium containing antacids, anticonvulsants and heparin [96, 147, 255].

Thiazide diuretics decrease urinary calcium excretion and may also decrease intestinal calcium absorption. However studies have failed to report a consistent increase in fracture risk. Instead a higher bone mass has been reported in men who use thiazides [256] and fewer fractures have been reported in woman users, despite the increased fall risk from syncope due to thiazide associated hypotension [96, 257].

The exact mechanism by which anticonvulsants independently increase hip fracture risk [147, 255] is not known but it is postulated that anticonvulsants may induce microsomal enzymes and interfere with vitamin D and oestrogen metabolism.

Although a significantly increased fracture risk is seen with antipsychotics, long acting hypnotics and tricyclic antidepressants use, no significant independent risk exists with short acting (< 24hours) hypnotics or anxiolytic [147]. The use of selective serotonin reuptake inhibitors is associated in a dose dependent manner with increase fall risk, lower bone mass and a 2 fold increase in fragility fracture risk [258]. An increased fracture risk has also been reported with benzodiazepines and tricyclic antidepressants [259]. A more recent study however failed to show a decrease in bone mass in men and woman on TCA. [258].

The confounding factor in determining the risk in these drug classes is that the indication for the drug may possibly contribute to increasing hip fracture risk [33, 260]. In an attempt to delineate the actual risk of psychotropic medications, a study in dementia subjects found that these drugs result in sedation and autonomic

dysfunction in the elderly, and therefore increased fracture risk indirectly via an increased fall risk.

Heparin has a direct toxic effect on osteoclast development and activity and long term use has been associated with low bone mass and higher fracture risk [261].

2.12.11 Secondary osteoporosis

A number of medical conditions (Table 2.1) [147, 262-264] are associated with osteoporosis, while rheumatoid arthritis (RA), type 2 diabetes mellitus (DM), neurological diseases and visual impairment are also independently associated with an increased fracture risk. In RA, chronic inflammation, decreased physical activity, GC use and an increased fall risk due to mechanical problems contribute to bone loss and an increased fracture risk [265, 266].

The effects of DM on bone health are not well understood. Contributing factors include obesity, hypercalciuria with glycosuria, decreased intestinal calcium absorption, decreased renal function, inappropriate PTH response, angiopathy, inflammation, neuropathy [267], modification of vitamin D regulation and modification of insulin and IGF-1 [268]. Type 1 DM is associated with bone loss and fragility fractures [269], whilst individuals with type 2 DM despite having a higher bone mass have an increased non vertebral fragility fracture risk [268].

In cerebrovascular accidents the increased fracture risk is secondary to loss of mobility and decreased load bearing on parts of skeleton, and increased fall risk

[270]. In contrast the increased risk for hip fractures in Parkinson's disease is thought to be due to falls rather than disuse osteoporosis [77].

Impaired cognition in the elderly has also been associated with increased fracture risk and subjects with Alzheimer's disease living in nursing homes showed an overall three-fold increase in hip fracture rate compared to community dwellers [136, 172, 173]. The exact mechanisms for the increased fracture rate are not clear but probably include neuromuscular, fall and gait abnormalities.

Poor vision has been implicated as a risk factor for falls and subsequent fractures. In the Framingham eye study poor visual acuity, cataracts and retinopathy were associated with an increased fracture risk [271]. Other contributing factors to the increased risk include poor depth perception and decreased contrast sensitivity [147].

2.12.12 Smoking

A meta-analysis of 10 prospective international osteoporosis studies by Kanis et al., [158] confirmed smoking to be an independent significant risk factor for all osteoporotic fractures (RR 1.29; 95% CI 1.13-1.28) and especially for hip fractures (RR1.84; 95%CI 1.52-2.22) [272]. In another meta-analysis, smoking in post-menopausal women added an additional 0.2% bone loss a year, however no increased bone loss was seen in pre-menopausal women smokers [273]. In contrast studies in premenopausal twins show a lower bone mass in smokers [274].

The negative effect of smoking on bone is multifactorial; contributing factors include lower body mass, premature menopause [96], associated decreased physical activity, increased alcohol use, poor calcium intake and other nutritional deficiencies. A direct toxic effect on bone and calcitonin resistance with resultant increase resorption has also been reported [275]. Smoking is a cumulative risk factor with the risk increasing with the duration of smoking [274]. The risk of fractures with smoking also increases with age from a 17% greater fracture risk in smokers compared to non-smokers at age 60 years to a 71% greater risk by the age of 80 years [273].

2.12.13 Alcohol

Alcohol decreases BMD directly by suppressing osteoblast activity and decreasing osteocalcin levels resulting in decreased bone volume and trabecular thickness with associated mild demineralization and indirectly by liver damage, nutritional deficiencies and associated hypogonadism [276, 277].

Recent cohort studies have questioned earlier findings that a lower bone mass is seen in all alcohol users. It has been shown that the effect of alcohol is dose dependent, and that heavy drinkers have an increased osteoporosis risk due to a direct negative effect on osteoblasts, while moderate drinking may be protective as it increases conversion of androstenedione to oestrogen and indirectly increases bone mass [33, 147, 278]. Berg et al., in a meta-analysis reported the lowest fracture risk in the low alcohol group (0.5 -1 drink per day), followed by a higher risk in abstainers and the highest risk in the high alcohol intake (>2 drinks per day) group [279]. A

possible explanation considered for the “J shaped curve” in the pooled risk data, was that former drinkers who stopped for health reasons may have been classified as non-drinkers. The beneficial effects of low dose alcohol however cannot be ignored [279, 280]. The risk ratio with alcohol is similar in men and women, although prevalence is greater in men [80, 281].

A unique problem has been identified in African males from sub-Saharan Africa who partake of sorghum (African beer) which is brewed in iron pots. The iron is leeched by the acidic beer and individuals clinically present with an iron overloaded state (siderosis). Manifestations include cirrhosis, portal hypertension, scurvy and osteoporosis and femoral neck fractures [53, 282, 283].

2.12.14 Caffeine

Heaney and Recker, in 1982, were the first to show a deleterious association between caffeine and bone mass [284]. They postulated that caffeine increases urinary calcium excretion and decreases bone mass. An increased risk of hip fractures was subsequently reported in caffeine drinkers [147]. However, later case control studies showed conflicting findings and Heany et al., revisited their initial conclusions and proposed that the association between caffeine and low bone mass was due to a low calcium intake and not the caffeine in coffee itself, which had no harmful effects on the skeleton [284].

The consumption of tea has been found to be protective and is associated with a decreased risk of hip fracture as it contains phyto-oestrogens [33, 76].

2.12.15 Physical activity

Fracture risk correlates with physical activity. Higher levels of physical activity increase skeletal strength and are protective against osteoporosis [285, 286]. The effects of exercise in childhood result in wider bones with increased cortical bone which persists in adulthood [287] and bone loss is prevented in women who exercise three-five times a week [288]. Additionally, exercise may help decrease fall risk as it promotes better health status. Despite these positive findings on bone, no direct relationship has been shown to exist between increased physical activity and decreased fracture risk. The lack of direct relationship does not however negate the importance of physical activity and studies conclusively show prolonged immobilisation can result in up to 1% loss of bone per week [96].

2.12.16 Self-reported health status and quality of life

Although it is intuitive that poor self-reported health status and prior hospitalization will increase hip fracture risk, the literature is conflicting [147, 289]. While in the CaMos study, quality of life (QoL) as measured by the Short Form Health survey (SF-36) predicted incident non vertebral and VF risk in postmenopausal women [125], other studies have not shown a correlation between QoL and fracture risk. It

is however thought that underlying health status and QoL are more important in determining outcomes post fracture than predicting fracture risk. This too is controversial, as although functional limitation both basic and instrumental activities of daily living (IADL) is greater in women than men, the higher mortality rates seen in men post fracture is not explained by pre-fracture functioning levels [290].

2.12.17 Prior fracture

A prior fragility fracture is one of the most significant independent risk factors for subsequent fractures. A prior fracture after the age of 40 years is associated with a 1.5 - 9.5 times higher fracture risk depending on the patient's age, the number and sites of the previous fracture [9, 26, 57, 291, 292]. Although an increase future fracture risk is seen with all fragility fracture, the association is strongest for a previous VF (4 fold) [293] (Fig. 2.6). In the European Vertebral Osteoporosis Study (EVOS) study a pre-existing vertebral deformity increased hip fracture risk by 2.8 - 4.5 fold and the risk increased further with increasing number of VFs [155]. Similarly in the SOF the presence of a VF was associated with a 5 fold increase risk for a second vertebral fracture and 2.8 fold increased risk for a hip fracture [10].

The degree of the VF correlates with future non vertebral fracture risk. A severe VF deformity (>40%) has been associated with a 12 fold future fracture risk, while no correlation was seen between mild VF deformities (20-25%) and future fractures [80, 294].

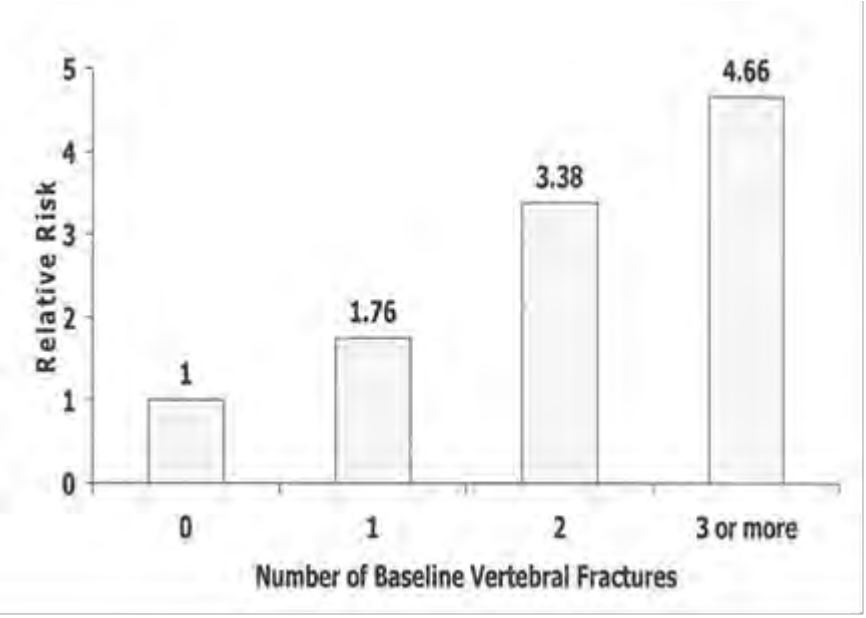

Figure 2.6 A higher number of prior vertebral fractures independently increases the risk of future fractures

Adapted from Kanis et al 2004,[295]

2.12.18 Falls

Falls are common in the elderly population and increase in frequency with increasing age; from 30% in persons aged 65 years and over to 40 - 50% by the age of 80 years [296, 297]. Falls are more likely to result in hip fractures in older women than men by 40 - 60% [298]. This is possibly due to differences in the incidence of osteoporosis and levels of physical activity. The association of falls and fractures also increase with age. In persons aged 50 years and older, 53% of minimal trauma fractures follow a fall. This rate increases to 80% in those aged 75 years and over [299]. The age-related increase is explained by the decreased ability of the femur to absorb force with ageing; the femur of a 33 year old is able to absorb twice the force and three times the energy of a femur in a frail 74 year old [299].

The risk of a major injury after a fall appears to be higher in Whites, older persons, falls associated with loss of consciousness and persons with cognitive or neuromuscular impairment [300]. The risk of fracture is also greater in persons who have had a previous fall, with a fall in the previous year being associated with a 50% increase in subsequent hip fracture risk [289, 300-302].

Gait, balance and lower extremity strength all play a critical role in falls and hip fracture risk independent of BMD [33, 147]. In epidemiological studies, 50% of osteoporotic subjects had muscle loss, with 30% experiencing postural hypotension and significant numbers having visual and perceptive disorders which contribute to fall risk. In the Frailty and Injuries: Cooperative Studies of Intervention Techniques (FISCIT), improving muscle strength and balance reduced fall risk by 10% [303].

Although the majority of hip fractures are associated with a fall from a standing height or less, only 10% of falls result in a hip fracture [33]. The subsequent injury after a fall is also dependent on falling height, type of fall (sideways), poor protective arm movements, surface hardness, and decreased soft tissue protection [33, 304, 305].

2.13 Cumulative risk factor assessment

The diagnosis of osteoporosis is based on the presence of a fragility fracture or measurement of BMD with DXA. While fracture risk increases with a decrease in BMD [32, 80], the sensitivity of BMD varies widely. Fracture risk is known to increase by about 30 fold between the ages of 50 - 90 years, however if BMD alone

is used to predict fracture risk, the risk increases by four fold only [306-308]. Bone mineral density on its own is therefore not a reliable intervention threshold [174]. Further clinical risk factors have a limited predictive value for future fracture risk [147], as risk factors are not consistent between studies and between developed and developing countries [42, 238, 309].

The fracture prediction algorithm (FRAX®) was developed to compute a 10 year probability of a hip or major osteoporosis-related fracture by combining CRF with or without BMD. Clinical risk factors for osteoporosis independent of BMD were identified from 12 large prospective studies (comprising 60 000 women and men) from the USA, Europe, Asia and Australia (Appendix 2.A) [310]. The primary data of these cohorts, which had been validated in independent cohorts of similar geographic distribution, were used to determine the predictive significance of each risk factor and optimise the accuracy of the computerized fracture probability. On the recommendation of the IOF and WHO, the fracture risk is expressed as a short term absolute risk i.e. probability over a 10 year interval [31]. The model allows for risk stratification in both genders and various race groups [80].

However, there is considerable variation in fracture probability and mortality in different countries, and probability models need to be calibrated to the fracture incidence and mortality rate for the specific population [31, 80]. Country specific FRAX® models have been developed for much of NA, Europe and Asia.

Limitations of FRAX® includes: it is not suitable for younger patients with secondary osteoporosis; it excludes important risk factors such as falls, requires technological

support, and very importantly has not been validated in developing countries. The FRAX® model cannot be used if suitable epidemiological data are not available [80].

2.14 Epidemiology of osteoporosis, hip and vertebral fractures

Osteoporosis is estimated to affect over 200 million people globally and it is estimated that the incidence will increase with ageing resulting in one tenth of women aged 60 years and over, one fifth of women in their seventies, two fifth of women in the eighties and two thirds of all women above 90 years of age developing osteoporosis [3, 90]. In the developed world, the risk of osteoporosis in a 50 year old woman exceeds that of breast cancer, stroke or coronary heart disease (Figure 2.7). The burden of osteoporosis is largely due to the incidence and direct and indirect costs of fragility fractures, the most serious of which are hip fractures.

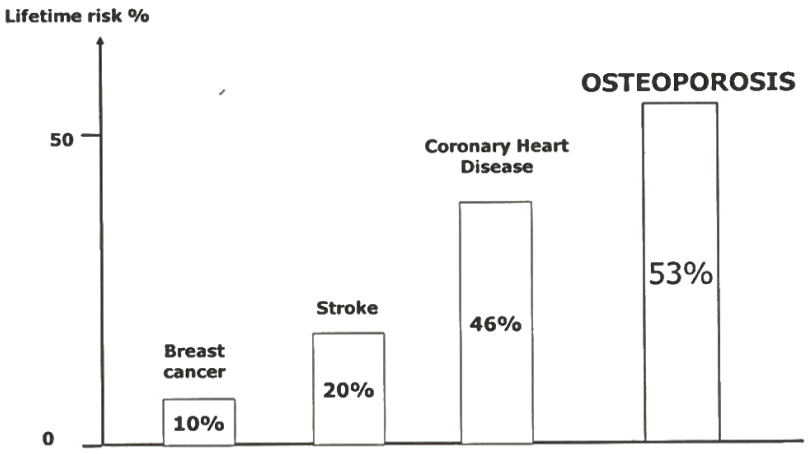

Figure 2.7 The lifetime risk of osteoporosis compared to other common non communicable diseases.

Adapted from Dennison E et al. [311]

The prevalence of osteoporosis and incidence of hip fractures, which closely follow each other, vary significantly by geographic area, ethnicity, age and gender (Table 2.3). In a recent systematic review by Kanis et al., [312] a greater than 10 fold variation in the age standardized rates (ASR) of hip fracture risk was seen in the 63 countries from which data was available.

2.14.1 Developed world: Europe, North America and Australia

The highest prevalence of osteoporosis is seen in the European Union, where it is estimated that 22 million women and 5.5 million men aged between 50 - 84 years have osteoporosis. This is expected to increase by 23% to a total 33.9 million persons by 2025 [313]. A north - south gradient in hip fracture incidence has been reported in Europe with the highest incidence in Northern Europe (Norway and Sweden) and lower rates around the Mediterranean Sea. In the 17 countries which participated in the Mediterranean Osteoporosis Study (MEDOS), an eleven and seven fold difference in hip fracture incidence was seen in women and men, respectively [314]. While the female to male ratio in Europe is about 2:1 [313], a three-fold difference in the gender ratio in the participating countries was reported in the MEDOS study. The differences in rates between countries however was larger than the differences between men and women, implicating genetic and environmental factors in hip fractures [314].

Table 2.3 World age-standardized hip fracture rate (per 100 000 persons)

Country	Reference	Year	Women	Men	Total
Europe, North America and Australia					
**Austria	[315]	2001-2005	501	246	380
*Norway	[316]	1994-2008	563	262	420
*Sweden	[317]	1991	539	247	401
*UK	[318]	1992-1993	349	140	250
**USA	[319]	2010	260	122	195
**Canada	[320]	2005	290	131	215
**Australia	[+]	2006-2007	252	105	183
Latin America					
*Argentina	[321]	2001-2002	390	124	264
*Brazil	++Silveria et al 2005	2001-2002	199	77	141
**Mexico	[322]	2000-2006	225	115	173
*Venezuela	++Riera-Espinoza 2008	2005-2006	150	45	100
Asia					
*China	[323]	2002-2006	173	103	140
**Hong Kong	[324]	2000-2004	324	148	240
*India	[43]	2009	159	109	135
*Indonesia	[++]Hutagalung and Tirtarahardjia 2011	2007-2010	173	59	119
**Japan	[++]Orimo and Sakata 2006	2002	266	165	218
*Malaysia	Chionh and Heng 2010	2007-2009	269	114	205
**Taiwan	[325]	2002	392	196	299
Middle East					
*Iran	[326]	2000-2003	402	269	339
**Jordan	[++]Azar et al 2011	2008	198	114	158
**Turkey	[327]	2009	357	110	240
Africa					
*Morocco	[47]	2006-2009	73	66	69
*Nigeria	[40]	1998-1999	2	2	2
*S Africa	[39]	1957-1963	20	17	19
**Tunisia	++Zakaroul 2010	2001	58	41	50

Adapted from Kanis et al 2012 [312]

[+]Australia Institute for Health and Welfare

++Abstract only available in English/citation

*Regional study, ** National Study

Similarly in NA, osteoporosis is common, affecting 30% of post-menopausal White women and 70% of White women aged 70 years and above [2]. In Canada, one in four women and one in eight men above the age of 50 years have osteoporosis [328] and in the USA, it is estimated that 33.5 million and 10 million have osteopaenia and osteoporosis, respectively [329]. By 2020, 61.4 million will have either osteopenia or osteoporosis in the USA [330].

In a large multi ethnic study in USA of 197 848 subjects, comprising White, African American, Hispanic, Asian and Native Americans; BMD was highest in African Americans independent of weight in every age group. White and Native American had similar BMD findings, Hispanic individuals a slightly lower BMD and the lowest BMD was seen in Asians [82, 142, 220, 221]. Similar findings were reported in the NHANES III study [65, 128]. Since BMD is an areal measurement, it is possible that the differences observed are due to skeletal size i.e. BMD will be over-estimated in taller/larger subjects and under estimated in shorter/smaller subjects. The differences seen in ethnic groups however may remain even after adjustment for body or bone size [220, 221, 331, 332]. Other reasons for the differences in BMD include a higher PBM, [220, 319, 331] a lower or similar rate of bone loss [142, 222] and longer period for bone formation with possibly increased mineral deposition and potentially better bone quality in African Americans [333, 334]. Despite lower vitamin D levels, from decreased dermal synthesis in African Americans, and secondary hyperparathyroidism, bone turnover rates remain low suggesting possible skeletal resistance to PTH [335].

Irrespective of higher bone mass findings, low BMD has been seen in all ethnic groups and in each group fracture risk increases by 54% for each SD decrease in T - score [65] but the absolute risk differs between different ethnic groups. White and Hispanic women have the highest absolute fracture risk and African and Asian women the lowest. In addition to the BMD differences, skeletal geometry may influence fracture risk. The shorter HAL and differences in femoral shaft angle in Asians and African Americans and the thicker trabeculae with a larger cross-sectional area in African Americans may be protective [220] and decrease fracture risk.

Compared to Whites, fractures appear to occur 10 – 20 years earlier in Asian men and women residing in USA [336, 337]. A lower BMD at the proximal femur and trochanter with a shorter HAL has been reported in American Indian and Pakistani women compared to Whites. Asian women were also significantly shorter, with a lower lean body mass but higher body fat content [336]. Lower spinal BMD, but normal BMAD, and shorter HAL has also been reported in women of Indian, Pakistani and Bangladeshi origin, living in the UK [44].

The differences in BMD are reflected in the differences in the prevalence of osteoporosis in the USA; 20% in Whites, 10% in Mexican and 5% in African American women. It is therefore not surprising that Whites have the highest hip fracture incidence rates compared to Asians, African Americans and Hispanics. In all ethnic groups except for African Americans, the female to male ratio was 2:1.2, [34] whereas a more equal ratio (or higher incidence rate in men) is seen in African Americans [61]. In addition to the differences in BMD and bone geometry, activity

levels, diet, neuromuscular functioning, fall frequency and fall orientation also influence fracture rates [33, 61].

Despite being in the southern hemisphere, Australia has a similar prevalence of osteoporosis as seen in Europe and NA with 11% of men and 27% of women aged 60 years or more being affected by osteoporosis [338]. The Dubbo Osteoporosis Epidemiology Study (DOES) [151] has confirmed a significantly higher hip fracture incidence rate in women compared to men, with the incidence increasing with age in both groups. However, men tended to fracture at an earlier age, possibly due to a shorter life expectancy (LE). The gender distribution for hip fractures was 2.3:1 for females to males, but decreased as the population aged [151].

The hip fracture incidence in high risk populations of Europe, USA, Canada and Australia increased from 1940 to the 1980s, but has started to stabilise or even decline in the last two decades in women. This may be due to improved screening and treatment, healthier ageing populations, improved functional ability, increase in average body weight [339], improved perinatal nutrition [26], improvement in lifestyle risk factors [33, 158, 232, 340, 341], an increased exposure to exogenous oestrogens [342, 343] and use of bisphosphonates [344]. The total number of hip fracture however is still increasing at a rate of 1 - 4% annually due to increase in total number of elderly [26, 345].

In contrast, the ASR for men in developed countries continues to increase, with the female: male ratio decreasing from 2.5 - 2.7:1 to 2.2:1 [315]. The highest incidence of hip fractures in men is seen in Europe, the Middle East (Iran, Kuwait, Oman) and

Far East (Singapore, Japan, Taiwan and Korea) with the lowest incidence in US Hispanics, Argentina, Africa, Saudi Arabia, Indonesia and Thailand [312]. Globally however it is predicted that due to the preferential increase in hip fracture rates in men and the faster increasing LE compared to women, the incidence of hip fractures will be equal in men and women by the year 2040 [346].

Although the gender difference in fracture rates was initially thought to be due to differences in BMD, the Rotterdam and the European Prospective Osteoporosis Study (EPOS) studies found no difference in BMD data between men and women [79, 347]. Other postulated factors for the difference include larger skeletal size and decreased fall risk in men [26, 79, 348].

The epidemiology of VF is less well understood [26]. The prevalence ranges from 14.7 to 23.5% due to differences in methodology, ethnicity and age of study participants. Although VFs are more commonly reported in Whites than in African American or Asian women, the ethnic difference is not as marked as that observed with hip fractures [349]. In community based studies, the prevalence of VF (25.3%) in women aged 50 years and over, is almost double that of hip fractures [350]. Both the incidence and prevalence increase with age, from 0.9% and 5 - 10% respectively, in 50 - 60 year olds to 1.6% and 30% respectively, in persons aged 80 years and older [180, 350]. Vertebral fractures are two to three fold more common in European and North American women compared to their male counterparts [26, 351]. While the prevalence in men was higher in the Canadian Vertebral Fracture and EVOS studies, the prevalence remained static while the rate increased with age in women [352, 353]. Possible explanations are that that men may suffer trauma

earlier in working life compared to women, and that they have a more stable bone mass unlike the more rapid peri-menopausal bone loss in women [352, 353].

2.14.2 Developing countries

In 1992, Cooper et al., [354] predicted that with the expected demographic changes and urbanization, the burden of osteoporosis will shift to Asia and Latin America who will experience 50% of all osteoporotic fractures, by the 2050 (Figure.2.8).

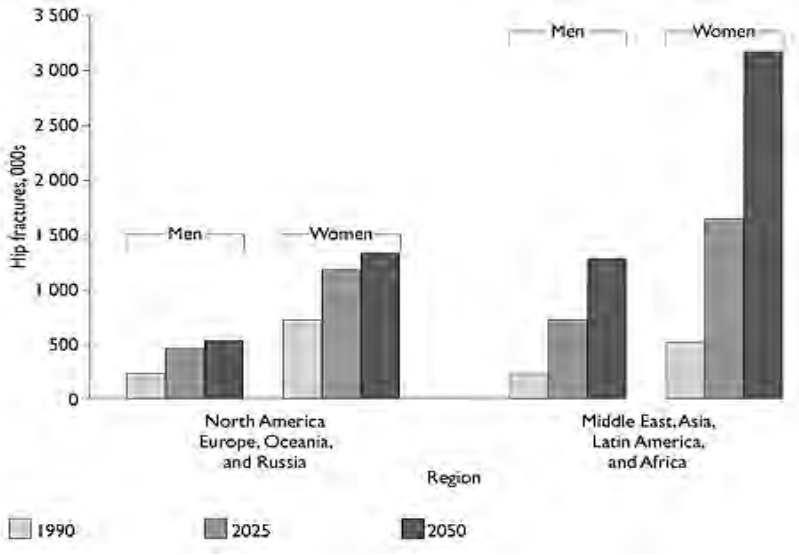

Figure 2.8: Estimated change in the global burden of hip fractures in men and women from 1990 to 2050 in developed and developing countries.

Adapted from Harvey N, Earl S, Cooper C (2006) [355]

2.14.2.1 Latin America

The population of Latin America is a heterogeneous group of mixed ethnicity comprising of original South American Indians mixed with Whites from Europe especially of Portuguese descent, Africans and Asians resulting in an interesting genetic pedagogy [356]. The number of persons aged 50 years and over is expected to increase by 28% with LE in most countries expected to be above 70 years.

The country of origin plays a role in determining subsequent osteoporosis risk and while it is predicted that 12 - 18% of the population have vertebral osteoporosis and 8 - 22% have femoral neck osteoporosis, [356] there are significant variations in the different countries. In Mexico, despite LE increasing on average by 39 years in the last seven decades, the prevalence of osteoporosis is lower than that of developed countries with 16% of women and 6% of men over the age of 50 years having osteoporosis at the hip [357]. Similarly, in Brazil one in 17 people above the age of 50 years has osteoporosis [358]. In contrast, pooled data from studies in Latin America found femoral osteopenia in 46 - 57.2% and osteoporosis in 7.9 - 22% in woman aged 50 years and over. [356]. The number of woman aged 50 years and over with osteoporosis is expected to increase to 2.6 million women by the year 2050 [359]. Hip fracture rates similarly vary between countries, from 40 to 362 per 100 000 persons [356]. Hip fracture rates are projected to increase by 431% from 21 000 in 2005 to 110 555 by the year 2050 [357] and by 400% in 50 - 64 year age group and by 700% in those older than 65 years [90].

There is limited data on VF rates. In the Latin American Vertebral Osteoporosis Study (LAVOS) the number of VFs increased with age [360]. Vertebral fractures have been reported in 19.2% and 9.7% of Mexican women and men respectively [361]. Similar results were reported from Beijing, Hiroshima [154, 362] and in India (Delhi Vertebral Osteoporosis Study (DeVOS)), except that in the DeVOS study, the prevalence rate was similar in men and women [363].

2.14.2.2 Asia

The largest increase in elderly population will occur in Asia, and by 2050, 54% of the world's population of two billion persons aged 60 years and above, will reside in Asia [364]. Ethnic differences have been reported in the prevalence of osteoporosis and hip fracture rates within and between countries in Asia. In China, 40.1% of women and 22.5% of men aged 50 years and over have osteoporosis [365] compared to 38% and 11.6% of Japanese women who have osteoporosis at the spine and hip, respectively [366]. The reason for the high rate of osteoporosis in China may be due to differences in classification as not all the studies used the WHO criteria. At least 7 studies used the Chinese criteria which may overestimate the prevalence of osteoporosis [365].

Hip fractures are predicted to increase exponentially in Asia and it is predicted that 37% of all hip fractures will occur in Asia by 2025 [4]. This projection is supported by studies from Japan which showed a threefold increase in fracture rates from 1987 to 2004 [367]. Similarly in Singapore, the fracture rates in women between 1991 and

1998 were five times higher than in 1960 [368]. In the first multi-centre Asian Osteoporosis Study (AOS) the observed rate of hip fractures was lower than USA with moderate variations amongst the four countries (Table 2.4). Although the gender ratio is lower than the USA, this is not significantly different. Similar to other studies, fracture rates increased with age with the highest incidence rate being observed in the 85 years plus group [35].

Table 2.4 Hip fracture incidence in the Asian Osteoporosis Study

	Men per 100 000	**Women per 100 000**
***Hong Kong**	180	459
***Malaysia**	88	218
***Thailand**	114	289
***Singapore**	164	442
****USA**	187	535

Adapted from the *AOS (1997-1998) [35]

**USA 1989 [369]

Significant ethnic differences have been noted in Singapore, with the highest hip fracture rates in Chinese men and women, followed by Indian men and women and the lowest rates in Malay men and women [368]. This was confirmed in the AOS where Chinese women had twice the number of fractures compared to Malays and Indians [35]. In Malaysia, however Indian women had a similar rate as Chinese

women; with the lowest rates occurring in Malays [35]. In both countries, Chinese and Indian men had similar rates with Malay men having a 25% - 50% lower fracture rate. Urbanization is thought to play a role in the higher rates of hip fractures in Hong Kong and Singapore [35, 90].

In India, it is estimated that 25 million Indians may have osteoporosis based on radiological data, with 50% of women (30 million) and 36% of men above the age of 50 years having osteoporosis [370, 371]. In recent studies 8.5% and 42% of men had osteoporosis and osteopenia, respectively [372]. Factors contributing to high osteoporosis risk include low vitamin D levels secondary to lack of sunlight exposure and increased skin pigmentation, and poor dietary intake [66]. A 15% lower BMD compared to Whites has also been reported in Indians residing in UK and USA [373, 374], but not in wealthy Indian women in India whose BMD is similar to White women [375, 376].

There are few hip fracture studies from India and early studies reported that Indians sustained fractures ten to fifteen years earlier than Whites [370, 371, 373]. In a recent retrospective study the crude incidence rate of 129 per 100 000 persons over the age of 50 years old (with 159 per 100 000 women and 105 per 100 000 men over the age of 50 years old respectively) was similar to some countries in South East Asia, but lower than in the more developed Asian countries of Japan or Singapore [43]. The rate increased with age to reach 962 per 100 000 in the 90 - 94 year age group. In agreement with previous studies, the mean age at 58.2 years was lower than developed countries.

2.14.2.3 Middle East

In the IOF Middle East and Africa Regional Audit in 2011 [28], although data on osteoporosis and hip fractures was only available in 17 and nine countries respectively, these were not from population based studies. There were no published studies on VFs. The audit also highlighted the lack of awareness of osteoporosis amongst health care workers and the lack of inclusion of osteoporosis in medical curricula with resource allocation focused on major communicable diseases such as infectious human immunodeficiency virus infection (HIV) and tuberculosis (TB). Nonetheless, it is predicted that with the projected increase in the proportion of the population 50 years and over from 8 - 20%, to 25% and 40% by 2020 and 2050 respectively, (World Bank online data http://web.worldbank.org), [377] a proportional increase in hip fractures will occur in Africa.

Compared to the standardized US population, lower incidence rates for both men and women have been reported in Iran [378] and Lebanon [379]. In contrast, the higher ASR in Kuwaiti women was similar to that in some southern European countries (Italy, UK, France) and higher than Asian countries such as Korea Singapore, China, Malaysia, and Japan [380]. Interestingly, the incidence rates in Kuwaiti women are similar to that in Asian women living in the US.

Incidence rates are also lower in Turkey compared to other European countries. However, the study on the incidence of hip fractures in Turkey (FRACTURK) [327] showed a significant increase in the incidence of hip fractures in Turkey compared to that reported in the earlier MEDOS study [381]. In addition, 35.5% and 7.5% of

Turkish women and men have osteoporosis and at age 50 years the lifetime probability of sustaining a hip fracture is 14.4% in women and 3.5% in men [327]. Although no epidemiological studies are available, the First and Second Jordanian National Osteoporosis Studies noted that vitamin D deficiency was common and recorded 1008 hip fractures in the year 2008. Based on the latter, a FRAX® tool specific for Jordan was developed [28].

2.14.2.4 Africa

Interestingly, osteoporosis has been recognized in Africa as early as 2687 BC, and differences in BMD have been reported in Egyptian mummies from different social classes [382]. However, epidemiological studies from Africa are scarce. A recent study has estimated that 28.4% and 21.9% of Egyptian women and men respectively, have osteoporosis [28, 383]. A similar prevalence of 24.5% has also been reported in a hospital-based series of women aged 50 years and over in Kenya [28].

An early study on hip fractures in Africa by Asprey et al., in the 1990's reported that osteoporotic fractures were rare in rural Gambian women, despite having a lower BMD and BMC at the lumbar spine and radius compared to White women from the UK [45]. The authors suggested that other factors contributed to the low fracture risk [45]. A subsequent study from Ibadan, Nigeria also reported a low hip fracture incidence rate compared to Southampton (UK) and failed to show an increase in hip

fractures with age [40]. Reasons suggested for this difference were possibly higher levels of physical activity and an inherent genetic predisposition [40].

However, a later retrospective study from Cameroon (1996 - 1998) [48] reported a hip fracture rate of 4.1 per 100 000 and 2.2 per 100 000 respectively, in women and men aged 35 years and over. The rate was lower at 1.2 per 100 000 for females and 0.2 per 100 000 for men with wrist fractures. Although these rates were significantly lower than in developed countries; the hip fracture incidence increased with age to 24.4 per 100 000 in persons aged 65 years and over. The mean age at hip fracture was also lower than developed countries at 72.6 years for women and 66.2 years for men, but it was noted that only 1.1% of women and 0.7% of men survived beyond the age of 65 years [48].

A further study from Rabat, Morocco, also demonstrated an increase in fracture rates with ASR, standardized for the USA population, of 80.7 per 100 000 for women and 58.5 per 100 000 for men and the rates increased with age [50]. The mean age of women and men was similar at 70.7 years and 70.4 years respectively. Similar to studies from developing world, the female to male ratio was 1.19 [50]. The lower rates and younger age at hip fracture may be explained by the LE of 72.4 years in women and 67.7 years with men with just 5% of the Moroccan population being over the age of 65 years. In a subsequent longitudinal study, conducted between 2006 and 2009 [47], the incidence in both women and men had increased to 85.9 per 100 000 in women and 72.7 per 100 000 in men. Based on this, the incidence of hip fractures is expected to rise further during the period 2010 - 2030.

Further confirmation of increasing hip fracture rates was seen in a study from Owerri, Nigeria (2002 - 2008) in persons greater than 50 years old. The study documented 42 hip fractures of which 68% occurred in women and men with a mean age of 67.5 years and 69.0 years, respectively [37]. Of note is that urban dwellers were younger than those who lived in rural areas. The incidence rate was 1.7 times greater in women than men and unlike the previous study from Ibadan, the incidence rates increased with age with the highest rates seen in women and men over the age of 80 years [40]. The low incidence rates are still difficult to explain, given the presence of multiple risk factors, namely, low calcium intake, multiple pregnancies and prolonged breast feeding, and may be explained by the low LE of 57 years. The incidence rates may have also been underestimated due to under reporting, miscoding, poor access to health care and use of traditional healers [48, 384].

2.14.2.5 South Africa

South Africa has a mixed population, comprising Africans, Whites, Coloureds (people of mixed ancestry) and Indians. Limited data exists on the prevalence of osteoporosis, hip fractures rates and especially on ethnic differences. There are no epidemiological studies on the prevalence of osteoporosis in SA, although several studies have examined differences in BMD and risk factors for osteoporosis in the African and White populations.

Earlier studies revealed conflicting results. In a radiological study, a lower prevalence of osteoporosis was seen in rural and urban African women, 3% and 2%

respectively, compared to 14% in White women [385] based on lumbar radiographs. In a further study, while lower metacarpal bone density were seen in 14 year old urban and rural school African children with a low calcium diet compared to White children with normal diets, there was no significant difference between older (70 - 79 years) African and White subjects [386]. There was however, an unexplained lower prevalence of hip and VFs in the older African subjects [385]. The higher bone mass at all ages in Caucasians compared to Africans was later confirmed by Solomon [52]. In the study of metacarpal bone density, Solomon also reported that while bone mass increased more rapidly and reached higher maximum values in Whites, there was also a more rapid loss after the third decade, while the bone mass remained static or continued to rise in African subjects.

In the limited studies employing more sophisticated technology, a similar BMD at the lumbar spine has also been reported in Africans, Coloured and Whites, but with higher values at the femur and calcaneus in Africans [387, 388]. To obviate the effect of age and BMI on BMD [389], Daniels et al., [390] calculated volumetric BMAD and BMC after correcting for body and bone size in African and White premenopausal and postmenopausal women. The study confirmed the previous findings of similar lumbar spine and distal radius bone mass in Africans and Whites but a higher femoral bone mass in Africans. The BMAD findings however, suggested that Whites have a marginally lower bone mass at the lumbar spine, significantly lower bone mass at the hip and similar bone mass at the distal radius compared to Africans. In addition PBM was higher and bone loss rate was slower in Africans compared to Whites. The advantage of a higher PBM in African women

however may be lost with the low calcium and high protein diet of urbanization [391]. Two recent studies have confirmed a higher femoral BMD and similar or slightly lower spinal BMD in African women compared to White women [56, 68] and a slower decline in bone mass with ageing in Africans [69]. These site specific differences in the SA population are only partially explained by SES, body composition and lifestyle factors, suggesting a role for the additional influence of genetic and environmental factors.

In contrast, however, Kruger et al., [392] reported a higher than expected prevalence of spinal osteoporosis (33.1%) and hip osteoporosis (8.2%) in Africans. However, the use of the White reference data from the NHANES III database may have overestimated the prevalence of osteoporosis as suggested by a small study, where in Indians BMD measurements were overestimated when the NHANES III White population reference range was used to calculate BMD as compared to a reference range for Indian women [393].

Significant differences have also been noted in skeletal geometry. Africans are significantly shorter and heavier compared to Whites [390]. The higher femoral neck BMD in Africans may be due to increased weight bearing [69]. Africans also have a shorter HAL [394]. Other skeletal changes, such as narrower endosteal diameter, thicker cortices and decreased buckling ratio, have been reported in both South African and American Africans compared to Whites in a comparative study, suggesting that Africans, regardless of their country have better bone strength than Whites [395].

Similarly, histomorphometric examination of the iliac cortical crest suggests that Africans have a stronger microarchitecture as evidenced by thicker trabeculae, better osteoid seam thickness, greater endocortical mineral apposition rates and better bone formation rates [396]. These findings have been verified in younger children who show increased cortical bone; which may possibly decrease hip fracture risk later in life [56].

Hip fracture studies from South Africa

There are very few studies on fragility fractures in SA. In the landmark study conducted by Solomon [39] in Johannesburg, hip fractures were seen in 26 and 38 urban African women and men, respectively in a geographic area consisting of 310 903 men and 291 455 women representing 27% of the estimated 11 million living in Johannesburg. The gender ratio was similar to that is other developing countries [39]. The incidence rates in men (4.5 per 100 000) and women (4.2 per 100 000) was one tenth that of comparative European populations (Table 2.5). Despite the fact that the highest rate in Africans was seen in persons aged 80 years and over, there was no consistent increase in the incidence rate with age as seen in Dundee and Malmo (Table 2.5). This low rate was not explained by differences in BMD and was thought to be due to qualitative differences in bone geometry and microarchitecture [39, 52].

In the second study designed specifically to examine the effects of drinking habits on minimal trauma fractures, Schnaid et al., [53], identified 72 subjects with minimal

trauma fractures. The calculated incidence rate was 12.0 per 100000; while double that seen 10 years prior was significantly lower than the 100 per 100 000 reported in SA Whites. Higher bone turnover rates with faster repair of micro-damage, better bone quality and stronger bone microarchitecture were advanced for the lower rates seen in Africans by the authors. This is however unusual as a higher bone turnover rate has been shown to be an independent risk factor for fractures [132].

Table 2.5 Hip fractures rates in White females in Dundee and Malmo and Africans in Johannesburg applied to a standard population (the Standard United States population for 1950) to show comparative rates per 100 000 per annum

Age (years)	Standard population (USA)	Standardized fracture rates per annum			
		Dundee Females	Malmo Females	African Males	African Females
Under 30	496 512				
30 - 34	76 424			2.5	0
35 -39	74 629			1.7	1.0
40 – 44	67 712			2.1	2.3
45 – 49	60 190			2.0	0.5
50 – 54	54 893	3.3	21.9	3.1	2.0
55 – 59	48 011	15.8	33.6	4.7	5.8
60 -64	40 210	14.9	48.3	5.5	6.8
65 - 69	33199	45.8	73.0	8.8	4.1
70 – 74	22 641	65.4	88.3	1.8	3.7
75 – 79	14 725	56.0	76.6	0	7.4
80+	10 835	135.6	127.0	12.6	8.7
Total	1 000 000	336.8	468.7	44.8	42.3
Rate per 100 000		33.7	46.9	4.5	4.2

Adapted from Solomon L [39]

Vertebral fractures

Studies on VFs are also scarce. Dent et al., in 1968 reported a lower prevalence of VFs in urban and rural African compared to White women [385]. However this study was based on the visual assessment of lumbar vertebrae on radiographs, the subjects were not age matched, had been admitted for unknown indications and whose diet differed markedly according to their ethnic groups.

Recent studies, however question the belief that VFs are rare in Africans. In a longitudinal study, 38% of African women aged 60 years and over developed new vertebral deformities over a 5 year period [54] and a similar prevalence of VFs has been reported in African and White postmenopausal women in Cape Town (11.5% and 8.3% respectively) [69].

2.15 Outcome post hip and vertebral fractures

While any fragility fracture is associated with an increased mortality compared to the general population, mortality and significant long term morbidity are highest with hip fractures [14]. The increase in mortality is due to the co-morbid diseases rather than the fracture itself and persists for many years after a fragility fracture. The number of year's life lost due to premature death, recorded as the Disability Adjusted Life Years (DALY), for osteoporotic fractures is 5.8 million worldwide. In Europe the DALY due to osteoporotic fractures alone accounts for more deaths than all common cancers except for lung cancer [3].

A significant number of patients who survive a hip fracture will experience impairment in independent living, mobility and chronic pain which they may never fully recover from [397]. The loss of function in previously independent subjects is often devastating and in a survey of healthy women aged 75 years and over, 80% reported they would prefer death over loss of quality of life post fracture [398].

In addition, the risk of a second hip fracture is often not recognized [399].

2.15.1 Mortality post osteoporotic fractures

The mortality rate (MR) post hip fracture, previously reported as 12 - 20% [98], increased to 18 - 31% per annum in a recent review [343]. In a further review of 63 studies predominantly from the USA, Europe, Australia, New Zealand and Japan, an unadjusted MR of 2.3 - 13.9% during hospitalization and increasing to 5.9 - 50% at the end of one year was reported in subjects with a mean age of 80 years[400, 401]. The excess MR (deaths due to hip fracture which might have been preventable) compared to local population has been reported as 8.4% in Sweden [402]and 36% in the USA [403]. Furthermore, the mortality risk post fracture was double that of age matched controls with the greatest risk seen in the first six months post fracture [184]. Survival analysis of the DOES confirms that LE is decreased in hip fracture subjects and that a hip fracture is an independent risk factor for mortality, with women dying 4 years earlier than expected and men 5 years earlier [404].

While there is agreement that the highest MR is seen in the first six months [405], data on the duration of the excess MR associated with hip fractures is conflicting with the duration from two to twenty years [406]. In contrast, after correcting for age, sex, SES, pre-fracture functional status, BMI, co morbid illnesses and overall health status the excess MR did not persist beyond six months in other studies [13, 15].

Almost all studies have shown a higher MR in men post hip fracture, both during the initial hospitalization and subsequent years [407]. In a retrospective review from the USA, in hospital mortality for men was almost double than in women [408]. In a further study, the MR was 26% higher in men with a hip fracture compared to age

and gender matched controls with only a 12% difference seen in women [14]. In addition, the increased MR appears to persist for longer in men, up to two and half years and even more [14, 409, 410]. The difference in MR between men and women is further supported by the eight fold increase in MR in men compared to the five fold in women in the first three months post fracture, with a difference persisting at the ten year follow up [411].

The reason for the higher MR in men is not well understood and may be due to a difference in infection rates (pneumonia or septiciemia) [408, 412, 413], however this has not been conclusively proven. Men have also be shown to have poorer pre fracture function and walking abilty compared to women [414], higher American Surgical Association (ASA) rating suggesting a higher comorbid burden of disease, and poorer outcomes [14], due to higher complication rate post operatively [408, 412, 413]. The increased respiratory risk may be due to a higher frequency of smoking in men [415].

The MR post fracture is clearly higher with increasing age however the excess MR decreases with age in age matched populations, in other words as people in the younger age groups have a lower risk of death for all causes the relative risk is greater in younger age groups with hip fractures compared to older [14].

The increased MR in African American women compared to White women in the USA, despite a lower fracture rate in African American women, is unexplained [416]. African American and White men however, had a similar MR which was higher than that in women. This was not explained by their comorbid disease profiles, but a

possible difference in medical care utilization pattern could have contributed [416]. Age, gender, type of fracture and treatment modality may also influence the difference between African Americans and Whites [410].

There are limited mortality studies in developing countries. The first study from Delhi, (unpublished) [417] has shown a MR of 30.4% at one year post fracture, in 188 hip fracture subjects with a mean age of 64.7 years. There are no published studies from Africa on mortality post fracture.

While comorbid illnesses such as congestive cardiac failure, renal failure, infection, weight loss, metastatic malignancy, may contribute to excess mortality they alone do not account for excess mortality observed [161, 418, 419]. Several studies have failed to show an association between the presence of comorbid diseases and the excess mortality risk associated with hip fractures [14, 16, 17, 420].

Other factors useful in predicting mortality post hip fracture are being a nursing home resident, poor activities of daily living, preoperative walking ability and global physical status, low surgical fitness as determined by the ASA grading, dementia, cognitive impairment, DM, cancer, cardiac disease [421, 422], a low albumin and a delay in surgery [423]. The most common causes of death post-operatively are infection, cardiac and pulmonary complications including pneumonias and thromboembolism [419, 424].

Post VF the risk of increased MR persists for greater than a year [150]. Women with clinically diagnosed VF have a 15% higher mortality than women without fractures. [150]. The increased mortality is not directly attributable to the VF, and is more likely

due underlying conditions [425]. The MR is higher with advancing age and multiple VFs [165]. The risk of death due to pulmonary complications is 2 - 3 fold higher, independent of steroid or smoking use [12]. There is also a higher MR in cancer subjects [12]. The MR in VF may be biased as data is based on studies of clinical VF and the impact of morphometric VFs is not known [12].

2.15.2 Morbidity post osteoporotic fractures

Osteoporotic hip fractures result not only in acute pain and loss of function, but are associated with significant long term morbidity [216]. In an earlier study in White women, 30.1% of survivors were unable to ambulate independently one year later. [426]. Ten years later, Riggs et al. [41] reported that 50% of hip fracture survivors were unable to walk unassisted and 25% required long term frail care. Several other studies have reported similar outcomes post hip fracture with 50% of women who had lived independently previously, requiring assistance with tasks of daily living or needing to remain in long term care facilities [96].

The recovery pattern following a hip fracture follows a specific pattern. At six months, the recovery of walking and activities of daily living (ADL) is better than that of IADLs, with 60% recovering full walking ability, 50% able to perform ADL but less than one third able to complete IADLs [410]. The disability persists at one year and eventually up to 40% are still unable to walk unaided, 60% unable to perform all ADLs and 80% unable to perform all IADLs. In a prospective study, only 47% of survivors were able to live independently [427]. The level of deterioration was most

marked in the first four months and after 6 months only every fifth patient continued to deteriorate. Predictors of a poor outcome are older age, male gender, pre-fracture functioning and discharge to institutional care rather than home [427]. Poor QoL pre-fracture, is more common in women, older individuals and those with multiple comorbidities, and has been associated with a poorer outcome [410]. Outcomes are also poorer in subjects who have a protracted hospital stay, require rehospitalisation for complications, have underlying cognitive or cerebral impairments and decreased social contact [19]. In contrast, individuals with strong social support have better post fracture QoL scores [428].

While sub-trochanteric fractures were previously associated with a poorer outcome, with recent advances in surgical management, post repair outcomes are no different to that seen with other fracture types [382, 399] and QoL scores remained significantly below pre-fracture levels at 2 years. Poor QoL pre-fracture was also associated with a nine fold deterioration three months post fracture in sub-trochanteric fractures [382, 400].

Vertebral fractures are also associated with a significant morbidity [12]. Multiple fractures can lead to significant pain, height loss and decrease in QoL with associated complications of cardio respiratory disease [362].

Few studies report differences in hip fracture outcomes in ethnic groups. In the USA, poor outcomes have been reported in African Americans and Hispanics [429] while in India, one year after a fracture 13.7% of subjects were bed ridden, 19.5% needed a walking frame and 14.9% needed help to ambulate with only 21.9%

regaining full ADLs [417]. All eight domains of the SF 36 which measures disability and quality of life were significantly impaired in hip fracture subjects compared to controls at six months [430]. Similarly in a recent report from Mexico, mobility, daily activities, and self-care were the most affected in the first month after a hip fracture [431]. Older subjects suffered more from anxiety and depression, while younger subjects complained more of pain and discomfort. Function improved over six months, disability worsened only in subjects aged 85 years of age.

Hip fractures account for significant number of days spent in hospital. Lippuner et al., in a review of hospitalization in Switzerland for the period 2000 - 2008 for all major osteoporotic fractures, found that the number of hip fractures requiring admission decreased over the years, despite an increase in number of other osteoporotic fractures requiring admission [432]. Women spent three times the number of days in hospital for fractures compared to chronic obstructive airway disease or breast cancer and 1.5 times compared to a major cardiovascular event [432]. The length of hospital stay is variable and determined by a number of factors including resources, co-morbid illness and rehabilitation programmes. Hospital stays are usually longer in men and estimated to be greater than for days for prostate cancer [261].

Understandably, with the perceived low incidence of hip fractures and the very limited number of studies in SA and the rest of Africa, there are no studies on outcome in this region.

2.15.3 Risk of a second hip fracture

In the immediate phase post fracture, a marked increase in bone turnover has been observed with a resultant decline in BMD in the opposite hip of between 4.6 - 7% in next year. The loss in bone mass and metabolic changes result in an associated loss of lean body mass of between 5 - 6% and increase in fat mass of between 4 - 11% [433]. These changes increase the risk of second hip fracture. In the USA, 10.3% of hip fracture subjects will experience a second hip fracture in the following three years. The risk of subsequent fracture is highest in the first year with 51% of hip fractures occurring in the first six months and 75% in the first year [434].

2.16 Management of hip fractures

Management consists of immediate management of the hip fracture and assessment and management of the underlying osteoporosis and secondary prevention of fragility fractures.

2.16.1 Surgical management

The definitive management of hip fractures is surgical with either a repair or a hip replacement depending on the type of fracture. Subjects with hip fractures are usually older with multiple co-morbidities and at higher risk for post-operative complications and integrated, holistic management preferably in an orthogeriatric

unit is recommended [435]. Management in an orthogeriatric unit decreases length of hospital stay and cost, results in more patients being discharged home rather than to a to a frail care facility, improves functional outcomes, mortality and morbidity [435].

Current guidelines recommend that surgery is as soon as possible and preferably within 24 hours [436]. Earlier surgery has been shown to improve functional outcome, decrease hospital stay and post hip fracture complications, however the impact on mortality is more controversial with varying outcomes [436]. In contrast, a delay of greater than 48 hours has been associated with an increased MR [423]. Protagonists for early surgery argue that the challenges faced in providing early surgery can be overcome by system based solutions such as a readily available specialized operative team, which will prevent surgical delays and long term morbidity [437].

Despite these conflicting findings and that surgery within 48 hours may be difficult due to operational and cost factors, it has become widely accepted that early surgical repair is recommended and these time guidelines have also been incorporated in the management guidelines for acute hip fractures in SA endorsed by the National Osteoporosis Foundation of SA (NOFSA) [87].

2.16.2 Medical management of osteoporosis

With the introduction of fracture risk assessment tools, intervention thresholds have been developed and differ with regional MR and health economics. Currently a limited number of drugs are available for the treatment of osteoporosis and a number are in development [438, 439]. Anti-osteoporosis drugs are conventionally divided into anti-resorptive drugs which suppress bone resorption, anabolic drugs which stimulate bone formation and dual acting drugs (Table 2.6). Their mechanisms of action, effects on bone mass and fractures rates, indications, contraindications and side effects have been extensively reported [178, 313, 440, 441]. Anti-fracture efficacy at the spine varies from approximately 41 - 70% with and at the hip from 16 – 41% depending on the drug used [92, 438, 442]. The number of new VF can be decreased by 40 - 60% with appropriate treatment in the first year [149].

Despite the fact that a hip fracture indicates severe underlying osteoporosis and there is a significant risk for second hip fracture [443], only 15% of persons with a hip fracture will have a BMD measurement and a diagnosis of osteoporosis is made in less than 30% [427]. Paradoxically, older women and men are less likely to be diagnosed or treated for osteoporosis [29]. Of concern is that even in the presence of a prior fragility fracture less than 30% of subjects receive calcium and vitamin D supplementation which is inexpensive and readily available [444].

Table 2.6 Classes and examples of drugs for osteoporosis treatment

Class of drug	**Examples**
Antiresorptive Agents	Calcium and vitamin D Oestrogen/progestin Selective oestrogen receptor modulators Testosterone Bisphosphonates Denosumab
Anabolic Agents	Parathyroid Hormone
Dual agents	Strontium Ranelate

2.17 Health care costs

Osteoporotic fractures contribute significantly to both direct and indirect health care costs and pose a serious burden to not only health care facilities, but to families and communities as well. Medical and hospital costs of any osteoporotic fracture have been estimated to be 2.2 - 3.5 fold greater than that of age matched controls [445]. Hip fractures are the most expensive to treat and exceed that of any other fracture by 1.6 - 6.2 fold [445].

Almost 20 years ago the annual health care of osteoporosis in the USA was between US$ 5 - 10 billion [25]. This doubled by 2002 and with the projected increase in longevity and hip fracture rates is predicted to further double or triple by 2040 [27]. Similarly, in Europe, which has the highest burden of osteoporotic fractures, the cost of fractures is expected to increase from 32 billion Euros in 2005 to 37 billion Euros by 2025 [313]. In the UK the cost of treating hip fractures, without accounting for inflation, is expected to be in excess of £ 1.6 billion by 2015 [446]. The individual cost for hip fractures, however differs little between countries within Europe [447].

Little is known about the costs of treating hip fractures in developing countries with only a few studies available. However, similar to developed countries, in China, the cost of hip fractures is expected to increase from USD 1.6 billion to USD 12.5 billion to USD 26.5 billion by the year 2020 and 2050 respectively [448] and in Mexico, the costs is estimated to increase from the US$ 97 million USD in 2006 to between USD 213 to 466 million by the year 2025 [449].

Similarly, there is little data on the costs of hip fractures in Africa and the Middle East. Unpublished data reported in the IOF regional audit shows that the cost per patient varies between USD 1000 – 3000 in Iran to USD 12 000 in the United Arab Emirates [28]. In SA cost per hip fracture is estimated at USD 24 000 in the private sector [28].

Independent of the type of surgical procedure, the major factors affecting cost are patient's age, functional status, duration of hospital stay and nursing home care [23, 450]. Costs are generally highest in the first six months to one year, largely accounted for by costs of hospitalization [20, 22] and fall below pre fracture levels only by the 3rd to 4th year [451], by which time a significant number of the individuals with hip fractures will have died. In contrast, in survivors the costs remain above normal up to 5 years later [451]. Vertebral fractures are similarly associated with considerable costs (13.8 billion USD in the USA in 2011) [452, 453] and increased number of visits to a primary care physician [454, 455].

The duration of hospital stay is the most important contributor to cost and may account for up to 84% of the total cost of hip fractures [446, 450, 451]. The number of days in hospital for osteoporotic fractures has been shown to exceed that for stroke or myocardial ischemia in women [403] with mean duration of stay varying between 11 to 23 days [456, 457]. Factors contributing to a prolonged hospital stay include the presence of co-morbid diseases, a lack of operating theatres and orthopaedic surgeons, and prolonged post-operative recovery. One in four women presenting with a hip fracture will have pulmonary disease or cardiac failure, one in five DM and one in ten a previous myocardial infarct or stroke, and these patients will

require pre-operative optimization and longer postoperative recovery periods [458]. In addition, poor nutritional status is also associated with a longer stay, higher costs and an increased mortality [459].

The significant indirect costs from a loss of productivity, special transport needs, special diets, home alterations and caregiver costs are challenging to calculate [446]. Loss of productivity is difficult to estimate in older persons who are often not formally employed but contribute indirectly e.g. as baby sitters [449]. Intangible costs e.g. pain and decreased health status are also difficult to estimate and therefore rarely documented [460].

Various strategies have been proposed to decrease costs of osteoporosis and hip fractures, including earlier surgery and a multidisciplinary approach to rehabilitation to reduce costs and improve outcomes post hip fracture [449], and the identification and treatment of those at high risk for fractures. Treating all post-menopausal women at risk for osteoporosis however, will result in significant over treatment and will equate to cost of treating hip fractures [26]. A more targeted approach to prevent fracture is therefore required. In developed countries, where the incidence and risk profile of hip fractures is clearly defined, treatment of high risk patients, identified by utilizing the FRAX®, has been found to be cost effective [26]. However, management of osteoporosis remains sup-optimal. In the Prospective Observational Study Investigating Bone Loss Experience in Europe (POSSIBLE EU®), just over half the subjects (52%) on osteoporosis medication had had a BMD measured on DXA, despite the fact that 40% had had a previous fracture and 30% at least two fractures [461]. In another study, 50% of patients who present with a hip fracture,

had had a prior fracture and had not received appropriate treatment after the first fracture [462].

To address this shortcoming, the global Capture the Fracture Campaign was launched by the IOF in 2012 [462]. It aims to prevent secondary fractures by developing Fracture Liaison Services (FLS), which will assist to initiate appropriate and multidisciplinary management for the first osteoporotic fracture. A Best Practice Framework (BPF) has been designed to assess the effect of FLS in improving the care offered to hip fracture subjects and outcome, lowering MR and decreasing health care costs [94].

2.18 Assessment and management of osteoporosis in South Africa

The South African health care system is made up of the public sector which caters for the majority of citizens and the private sector, utilized mainly by those with medical insurance or the means to afford such care. Less than 10% of the older population has medical insurance and use the public health sector which is free for the elderly and the indigent.

There is limited data on health care costs for NCDs in SA, especially in the public sector. Although the cost of a hip fracture was determined in a small study in 2005 [463], there is no data on the length of hospital stay or direct and indirect costs associated with hip fractures, either in the private or public sector [464].

A low awareness of osteoporosis has however been reported in two studies from the private sector. In the first study, BMD was measured in only 11.8% of subjects admitted for reduction of a wrist fracture and in only one of ten patients with a hip fracture [292]. Similarly, the majority of subjects on glucocorticoid therapy were not assessed for osteoporosis [465].

There have however been several initiatives to improve the awareness of osteoporosis and hip fractures. The NOFSA has published several guidelines on the assessment and management of osteoporosis and recommendations for the management of hip fractures [87, 88]. Approximately 180 DXA machines are available in SA with majority located in large urban centres. There are only two DXA machines in the public sector in the eThekwini area. While a BMD measurement is free in the public sector, it is less readily available. In the private sector on the other

hand, a DXA study costs approximately 100 USD and requires authorization from the medical insurance scheme.

A major drawback is that osteoporosis is not classified as a PMB. The medical insurance companies are therefore not obliged to reimburse clients for osteoporosis medication. Individuals are often required to take a more expensive plan or provide a motivation to access appropriate medical therapy.

2.19 Summary of literature review

This literature review is an overview of the pathogenesis, epidemiology and outcomes of osteoporotic hip fractures. There have been many advances in understanding the pathogenesis of osteoporosis, identification of individuals at high risk of fractures and medical therapy for osteoporosis. Hip fractures are the most serious consequence of osteoporosis and, even in developed countries, are associated with an increased mortality, morbidity and health care costs. Large epidemiological studies in the developed world have established the risk factors for osteoporosis and incidence of hip fractures and, have led to the development of the FRAX® tool, a cumulative risk score, which predicts the 10 year probability of a major and hip fracture. Based on this, intervention thresholds have been recommended for the appropriate management of osteoporosis. Despite this, treatment for osteoporosis, even after a fracture, remains sub-optimal.

A significant geographic, ethnic and gender variation in the prevalence of osteoporosis and its risk factors, and in the incidence of hip fractures has been reported. A lower incidence has been reported in the developing countries, with the lowest incidence in SA Africans. This is however based on a single study reported more than 40 years ago. Subsequent reports suggest that there is no difference in BMD or the prevalence of vertebral fractures in SA Africans and Whites.

In addition with the increasing LE and rapid urbanization with decrease in physical activity levels and other lifestyle changes, it is predicted that the number of hip fractures will increase exponentially in Africa.

Chapter 3 Methodology

3.1 Ethical approval

Ethical approval for the study was granted by the Biomedical Research Ethics Committee (BREC) of the University of KwaZulu-Natal (UKZN) (Appendix 3.A) and approval to conduct the research was obtained from the KwaZulu Natal (KZN) Provincial Department of Health (DOH) (Appendix 3.B) and individually from the hospitals involved in the study. The Department of Orthopaedic Surgery in each of the hospitals was informed of the study.

All subjects (hip fracture and control) who participated in the study were given an information sheet and signed informed consent in their language of preference (English or Zulu) (Appendix 3.C; English version). To ensure that all fractures were captured, ethical approval was obtained to extract the demographic data (age, gender, ethnicity, hospital name, residential address), management, i.e. surgical or conservative of the hip fracture and duration of hospital stay from a retrospective chart review of the subjects who were either unable to give consent or did not want to participate in the prospective study.

3.2 Study design

A descriptive, prospective study on hip fracture incidence, demographic profile, risk factors, outcomes and health care costs in patients aged 60 years and over with and

without osteoporotic hip fractures was conducted in the public health sector of eThekwini area, SA.

There were two phases in the study

The **first phase** was a comparative study of subjects, aged 60 years and over, with minimal trauma hip fractures admitted to the public sector hospitals in the eThekwini catchment area. The subjects were assessed for the presence of established risk factors for osteoporosis and falls and the immediate outcome post hip fracture including health care cost utilization.

The **second phase** was a one-year longitudinal study to determine the outcomes (morbidity and mortality) of the hip fracture subjects.

3.3 Study area

Africa is the second largest and second most populated continent in the world after Asia with a population of 1.033 billion. There has been a rapid growth in the population size from 221 million in 1950 to 1 billion in 2009. The population growth is estimated to continue increasing to reach 2.4 billion by 2050 [466].

South Africa, located at the southernmost point of Africa has the fifth highest population in Africa at approximately 50.6 million. The population is expected to quadruple in next 90 years with the number of older persons expected to increase significantly to greater than 30% of the population despite the population growth remaining static [28].

This study was conducted in the in the coastal city of eThekwini (formerly known as Durban) which is the largest city in the province of KZN and has a mixed ethnic population of 3 468 087 persons. Of these 236 035 persons (6.9%) are 60 years and older, 144 587 aged between 60 to 69 years and 91 448 above the age of 70 years (Table 3.1).

The majority are African (108 240; 33 811 men and 74 429 women), followed by Indians (62 149; 25 485 men and 36 664 women), Whites (59 187; 25 573 men and 33 614 women) and with a small number of Coloureds (6459; 2 641 men and 3 818 men) [2007 Consensus Stats SA] [467]. The African population consists of the Nguni (Zulu Xhosa, Ndebele, Swazi), Sotho-Tswana, Tsonga and Venda. The Zulu group is predominant group in eThekwini. Whites include English speaking descendants from the British Isle, Afrikaners who are descendants from Dutch, German and French Huguenots and immigrant descendants from the rest of Europe. 'Coloureds' (the label is contentious, but widely acceptable in SA) are a people of mixed ancestry of Khoisan, African, Whites, and slaves from East and West Africa while the Asian population consists largely of Indians from the Indian subcontinent brought as indentured labourers in the 19th century and a smaller group of Chinese [467]. The inhabitants are predominantly urban and peri urban dwellers. The city enjoys a fair amount of sunshine and the climate is tropical with hot, humid summers and warm winters [468].

The eThekwini area is well defined geographically and is divided into health districts with a regional hospital in each district (Figure 3.1). Health care is provided on a

structured fee basis and health care for pensioners (retired persons or those receiving an old age social grant) is free.

3.4 Study sites

The area has 6 large hospitals of which two are classified as central hospitals and 4 regional levels hospitals which all offer an orthopaedic service. BMD testing is available at the central hospitals only, however acute hip fracture management is not performed at one of the central hospitals Inkosi Albert Luthuli Central Hospital (IALCH). There are also several private hospitals in the area which offer an orthopaedic service on a fee based structure or accept patients with a medical insurance.

The study was undertaken in the following five public sector hospitals in the eThekwini region, namely King Edward VIII (KEHVIII), Addington (ADD), RK Khan (RKK), Mahatma Gandhi Memorial (MGH) and Prince Mshiyeni Memorial Hospitals (PMMH). All subjects with a hip fracture presenting to a primary or district level hospital in the public sector are referred to one of these hospitals for further evaluation and treatment.

Table 3.1 Population breakdown of eThekwini according to age, gender and ethnicity

Age (years)	African		Coloured		Asian/Indian		White		Total
	Male	Female	Male	Female	Male	Female	Male	Female	
60 – 64	15 437	25 239	858	1 174	10 009	13 458	7 220	9 644	83 039
65 – 69	8 102	18 820	718	957	7 980	9 837	6 899	8 234	61 547
70 – 74	5 062	13 307	603	625	3 444	7 046	4 341	5 980	40 408
75 – 79	2 946	8 361	456	706	2 264	4 133	3 548	4 174	26 588
80 – 84	1 240	4 494	3	249	1 170	1 289	1 920	2 612	12 977
85 – 120	1 024	4 208	3	107	618	901	1 645	2 970	11 476
Total	33 811	74 429	2 641	3 818	25 485	36 664	25 573	33 614	236 035

Created on Thursday, October 30, 2008; Statistics South Africa Web page: www.statssa.gov.za

Statistics South Africa support: info@statssa.gov.za [467]

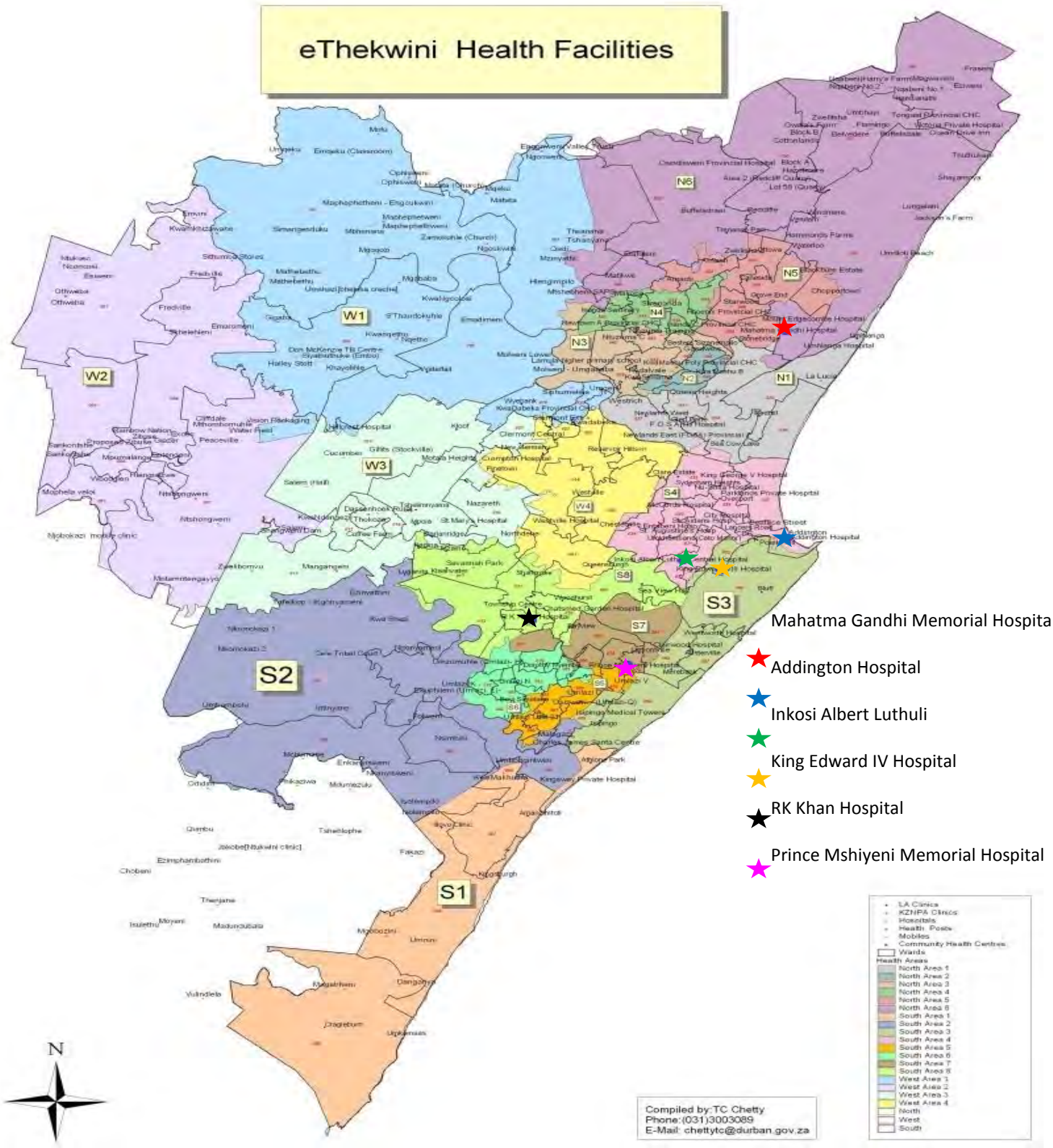

Figure 3.1: Map of eThekwini health areas [468]

The figure represents the different health regions in eThekwini and the location of the 6 hospitals are highlighted*. Clinics and district level hospitals in the area refer patients to regional centres.

3.5 Sample selection

3.5.1 Subject selection: The study population consisted of persons aged 60 years and over who resided in the eThekwini area and were admitted with a diagnosis of minimal trauma hip, neck of femur or trochanteric fracture in the five selected hospitals during the study period.

3.5.2 Control subjects: Volunteer subjects aged 60 years and over, with no previous history of osteoporosis or hip fractures were recruited from the hospitals being studied. Additionally they were recruited by word of mouth and through local community centres for the aged in the defined geographic area.

3.6 Recruitment

Recruitment and follow up of hip fracture subjects and age matched controls commenced in August 2010 and was completed in May 2013. Trained medical and nursing staffs were employed to assist with the recruitment.

The age of subjects was determined from the admitting hospital records and if not known an estimated age was obtained from the subject or a family member. Ethnicity was self-reported by the subjects.

All hip fracture subjects who consented to participate in the longitudinal study were followed up at IALCH.

3.7 Sample Size

For the case study the number of subjects required to ensure validity of results was calculated using the most important established risk factors for osteoporotic hip fractures. The risk factors identified were age, gender, ethnicity, a known diagnosis of osteoporosis, previous fragility fractures and a maternal history of fractures. The prevalence of these was estimated from international and local literature. The number of subjects required to show statistical significance, calculated using an epidemiological statistics software package and disease prevalence was 200 subjects and 200 controls (Table 3.2).

Table 3.2 Prevalence of risk factors used to calculate sample size.

Risk factors	**Cases with hip fractures**
Age	>70 years 60 %; n = 183
Gender	Males 30%; n = 78
Ethnic	Whites 30%; n = 189
Osteoporosis risk (<-2.5 on BMD)	70% ; n = 21
Previous fracture history	20 to 40%; n = 158
Family history of hip fracture	5 to 31%; n = 194

3.8 Inclusion and exclusion criteria

3.8.1 Inclusion criteria

Hip fracture subjects

1. Age 60 years and over.
2. New minimal trauma hip fracture (defined as any fracture of the femur between the articular cartilage of the hip joint to 5 cm below the distal point of the lesser trochanter, subsequent to a fall from a standing height or less) [469, 470].
3. Ability to give informed consent. This was applicable to the case control study only. Ethical permission was obtained to record age, gender and ethnicity of all patients admitted with hip fractures to calculate incidence rates (see section 3.11).

Control subjects

Age (± 3 years), gender and ethnic matched controls from the eThekwini area who met the following criteria were recruited.

1. Ability to give informed consent.
2. Not previously investigated or treated for osteoporosis.
3. No history of a prior hip fracture.

3.8.2 Exclusion criteria

1. Pathological fractures of the hip
2. Fractures distal to the lesser trochanter
3. Traumatic hip fractures
4. Subjects readmitted during the study period with complications due to a previous hip fracture.
5. Subjects who were not native South Africans and/or did not have a South African citizenship.

Subjects admitted to more than one site were recorded at the site where the primary surgery occurred.

3.9 Case identification

Hip fractures subjects were identified from the orthopaedic wards' admission registers which record the following data: date of admission, name, age, gender, residential address and admission diagnosis based on the clinical and radiological findings of the admitting doctor. Original medical records and radiographs of all subjects identified from the admission registers were reviewed to verify the diagnosis before they were enrolled in the study.

Of the total of 277 subjects identified for possible inclusion, 53 subjects refused to participate in the case control study and 24 were confused and unable to give consent. These subjects were not followed up and the reasons for the confusion are

unknown. The demographic profile of the excluded subjects is discussed in Section 4.

Control subjects were identified from the Outpatients departments of KEH VIII hospital (n=41) and IALCH (n=49), family and or friends of hip fracture subjects (n=20), staff or their relatives (n=21) and from old age organizations (n=69). These subjects were pre-identified by the study coordinator and only subjects who consented to the study were referred to the investigator. The number of control subjects who were approached and refused to participate was not documented.

Control cases were recruited on an ongoing basis, and within a year of the hip fracture subject being enrolled.

Survival bias

All hip fracture subjects admitted to the selected hospital during the study period were seen within the week of admission. All subjects admitted with a hip fracture were recorded and no subject had died prior to the initial screening. It is therefore unlikely that there was a survival bias in this study.

3.10 Data collection instruments

A standard data collection form (Appendix 3.D) was administered by a trained interviewer and a standardized clinical examination and relevant laboratory and radiological investigations were performed.

Information recorded included demographic data, anthropometric measures, risk factors for osteoporosis, functional assessment, full physical examination findings, results of haematological, biochemical and radiological investigations.

3.10.1 Demographic data

The following information was obtained for both hip fracture and control subjects.

1. Age
2. Ethnic group
3. Gender
4. Physical address was recorded as the usual address of the subjects. Subjects outside the eThekwini boundary were excluded from the study.
5. Housing type : categorized as formal, informal, traditional or hostel.
6. Employment: categorized as pensioner, unemployed or self-employed. Permanent South African citizens aged 60 years and older are eligible to receive an older person grant from the government and free health care [471].
7. Educational level: categorized as never schooled, less than 5 years of education, completed secondary level or Standard 10 or tertiary education.

3.10.2 Anthropometric measures

1. Weight: Subjects were weighed on a balanced beam scale, wearing the minimum of clothes, to the nearest kilogram (kg)

2. Height: was measured using a stadiometer with a sliding headpiece to increase the accuracy of the reading and taken to the nearest centimetre (cm).

   Weight and height in hospital were recorded in 136 subjects only. Sixty four hip fracture subjects were unable to stand independently and to be accurately weighed by the time of discharge**.**

3. Body Mass index (BMI) was calculated using the standard formula BMI = weight (kg) / height (m^2) and expressed as kg/m^2 and according to the WHO categories for adults aged 25 years and older (Table 3.3) [472]

Table 3.3 WHO normal reference values for BMI in adults

Category	**BMI range (kg/m^2)**
Underweight	<19.0
Normal (healthy weight)	19.1 - 24.9
Overweight	> 25 - 29.9
Obese	> 30

- Adults: >25 year
- Adapted from WHO 1995 [472]

3.10.3 Risk factors for osteoporosis

Although a number of validated tools for the assessment of osteoporotic fracture risk exist, few have been used in clinical practice in SA. The WHO FRAX® has been validated by the IOF and is based on studies from NA, Europe, Australia and Asia

[31]. The osteoporosis risk factor assessment in this study was based on traditional risk factors for osteoporosis including those identified by the FRAX® [78, 79]. The FRAX® tool has been validated in 12 independent studies and found to be valid and reliable.

Therefore the factors used in predicting fracture risk in this study included:

- Age, sex, weight and height
    - The actual weight and height were recorded.
    - Subjects were categorized as being </> 57 kg as per the FRAX® tool, however only mean weight was used in the risk assessment analysis.
- Gynaecological history
    - age of menarche
    - age of menopause
    - use of HRT

      Age at which commenced use, duration and side effects of HRT
    - parity
- History of childhood fractures
- Previous fragility fractures after the age of 40 years
    - defined by site, date of occurrence and treatment received
    - screened or treated for osteoporosis
- Prior vertebral fractures (self-reported)
    - defined site, date, treatment received
    - screened or treated for osteoporosis
    - kyphosis(self-reported)

- Family history
    - Osteoporosis
    - Maternal history of falls
    - Maternal history of fractures
- Smoking history
    - The WHO Monitoring Trends and Determinants in Cardiovascular disease scale (MONICA scale), an internationally validated questionnaire was used to classify subjects as present or past smokers. The average number of cigarettes smoked was determined. The age of smoking, exposure to passive smoking and use of a pipe was also documented [473].
- Alcohol use
    - Subjects were asked to report the number and type of alcoholic drinks consumed in the past week using a self-report scale, validated in The Danish Health and Morbidity Survey [474]. This scale was used as recall periods of greater than one week duration are associated with a significant decrease in the report of alcohol usage and are less accurate.
- Calcium intake
    - The IOF Calcium Intake Diary [475] was used to record and calculate the dietary calcium intake based on the UK nutrient databank information. While calcium intake has been reviewed in the SA population, several different methods were used to quantify calcium intake in the different ethnic groups. Despite the IOF calcium intake

tool being freely available this has not been used in previous studies in SA.

- Lifestyle factors
    - Illicit drug use, caffeine intake and sunlight exposure (minutes/day) was recorded.

- Activity level (self-reported)
    - Subjects were asked to self-categorize their activity level as extremely active, moderately active, mildly active or sedentary based on their daily activities.
- Current drug use and previous use of drugs associated with bone toxicity, GC, anti-epileptics, heparin, lithium, antidepressants, was recorded.
- Presence of known causes of secondary osteoporosis including rheumatoid arthritis, type 1 DM, osteogenesis imperfecta, untreated hyperthyroidism, hypogonadism, premature menopause (<45 years), chronic malnutrition, malabsorption and chronic liver disease [31].
- Falls were assessed in three different questions
    - Current fall resulting in hip fracture (Appendix 4D Q 2)

      Date and type of fall
    - A history of the number/s, date/s and type of fall/s prior to the present fall were recorded in Q3.6
    - Elderly Fall Screening Test (EFST) was administrated (Q7)

      The EFST has been validated in a number of community studies and was used to assess fall risk. The tool has six items with no objective

testing required, and is therefore easy to implement and has a sensitivity of 93% with a specificity of 78%. The six items include previous falls, lifestyle factors, neurological disorders, medication use and recent illness, balance and gait, and environmental hazards. Subjects who score in more than 3 categories are at high risk for falls [476, 477]. The EFST has not been previously used in SA studies.

3.10.4 Functional assessment

The following scales were used to assess basic and instrumental activity of daily living, quality of life and level of pain:

1. Physical self-maintenance scale (PSMS)
2. Lawton Instrumental Activities of Daily Living scale (IADL)
3. Euro Quality of Life scale (QoL)
4. Oswestry Disability Index (ODI)
5. Visual Analogue Scale (VAS) for pain

The PSMS and the Lawton IADL are widely used in combination to assess daily living activities and are easy to administer. They correlate well with other activity scale scores, with good inter-rater reliability at 0.87 and 0.91 in the elderly [478, 479]. Possible limitations of these scales include under or over reporting as both scales are self-reported and are not observed. Both scales however if administered repeatedly can document functional improvement or deterioration [478, 479]. The

ability to administer the test repeatedly and maintain validity was important in assessing functional outcomes during the study period and at one year. The Lawton IADL scale has been reported to be a sensitive marker of function and correlated with the nutritional index in a SA study [480, 481].

The Euro QoL, a generic questionnaire, used and validated in hip fracture cost studies, enables the comparison between different ethnic and study groups [482]. It is short and easy to administer and provides valuable insight into subjects overall functioning. The Euro QoL has been shown to be sensitive in detecting moderate to severe functional impairment in a multi-ethnic SA population post stroke and in amputees in SA [483-485].

The ODI has been studied extensively in subjects with lower back and hip pain. It has been validated in cross cultural settings, [486, 487] is easy to score and is a good predictor of functional outcome post-surgery. It is scored out of 60 and converted into a percentage. If any section is not answered, the score is adjusted accordingly before the percentage is calculated (Appendix 3.D).

Pain is a significant contributing factor to hip fracture subjects' recovery. The VAS is a simple tool to administer and has good reliability and validity to measure pain at a particular moment in time. The subject indicates her/his subjective feeling of pain on an unmarked 10cm line and the point is measured and scored out of 10. A score above 4cm predicts a poor outcome and correlates with other functional scales in post hip fracture subjects. It is most useful to determine changes in individuals over time rather than comparing individuals at a discrete point [488, 489].

The ODI and VAS have been used primarily in orthopaedic studies in SA involving lower back pain or recovery after spinal surgery, and although the ODI pain score and VAS pain score may not reveal an initial correlation, with time both scores are considered useful tools for interpreting functional recovery [490, 491].

3.10.5 Physical Examination

All patients had a full physical examination undertaken by a specialist physician (the author) on enrolment to screen for secondary causes for osteoporosis and on subsequent follow up visits to detect any co-morbid illnesses.

3.10.6 Haematological and biochemical investigations

All patients recruited into the case control study had 20 millilitres of venous blood drawn from a vein in the antecubital fossa, for haematological and biochemical evaluation. The investigations were chosen to exclude secondary causes of osteoporosis and to determine if there are haematological or biochemical tests that may help predict risk or outcomes.

The investigations were performed immediately after consent was obtained, and this was usually within a week of admission for hip fracture subjects. The medical file was reviewed prior to performing any tests and any results from admission if

available were documented. Blood investigations were performed in control subjects on the day of recruitment.

The following blood tests were performed on the total cohort:

1. Blood was collected in an ethylenediaminetetraacetic acid (EDTA) tube an analysed in a Sysmex machine (Roche) for a full blood count (FBC). The haemoglobin (Hb) (g/dl), red blood cell mean corpuscular volume (fl) and mean corpuscular haemoglobin (pg), white blood cell count $\times 10^9$/l (WBC) and platelet count$\times^9$/l were measured.

2. Blood samples were collected in a gel tube and analysed in a Beckman Coulter DXC 800 for the following:

a. Urea and electrolyte: Sodium, potassium chloride, bicarbonate, urea and creatinine.

b. Liver function test: Total protein, albumin, bilirubin, alkaline phosphatase (ALP), gamma glutamyl transferase (GGT) and alanine transaminase (ALT).

c. Calcium, phosphate and magnesium: The serum calcium was corrected using the following formula

Corrected calcium = serum calcium + ((40 - albumin) × 0.025)

d. Random glucose: (collected in a potassium oxalate tube)

e. C- reactive protein (CRP)

3. The Beckman Coulter DXI 600 was used for measuring thyroid function tests and the parathyroid hormone level.
4. 25 hydroxy vitamin D was sent to the Central National Health Service laboratory in Johannesburg for analysis using the high performance chromatography (HBLC) based Chromo-systems diagnostic kit.
5. Oestrogen and testosterone levels were measured using chemical luminescence (Roche).
6. Erythrocyte Sedimentation Rate was measured using the Westergren method using non clotted blood.

All blood samples were processed at the admitting hospital by the National Health Laboratory Service (NHLS). The normal reference ranges for NHLS were used as reference range (Appendix 3.E).

3.10.7 Radiological investigation

3.10.7.1 Conventional radiographs

All hip fracture subjects had hip radiographs on admission. Due to logistic difficulties all subjects were unable to have spine radiographs on admission. Subjects who came for their follow up visits at IALCH had plain thoracic and lumbar spine radiographs performed. Separate antero-posterior (AP) and lateral radiographic views of the spine were acquired using a standardized protocol in 122 hip fracture subjects at their three month visit and 197 control subjects on the day of enrolment.

Of the 78 hip fracture subjects who did not have radiographs, 35 died before their 3 month follow up visit, 29 were unable to come to hospital and were followed up telephonically and 14 were lost to follow up.

A further 4 patients had radiology but did not have a DXA scans due to technical reasons (1 had a recent barium meal, 1 was unable to lie down and two refused). The comparison (gender and ethnic) between subjects in whom radiology was /was not performed is expanded in section 4.

All radiographs were reported by an experienced specialist radiologist blinded to hip fracture or control subjects, Dr J Maharaj (UKZN, Senior Lecturer in Department of Radiology). Thoracic and lumbar vertebrae were considered to be abnormal (morphometric fracture) using the fixed method i.e. if there was a decrease in height of >20% in its anterior, middle or posterior section compared to its own or nearest intact posterior vertebra [492, 493]. The percentage loss was calculated using the difference in height. Fractures were graded as mild (20-25%), moderate (25.1-39.9%) or severe (>40%) according to the degree of deformity [10]. This method has been validated in several studies including SOF correlates with clinical measures of height loss, age, back pain, baseline BMD. The measurements are easy to perform and requires no reference range and are accurate even for small sample numbers [183].

3.10.7.2 Bone mineral density

BMD and BMC measurements were obtained using DXA. The Hologic Discovery A densitometer was used to measure BMD of the spine and the opposite hip in hip fracture subjects. The BMD of the lumbar spine (L1 to L4) was obtained and a mean value calculated.

The BMD was measured according to a standardized protocol by trained radiographers, who had previously completed the National Osteoporosis Foundation of South Africa (NOFSA) / International Society for Clinical Densitometry (ICSD) training course, at KEH and IALCH. Phantoms were scanned weekly at each site to ensure reproducibility. A precision assessment tool, which is more accurate than a manual assessment, was used to calculate the percentage coefficient variant (% cv) between the sites. The % cv change was 4.84% across all systems or a change of 0.047 g/cm^2 (Appendix 3.F), was considered acceptable for comparison.

BMD was measured in (g/cm^2) and was calculated at the hip from BMC (g) divided by bone width (BW) and at the lumbar spine by total scan area. BMD is conventionally expressed as either an absolute value (g/cm^2) or a deviation from the norm defined as a Z - score or T - score. The Z - score is a comparison of the subjects BMD with an age, gender and ethnic matched control whilst the T - score is comparison to young adult reference range for that population. For this study, the NHANES III Caucasian data as recommended by the NOFSA [88] was used as there are no normative data for different ethnic groups of SA.

Numerous studies have shown that actual bone size affects areal bone mass measurements especially in different ethnic groups. Several techniques have been proposed to adjust bone mass measurements for volumetric differences in body size.

The volumetric assessment; BMAD was calculated at spine and hip, based on the premise that volume of bone can be calculated from DXA areal measurements as proposed by Carter [494] and Katzman [495] for the lumbar vertebrae and the femoral neck respectively using the formulae:

BMAD = Mean $BMC/(AREA^{*}\sqrt{AREA})$ at the lumbar area [494] and

BMAD = B$MC/(AREA^{*}\sqrt{AREA})$ at the femoral neck [495]

3.11 Outcomes post hip fracture: Mortality and morbidity

Hip fracture subjects were followed up for one year and functional outcomes documented at three, six and twelve months using the functional tests described in Section 3.10.4. Subjects were given an appointment for the Geriatric clinic at IALCH for their follow up visit on discharge from the orthopaedic ward. At the three month visit all subjects were assessed by the investigators. A clinical examination, an assessment of function (PSMS, IADL, QoL, ODI and VAS) was performed and radiological investigations (thoraco-lumbar spine x-rays and BMD) obtained. At the six and twelve month visits, functional assessments were repeated. Hip fracture who were unable to attend follow up visits, either due to mobility and/or transport

difficulties, were interviewed telephonically to assess function. Readmissions for fracture complications as identified were documented.

The number of deaths at one year post fracture was recorded and date and possible cause of death documented. The mortality rate was calculated as numbers of deaths compared to survivors at one year, excluding subjects lost to follow up.

3.12 Incidence rate calculation

All consecutive patients with hip fractures in the public sector presenting from the 1 August 2010 - 31 July 2011 who met the inclusion criteria were recorded. The crude and age specific hip fracture incidence rates for the eThekwini and SA were calculated using the number of new fractures as the numerator and the total population of eThekwini and SA above 60 years old as the denominator based on 2007 census data [467].

The calculated crude rate was used to calculate the estimated incidence rate for the entire South African population. To determine an accurate estimate, variables which affect incidence rates i.e. age, gender and ethnicity were taken into account. The direct method was used to standardize for age based on ASR for the sample population of eThekwini and the age structure of the South African population. The formula used to calculate incidence rate is shown in Table 3.4 [496].

The ASR for males, females, Indians, Africans and Whites (females only) were determined using the number of fractures in each group as the numerator and the

respective total population >60 years old for the denominator (Table 3.5). Due to low numbers, the ASR for the Coloured group and White men was not calculated [467].

Age specific rates were calculated in 5 year intervals and the coefficient increase or decrease calculated with increase in age by dividing the ASR of the older group into that of the younger group.

The crude incidence rate was determined by using the following formulae:

$$\frac{\text{Number of fractures in one year}}{\text{Number of persons in the at risk population per 100 000}}$$

Table 3.4 Formulae to calculate crude and age specific incidence rates.

No. of fractures	**At risk population**	**ASR / 100 000**	**SA standard population**	**Age distribution of standard population**	**Age adjusted rate**
1	2	(1) / (2) = 3	4	(4) / total population = (5)	(5)×(3)
a	**b**	**xxx**	**c**	**d**	**e**
Crude rate (a/b)x100 000 = y per 100 000			Age adjusted incidence rate (e)/(c) = z per 100 000		

Adapted from Schneider [496]

Table 3.5 Population of South Africa over 60 years old stratified according to age, gender and ethnicity

Age	African		Coloured		Indian		White	
	Male	Female	Male	Female	Male	Female	Male	Female
60 – 64	305 762	447 322	46 077	63 267	18 128	24 111	124 049	128 970
65 – 69	249 366	397 332	32 873	46 456	13 633	17 414	99 203	105 920
70 – 74	143 239	295 172	22 651	32 272	7 211	12 353	68 784	83 414
75 – 79	102 748	227 996	11 175	21 592	4 908	7 118	44 287	60 262
80 – 84	5 377	120 926	5 031	11 942	2 248	2 528	26 625	40 717
85+	51 127	130 087	3 748	8 212	1 376	1 675	14 453	30 559
Total	857 619	1 618 835	121 555	183 741	47 504	65 199	377 401	449 842

Created on Thursday, October 30, 2008

Statistics South Africa Web page: www.statssa.gov.za

Statistics South Africa support: info@statssa.gov.za[467]

3.13 Calculation of health care costs associated with acute hip fracture management

Acute management of hip fractures contributes significantly to health care costs with the majority of direct costs attributed to hospitalization. After sustaining a fall a potential fracture subject either visits a peripheral health care facility or may present directly to one of the five selected hospitals. Once admitted the patient is either surgically or conservatively managed (non-surgical) depending on his/her fitness for anesthesia and surgery. The potential pathway a subject may have followed from admission to discharge is shown in Figure 3.2. No study subjects required intensive or high care facilities in this study.

Surgical data was not available for four subjects and these were excluded from the cost analysis.

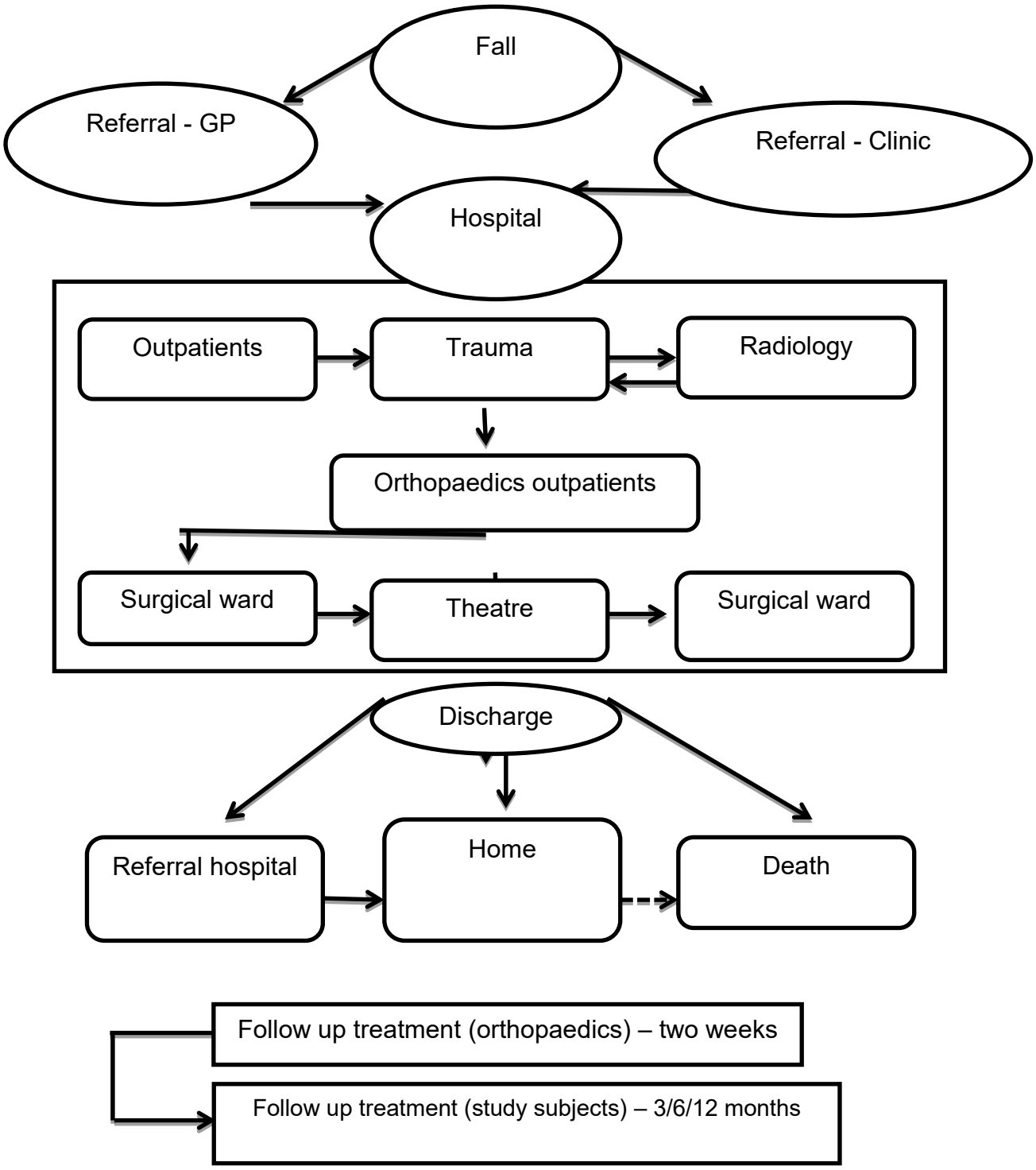

Figure 3.2 Flow process for hip fracture subjects from time of fall to discharge

3.13.1 Cost Calculation

A bottom up approach was used to calculate health care costs (aggregating the resource cost of individual patients). The acute cost of admission and management was calculated for 200 subjects enrolled in the prospective study. The cost of treatment was sub-divided into its major components:

- Acute ward costs
- Theatre costs
- Investigations performed

A detailed review of hospital records was undertaken for all patients. Ward expenses were computed, with the aid of the finance department, using the average cost per day as determined for the financial year 2010 / 2011 and the KZN DOH hospital fees manual for 2010/11.

Costs related to other resources were established from actual individual use. The length of stay in orthopaedic wards was recorded. In addition, number of days to surgery was documented for each patient and the total number of delayed days, with resultant costs, was calculated. The average daily cost of in hospital ward was R 2 560.06, inclusive of nursing care and other daily ward expenses (Appendix 3.F).

The surgical procedure, operation duration in minutes and type of implant used was recorded. The average cost incurred by one hour of operating time was calculated. This estimate included staff time in theatre and recovery area, use of equipment, sterile services and expendable items including those employed by the anaesthetic

team. The cost of each implant was incorporated separately. All pathology, microbiology and radiological investigations performed were carefully documented for each patient and their frequency recorded. Using this data the individual total cost incurred in the treatment of each patient was calculated.

The cost of valuation was based on observed market prices however these were recorded in units and amounts so if in the future total cost estimates can be updated if better cost evaluations become available.

The following costs were documented in each patient to ensure credibility of the costing calculation:

1. Doctor's initial consult
2. Initial Nursing consult
3. Radiology
4. Laboratory tests
5. Admission clerk
6. Transport from base hospital (where applicable)
7. Number of days in the ward
8. Number of daily doctor's consults
9. Daily nursing cost
10. Drug cost: analgesics /medication for co-morbidities/discharge medication
11. Physiotherapist cost
12. Theatre time
13. Anaesthetist cost

14. Anaesthetic drug cost
15. Surgeon's theatre cost
16. Hip replacement/repair–type and make
17. Repeat radiology post-surgery
18. Transport back to base hospital where applicable

The time frame for the study was fifteen months and resulted in the introduction of some uncertainty as traditionally costs are inflated according to the inflation rate to adjust for time. To correct for this, actual amounts per year instead of averaging amounts according to inflation were used.

The second important area where uncertainty possibly occurred was in the estimate of hospital costs. The study data is stochastic and thus sensitivity analysis for uncertainty due to sampling variation was assessed by use of conventional statistical inference and hypothesis testing.

Uncertainty was prevented as the process flow from admission to discharge was followed, and an audit of treatment and hospital records was done on discharge to ensure all costs incurred had been calculated.

The normative costing model was based on the recommended guidelines for hip fracture management as endorsed by NOFSA [87]. The actual calculated cost of treatment was compared to the normative cost (Appendix 3.G).

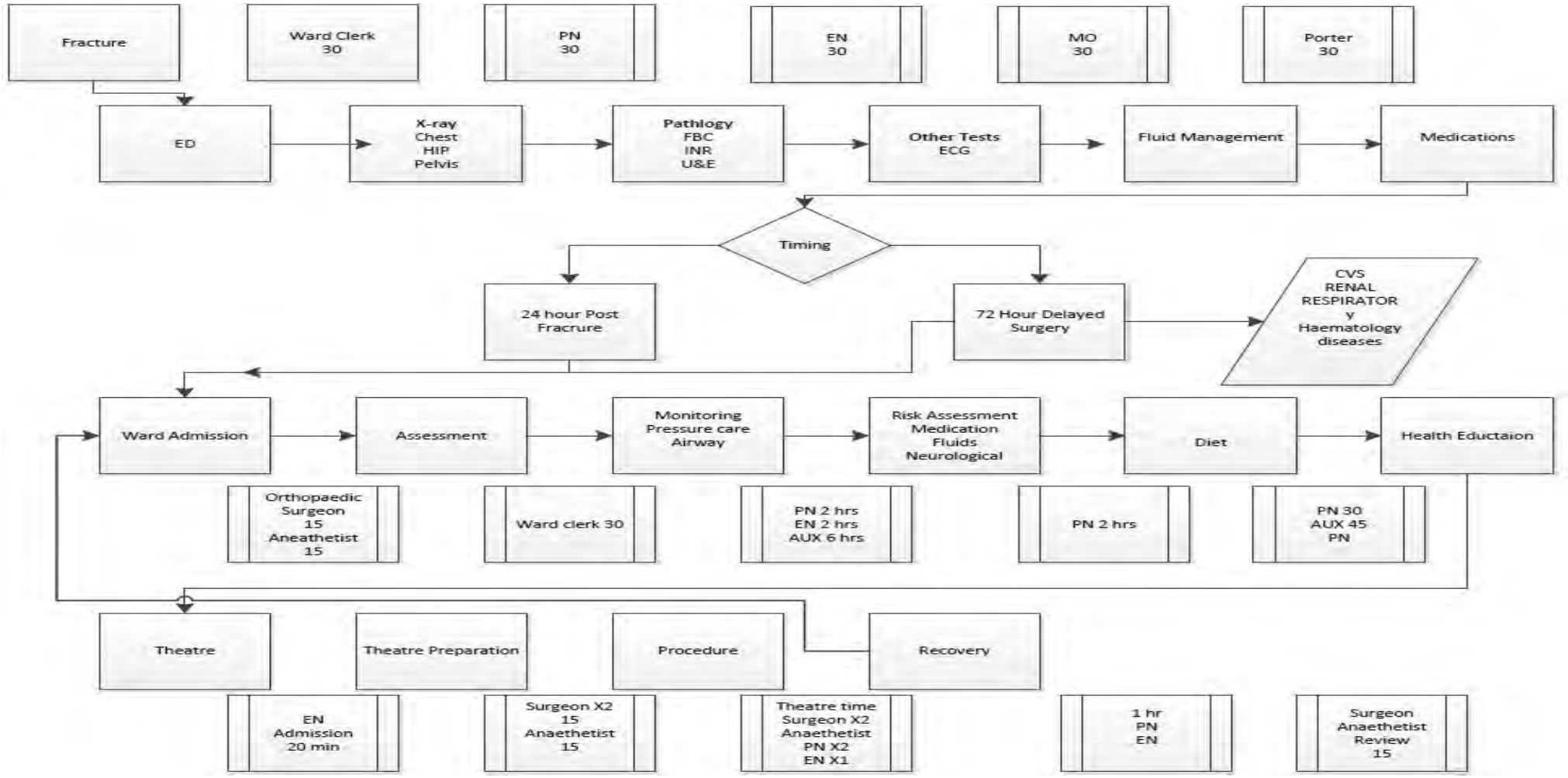

Figure 3.3 Flow diagram for normative costing of acute management of hip fractures

3.14 Data collection: Reliability and validity

The study sample represents both male and female subjects of the different ethnic groups in the eThekwini area. An over representation of subjects may possibly have occurred as the orthopaedic services are concentrated in the metropolitan area and patients outside the eThekwini functional area may also have potentially accessed the service. To correct for this subjects who did not have a permanent address in defined geographic locality would have been excluded.

Due to severity of pain and disability post hip fracture, one assumes most subjects with hip fracture will seek health care, but it remains possible that extremely frail subjects may have been possibly managed at home and not brought for medical care. Although traditional medicine is widely practiced, it is unlikely to have resulted in an under-representation of African cases in the urban setting.

The sample is not representative of certain ethnic groups with a high fracture risk that utilize the private sector preferentially. In order to compensate for the differential use of public and private sector by the different ethnic groups, the latest available quarterly report of council for medical schemes was accessed to determine the percentage of population with a medical aid. Further analysis from the latest results from the Private Health Care Funder's Board in 2007, indicates that only 14% of the population has medical aid cover as compared to the previous 20%. Furthermore, pensioners (persons aged 60 years and over) and Africans account for only 6.4% and 6.9% respectively of medical aid members. The General Household survey confirmed 66.9% of Whites compared to 7.4% of Africans had medical insurance

[497]. A more recent household survey shows that the 77% of White subjects have medical aid and 88% utilize private health care, while 46.1% of Indians have medical aid and 64.1% utilize private health care. In contrast only 10.8% of Africans have medical aid and 17.2% utilize private health care. The survey however does not have an age breakdown and may preferentially reflect the younger more economically wealthy population, especially in the Indian and African population groups [498].

This study is not able to make any significant conclusions regarding the epidemiology and risk factors for osteoporotic hip fractures in the White and Coloured population groups, but it may provide data for the African and possibly for the Indian population groups in SA.

Sample bias was eliminated as all subjects were enrolled in the demographic and incidence study, and there were no exclusion criteria apart from age, non-South African residents and pathological fractures and inability to consent. To further decrease the risk of bias minimal number of interviewers and simple data collection methods were utilized. No significant communication barrier was encountered in interviewing the subjects.

The study was prospective therefore the risk of missing records and incorrect data capturing was significantly decreased. Subject variation with regard to recollection of events, mood, and motivation to respond to questions, reaction to environment, and rapport with interviewer and language skills may still affect data reliability.

All subject's contact details were recorded and failure to arrive for appointment was followed by telephone call to assess the outcome.

3.15 Data management

All subjects were identified by a numbering system on being enrolled. The master copy of patients' names and numbers was available to the main investigator only after the data was captured.

Collected de-identified data encrypted by a number system was entered into a password-protected IBM® *SPSS*®19 database. The data was only handled by the research team and kept with the main investigator until submission for data analysis. Only de-identified data was submitted for analysis. The data was paired with the matched age, gender and ethnic control subjects prior to analysis.

Original data files are kept in locked office in Department of Geriatrics and will be destroyed in keeping with the university policy once 5 years have elapsed.

3.16 Data analysis

The data was analysed using IBM® *SPSS*®19 and SAS® version 21. The significance for all tests was set at $p < 0.05$. Descriptive statistics were applied to show differences in age, gender and ethnicity. Differences in means were compared using Student's t test for numerical variables. The Chi square test was used for

categorical variables. In cases where frequencies were small the exact test was used to determine the p value.

In the case control study matched conditional logistic regression analysis was used to investigate the relationship between hip fracture and control subjects and risk factors. Subjects were paired and stratified according to 1 = hip fracture and 0 = no hip fracture.

The odds ratio (OR) for conditional matched analysis was calculated using the formulae below:

$$\text{OR} = \left(\frac{\pi(x=1)}{1-\pi(x=1)}\right) / \left(\frac{\pi(x=0)}{1-\pi(x=0)}\right) = \frac{e^{\beta 0}.e^{\beta 1(1)}}{e^{\beta 0}e^{0}}$$

$$\frac{\pi(x=1)}{1-\pi(x=1)} = a \frac{\pi(x=0)}{1-\pi(x=0)}$$

OR: odds of a hip fracture with x=1 compared to the odds of hip fracture when x = 0;

(x) is the variable of interest, usually binary

.g. x = 1 for hypertension or x = 0 if no hypertension.

The study data was stratified to ensure the matched pairs of subjects and controls were retained in the analysis. Pairs were matched, and labelled with a paired sample number of 1 to 200. In comparing the tests for proportion of exposed controls, discordant pairs with the risk factor were identified. The OR is based on

how the paired data differs from the estimate based on an unmatched analysis of the same data. Unmatched data analysis will bias the OR towards unity.

Matched conditional logistic regression analysis was used in determining risk factors for osteoporosis and comparing functional activities and haematological and biochemical results. The proposed risk factor was considered significant if the OR was greater than one and the lower bound of the confidence interval did not go below one. In addition, gender and ethnic differences and predictors of death were analysed.

To control for confounders, logistic regression analysis was carried out. Independent variables found to be significantly associated with hip fractures or mortality on a univariate analysis were entered into a multiple Cox regression model in SPSS using backward likelihood ratios to arrive at a final model which detailed the independent effect of each of the predictors in the model.

Outcomes over a year were analysed using the McNemar test. This methodology was used to prevent errors in estimating the relationship of a disease and exposure as it compares a given subjects outcomes against time [499].

Costing analysis

The financial burden of hip fracture was calculated using the bottom up approach as detailed in Section 3.13. The amount and percentages for different components of hospitalisation were determined. The actual cost of hip fracture treatment was

compared to normative costing and the percentage difference calculated. The cost of treating acute hip fracture was compared to treatment of osteoporosis

Chapter 4 Results

In the study period, 1 August 2010 - 15 October 2011, two hundred and seventy seven (277) subjects with minimal trauma hip fractures were admitted to the five selected hospitals and were enrolled into the study. Their demographic and clinical characteristics are presented (Section 4.1).

- Of these, 230 subjects admitted in the one year period 1 August 2010 to 31 July 2011 were included in the calculation of the incidence rates (Section 4.2).
- Two hundred (200) subjects with minimal trauma hip fractures and 200 age, gender and ethnic matched control subjects consented to enter the case control study (Section 4.3).

  The 77 subjects who either refused to participate or were unable to consent were significantly older than the subjects who consented (80.0 ± 8.9 vs 74.3 ± 8.8; $p < 0.0001$) and although women (n=60) were more likely not to consent or participate compared to men (n=17) this was not significantly different (29.4 vs 23.3%; $p = 0.316$). Compared to Indian (n=36) and African (n=21) subjects a significantly greater proportion of White subjects (n=16) did not participate (24.7% and 24.1% vs 43.2% respectively; $p = 0.034$). The overall number of White and Coloured subjects was still lower than that of Indian and African subjects, and this study would still not have been able to draw significant conclusions for the White and Coloured population groups even if all the subjects had participated. It is also possible that risk factors specific for older

subjects e.g. memory loss, falls and dementia may be underestimated in this study.

- The one year outcomes and direct health care costs for 200 subjects with minimal trauma hip fractures were determined (Section 4.4 and 4.5).

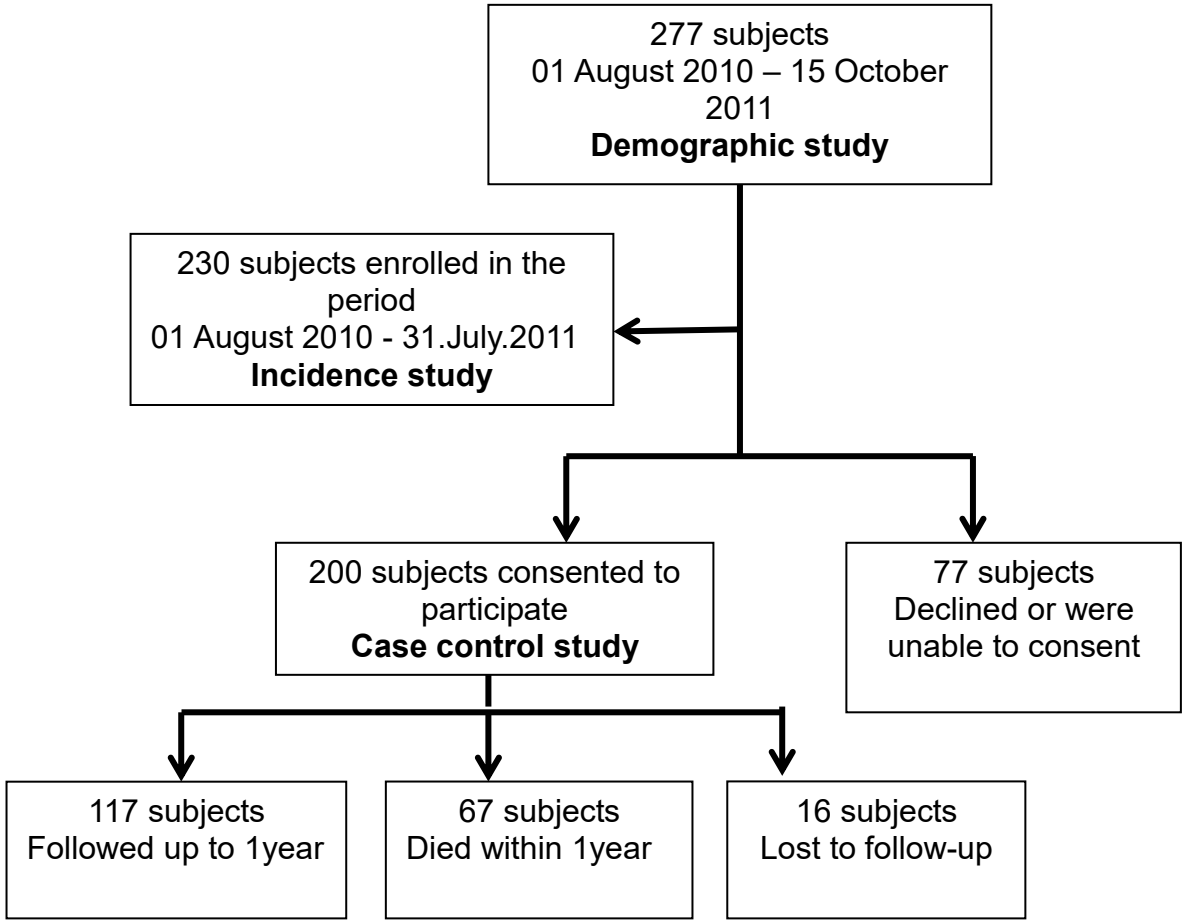

Figure 4.1 Flow diagram showing enrolment and follow up of hip fractures subjects (n = of 277).

4.1 Demographic characteristics of 277 subjects with minimal trauma hip fractures

4.1.1 Ethnic, age and gender distribution

The majority of hip fracture cases were Indian (52.7%) or African (31.4%). Whites (n = 37) and Coloureds (n =7) only represented 13.4% and 2.5% of the total cohort respectively (Figure 4.2 and Table 4.1).

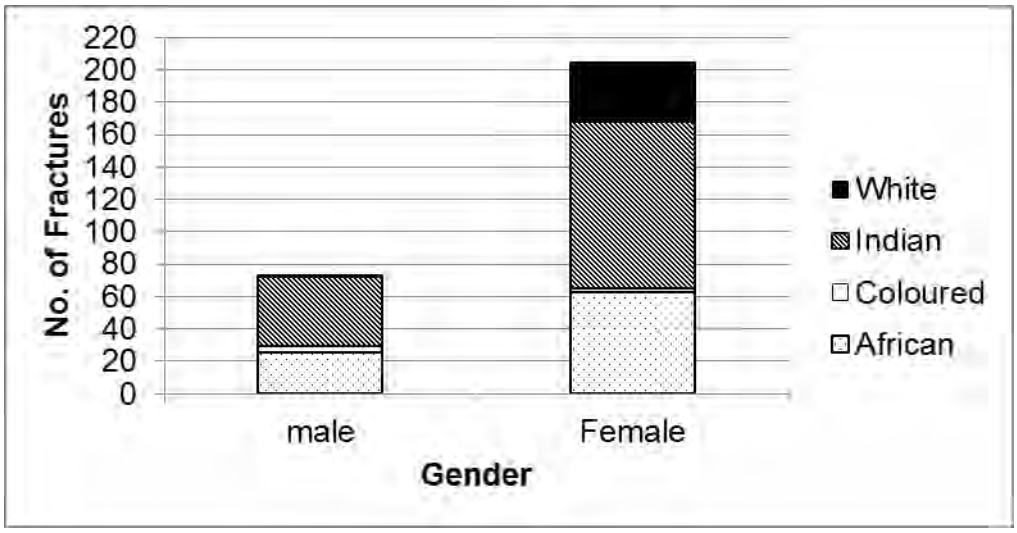

Figure 4.2 Gender and ethnic distribution in minimal trauma hip fracture subjects (n=277)

The mean age of the total group was 75.9 ± 9.2 years with a range of 60 to 113 years and the female to male ratio was 2.8:1. The female to male ratio for the Indian

and African was similar at 2.4:1 and 2.5:1 respectively. Men were significantly younger than women in the total group (75.2 ± 9.3 years vs. 77.2 ± 8.8 years; $p < 0.0001$) as well as in the Indian subjects (70.1 ± 6.7 years vs. 75.8 ± 8.1 years; $p < 0.0001$). There was no significant difference in the African subjects and the number of White and Coloured males was too small to draw any conclusions. White women were the oldest at 80.6 ± 8.4 years (Table 4.1).

Table 4.1 Age and gender distribution of hip fracture subjects in the different ethnic groups (n = 277)

	Total (n=277)	**Male (n=73)**	**Female (n=204)**	**p-value**
African				
Age (mean ±SD)	76.5 ± 10.5	74.2 ± 12.3	77.4 ± 9.6	0.189
n (%)	87 (31.4%)	25 (28.7%)	62 (71.3%)	
Coloured				
Age (mean ±SD)	80 ± 8.6	80.5 ± 8.5	79.3 ± 10.6	**
n (%)	7 (2.5%)	4 (57.1%)	3 (42.9%)	
Indian				
Age (mean ±SD)	74.2 ± 8.1	70.5 ± 6.7	75.8 ± 8.1	*<0.0001
n (%)	146 (52.7%)	43 (29.5%)	103 (70.5%)	
White				
Age (mean ±SD)	80.2 ± 8.5	67	80.6 ± 8.4	**
n (%)	37 (13.4%)	1 (2.7%)	36 (97.3%)	
Total				
Age (mean ±SD)	75.9 ± 9.2	72.2 ± 9.3	77.2 ± 8.8	*<0.0001
n (%)	277 (100%)	73 (26.4%)	204 (73.6%)	

- ** Student's T-test not done as sample numbers small.

4.1.2 Distribution of hip fractures according to age, ethnicity and gender

The majority of hip fractures in Indians 31 (21.2%) were documented in the 75 - 79 years age group whereas most of the fractures in African and White subjects, 19 (21.8%) and 11 (29.7%) respectively were seen in subjects ≥ 85 years (Table 4.2 and Figures 4.3.a, 4.3.b and 4.3.c).

Table 4.2 Distribution of hip fractures according to age and ethnicity (n=277)

Age group (years)	Hip fractures n (%)				
	African (n=87)	Coloured (n=7)	Indian (n=146)	White (n=87)	Total (n=277)
60 - 64	13 (14.9)	0	20 (13.7)	2 (5.4)	35 (12.6)
65 - 69	10 (11.5)	1 (14.3)	23 (15.8)	4 (10.8)	38 (13.7)
70 - 74	12 (13.8)	1 (14.3)	31 (21.2)	2 (5.4)	46 (16.6)
75 - 79	17 (19.5)	1 (14.3)	31 (21.2)	8 (21.6)	57 (20.6)
80 - 84	16 (18.4)	2 (28.6)	24 (16.4)	10 (27)	52 (18.8)
≥ 85	19 (21.8)	2 (28.6)	17 (11.6)	11 (29.7)	49 (17.7)

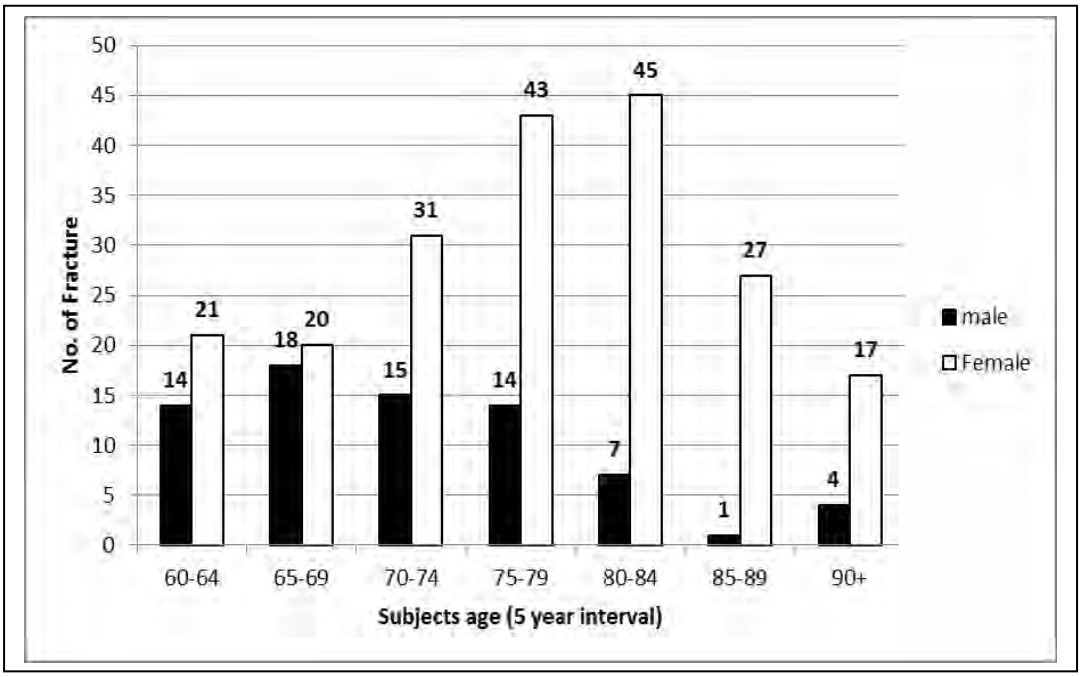

Figure 4.3.a Distribution of hip fractures by age and gender in total fracture cohort (n = 277).

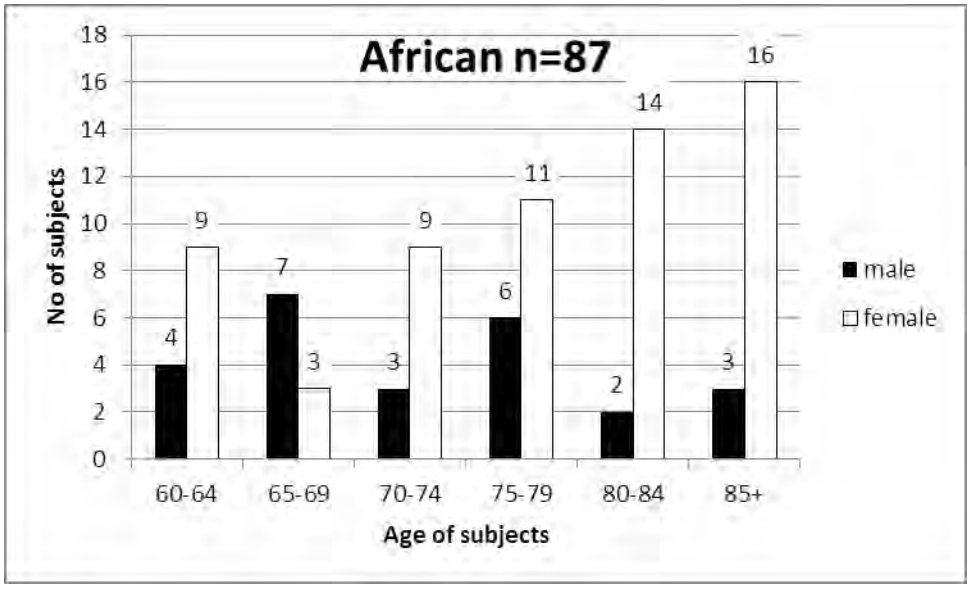

Figure 4.3.b Distribution of hip fractures by age and gender in the African fracture cohort (n = 87)

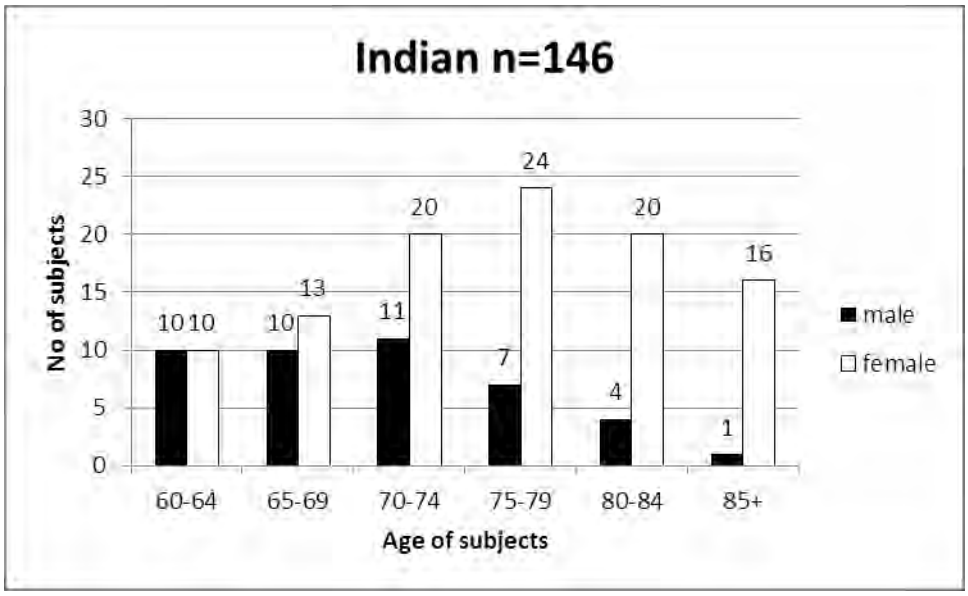

Figure 4.3.c Distribution of hip fractures by age and gender in the Indian fracture cohort (n = 146)

In further stratifying the 277 subjects into those 74 years and younger and those 75 years and older, men were more likely to have sustained a hip fracture at a younger age (≤ 74 years) compared to women (64.4%% vs. 35.3%; $p < 0.0001$). This difference was significant in the Indian subjects (72.1% vs. 41.7%; $p = 0.001$) but did not reach statistical significance in the Africans (56% vs. 33.9%; $p = 0.058$) and White subjects (Table 4.3).

Table 4.3 Frequency of hip fractures stratified by age, gender and ethnicity (n = 277)

Hip fracture subjects		**≤74 years n (%)**	**≥ 75years n (%)**	**p value**
All subjects (n = 277)	Women Men	72 (35.3) 47 (64.4)	132 (64.7) 26 (35.6)	*<0.0001
Indians (n = 146)	Women Men	43 (41.7) 31 (72.1)	60 (58.3) 12 (27.9)	*0.001
Africans (n = 87)	Women Men	21 (33.9) 14 (56)	41 (66.1) 11 (44)	0.057
Whites (n = 37)	Women Men	7 (19.4) 1 (100)	29 (80.6) 0	0.056
Coloureds (n = 7)	Women Men	1 (33.3) 1 (25)	2 (66.6) 3 (75)	0.846

4.2. Incidence rates of hip fractures

The incidence rates were calculated using the 230 subjects aged 60 years and older who presented with a hip fracture to one of the five selected public sector hospitals in eThekwini (the defined geographic area) in the period 1 August 2010 - 31 July 2011.

All hip fracture subjects presenting to a public health care facility in the eThekwini region are referred to one of the selected hospitals, which provide specialized orthopaedic services, for further assessment and management. The study therefore makes the assumption that all subjects presenting with a hip fracture (excluding private sector subjects) in the public sector in the eThekwini area will be represented in the numerator. For the denominator, age, gender and ethnic specific population statistics for the defined area (Table 4.4) were obtained from the 2007 South African population census [467].

Table 4.4 Population of eThekwini stratified by ethnicity, gender and age

	African		Coloured		Indian or Asian		White	
Age (years)	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**
60 - 64	15 437	25 239	858	1 174	10 009	13 458	7 220	9 644
65 - 69	8 102	18 820	718	957	7 980	9 837	6 899	8 234
70 - 74	5 062	13 307	603	625	3 444	7 046	4 341	5 980
75 - 79	2 946	8 361	456	706	2 264	4 133	3 548	4 174
80 - 84	1 240	4 494	3	249	1 170	1 289	1 920	2 612
≥ 85	1 024	4 208	3	107	618	901	1 645	2 970
Total	33 811	74 429	2 641	3 818	25 485	36 664	25 573	33 614

Adapted from Statistics South Africa Web page: www.statssa.gov.za

4.2.1 Crude Incidence Rate

The crude incidence rate for minimal trauma hip fractures was calculated according to formulae (Methodology section 3.12) and was 97.4 per 100 000 in the eThekwini public sector in subjects above the age of 60 years old. (Table 4.5 and Figure 4.4)

Table 4.5 Ethnic adjusted incidence rates for hip fractures in South Africa

Ethnic group	**Fractures (n)**	**At risk population (n)**	**ASR per 100 000**	**SA Standard Population**	**Expected**
	(1)	(2)	(1) / (2) = 3	(4)	(3) x (4) = 5
African	69	108 240	63.7	2 524 856	160 952 572
Coloured	5	6 459	77.4	305 296	23 633 380
Indian	125	62 149	201.1	112 703	22 667 903
White	31	59 187	52.4	827 243	43 327 982
Total	230	236 035	xxx	3 770 098	250 581 837
Crude rate (230 / 236 035) x 100 000 97.4 per 100 000			>	Ethnic adjusted incidence rate for SA 250 581 837 / 3 770 098 66.5 per 100 000	

The ethnic adjusted incidence rate for SA was 66.5 per 100 000. The highest rate of fractures were seen in the subjects of Indian descent at 201.1 per 100 000 followed by African at 63.7 per 100 000 and 52.4 per 100 000 in Whites (Table 4.5 and Fig.

4.4). The incidence rate in Whites is an under reflection due to a selection bias. The incidence rate in Coloureds was calculated to be 77.4 per 100 000. However there were very few Coloured subjects and the very small Coloured population in the eThekwini area makes it difficult to draw conclusions.

4.2.2 Age adjusted incidence rate

There was a steady increase in hip fracture rates with age; rising from 36.1 per 100 000 in the 60 - 64 years age group to 48.7 per 100 000 in the 65 - 69 years age group and by a co-efficient of 1.9 to 91.6 per 100 000 in the 70 - 74 year age group and 2.1 in the 75 - 79 years age group. The highest rate was noted in 80 - 84 years age group at 346.8 per 100 000. The overall age adjusted rate for SA was 109 per 100 000 (Table 4.6).

Table 4.6 Age adjusted incidence rates for all hip fracture subjects in South Africa

Age group	**Fractures (n)**	**At risk population (n)**	**ASR per 100 000**	**Co-efficient**	**SA Standard Population**	**Expected**
	(1)	(2)	(1) / (2) = 3		(4)	(3) x (4) = 5
60 - 64	30	83 039	36.1		1 157 686	41 824 420
65 - 69	30	61 548	48.7	1.3	962 197	46 899 834
70 - 74	37	40 409	91.6	1.9	665 096	60 898 691
75 - 79	51	26 588	191.8	2.1	480 086	92 088 107
80 - 84	45	12 976	346.8	1.8	263 796	91 482 891
85 +	37	11 475	322.4	0.9	241 237	77 784 479
Total	230	236 035	xxx		3 770 098	410 978 423
Crude rate (230 / 236 035) x 100 000 97.4 per 100 000			<	Age adjusted incidence of total fracture cohort 410 978 423 / 3 770 098 109 per 100 000		

4.2.3 Gender specific age adjusted incidence rate

The crude incidence rate in men was lower than in women; 68.5 per 100 000 compared to 133 per 100 000. The age adjusted hip fracture rate for men and women were similar and lowest in the 60 - 65 years age group at 35.8 per 100 000 and 36.4 per 100 000 respectively. In both genders the ASR increased with age but the coefficient for increase with age was lower in men. The highest incidence rates were documented in the 80 - 84 year old age group in both men and women (Tables 4.7 and 4.8)

Table 4.7 Age adjusted incidence rates for hip fractures in SA woman

Age group (years)	**Fractures (n)**	**At risk population (n)**	**ASR per 100 000**	**Co-efficient**	**SA Standard Population**	**Expected**
	(1)	(2)	(1) / (2) = 3		(4)	(3) x (4) = 5
60 - 64	18	49 515	36.4		663 670	24 126 144
65 - 69	17	37 848	44.9	1.2	567 122	25 473 140
70 - 74	25	26 958	92.7	2.1	423 211	39 247 255
75 - 79	39	17 374	224.4	2.4	316 968	71 150 869
80 - 84	39	8 644	451.2	2.0	176 113	79 458 665
85 +	33	8 186	403.1	0.9	170 533	68 746 506
Total	171	148 525	xxx		2 317 617	308 202 579
Crude rate (171 / 148 525) x 100 000 115.1 per 100 000			>	Female age adjusted incidence rate 308 202 579 / 2 317 617 133.0 per 100 000		

Table 4.8 Age adjusted incidence rates for hip fractures in SA men

Age group (years)	Fractures (n)	At risk population (n)	ASR per 100 000	Co-efficient	SA Standard Population	Expected
	(1)	(2)	(1) / (2) = 3		(4)	(3) x (4) = 5
60 - 64	12	33 524	35.8		494 016	17 683 427
65 - 69	13	23 699	54.9	1.5	395 075	21 671 695
70 - 74	12	13 450	89.2	1.6	241 885	21 580 818
75 - 79	12	9 214	130.2	1.5	163 118	21 243 933
80 - 84	6	4 333	138.5	1.1	39 281	5 439 326
85 +	4	3 290	121.6	0.9	70 704	8 596 231
Total	59	87 510	xxx		1 404 079	96 215 430
Crude rate (59 / 87 510) x 100 000 67.4 per 100 000			<	Male age adjusted incidence adjusted rate 96 215 430 / 1 404 079 68.5 per 100 000		

4.2.4. Ethnic and age adjusted incidence rates

The incidence rates were calculated for the Indian, African and White population groups only as the number of Coloureds were too small for analysis. The crude and the age adjusted rates were higher in Indians at 207.2 per 100 000 compared to Whites (women only) at 91.6 per 100 000. The incidence rate was lowest in Africans at 73.3 per 100 000 (Tables 4.9, 4.10 and 4.11 and Figure 4.4).

The highest hip fracture rate was noted in Indians and Africans older than 85 + year age group 855.8 per 100 000 and 305.8 per 100 000 respectively, whereas White women fractured at the highest rate in the age group 80 - 84 years. The number of White fracture cases in the study cohort was small and the results must be interpreted with caution.

Table 4.9 Age adjusted incidence rates for hip fractures in SA Indians

Age groups (years)	**Fractures (n)**	**At risk population (n)**	**ASR per 100 000**	**Co-efficient**	**SA Standard Population**	**Expected**
	(1)	(2)	(1) / (2) = 3		(4)	(3) x (4) = 5
60 - 64	18	23 467	76.7		42 239	3 239 877
65 - 69	19	17 817	106.6	1.4	31 047	3 310 844
70 - 74	26	10 490	247.9	2.3	19 564	4 849 037
75 - 79	29	6 397	453.3	1.8	12 026	5 451 837
80 - 84	20	2 459	813.3	1.8	4 776	3 884 506
85 +	13	1 519	855.8	1.1	3 051	2 611 126
Total	125	62 149	xxx		112 703	23 347 226
Crude rate (125 / 108 240) x 100 000 201.1 per 100 000			<		Indian age adjusted incidence rate 23 347 226 / 112 703 207.2 per 100 000	

Table 4.10 Age adjusted incidence rates for hip fractures in SA Africans

Age groups (years)	Fractures (n)	At risk population (n)	ASR per 100 000	Co-efficient	SA Standard Population	Expected
	(1)	(2)	(1) / (2) = 3		(4)	(3) x (4) = 5
60 - 64	10	40 676	24.6		753 084	18 514 210
65 - 69	7	26 922	26.0	1.1	646 698	16 814 821
70 - 74	8	18 369	43.6	1.7	438 411	19 093 516
75 - 79	14	11 307	123.8	2.8	330 744	40 951 764
80 - 84	14	5 734	244.2	2.0	126 303	30 837 844
85 +	16	5 232	305.8	1.3	181 214	55 417 125
Total	69	108 240	xxx		2 476 454	181 629 281
Crude rate (69 / 108 240) x 100 000 63.8 per 100 000				<	African age adjusted incidence rate 181 629 281 / 2 476 454 73.3 per 100 000	

Table 4.11 Age adjusted incidence rates for hip fractures in SA White women

Age in years	Fractures (n)	At risk population (n)	ASR per 100 000	Co efficient	SA Standard Population	Expected
Formula	(1)	(2)	(1) / (2) = 3		(4)	(3) x (4) = 5
60 - 64	2	9 644	20.7		128 970	2 674 616
65 - 69	3	8 234	36.4	1.8	105 920	3 859 121
70 - 74	2	5 980	33.4	0.9	83 414	2 789 766
75 - 79	7	4 174	167.	5	60 262	10 106 229
80 - 84	10	2 612	382.8	2.3	40 717	15 588 438
85 +	6	2 970	202.0	0.5	30 559	6 173 535
Total	30	33 614	xxx		449 842	41 191 705
Crude rate (30/33 614) x 100 000 89.2 per 100 000			<		White age adjusted incidence rate 41 191 705/ 449 842 91.6 per 100 000	

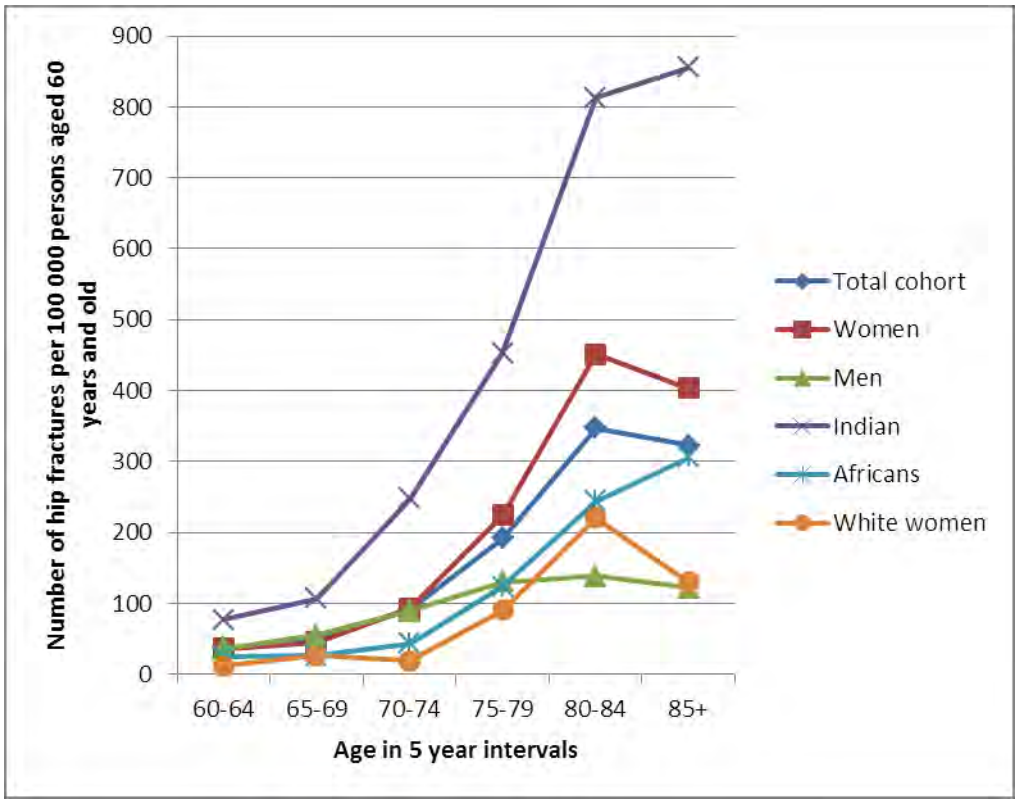

Figure 4.4 Age adjusted incidence rates for hip fractures by gender and ethnicity in South Africa (n=230)

4.3. Case control study; Assessment of risk factors for osteoporotic hip fractures

Two hundred subjects with hip fractures who consented to participate in the prospective longitudinal one year study were assessed for risk factors for osteoporosis and hip fractures, and compared to 200 age (± 3 years), gender and ethnic matched controls using conditional logistic regression for matched data.

4.3.1 Risk assessment in total hip fracture cohort

4.3.1.1 Socio-Demographic characteristics

Age, gender and ethnicity

The mean age of the hip fracture subjects was 74.3 ± 8.8 years and that of controls was 73.0 ± 8.1 years. There were 144 (72%) women and 56 (28%) men with a ratio of 2.6:1. The majority of subjects were Indians 110 (55%) followed by Africans 66 (33%), Whites 21 (10.5%) and 3 (1.5%) were Coloured. Indian women were the largest cohort at 76 (38%), followed by African women 46 (23%).

Social Status: employment, housing and education

All hip fracture subjects and the majority of control subjects (95.5%) were retired and were receiving an old age pension. All the control subjects and 86.5% of the hip fracture subjects lived in formal housing, while 7.5% of hip fracture subjects lived in

traditional housing, 5% in informal housing and 1% in hostels. In the univariate analysis, hip fracture subjects were significantly more likely not to have had any schooling (37% vs 12.5%; p < 0.0001; OR 11.56, 95%CI 4.38-30.49) or only a primary school education (32.5% vs 28.5%; p < 0.0001; OR 3.89, 95%CI 1.60-9.48) compared to control subjects.

Anthropometric measures

Weight and height were recorded in 136 hip fracture subjects and 200 controls. Weight and height could not be recorded in 64 hip fracture subjects who were unable to stand independently by the time of discharge.

There was no significant difference in height, but hip fracture subjects had a significantly lower weight compared to controls (54.7 ± 13.8kg vs. 72.0 ± 16.2kg; p < 0.0001; OR 0.906, 95%CI 0.87-0.94). This difference might be an underestimate as subjects who were not weighed may potentially have had a lower body weight. In the conditional logistic regression, for every one kilogram (1kg) decrease in weight the odds of hip fracture increased by approximately 10%.

Body mass index was also significantly lower in hip fracture subjects compared to matched control subjects (22.7 ± 5.7 kg/m^2 vs. 29.2 ± 6.0 kg/m^2; p < 0.0001; OR 0.786, 95%CI 0.7-0.87) (Figure 4.5 and 4.6). When the BMI was categorized according to the WHO classification, only 1.5% (3 cases) of control subjects were underweight compared to 21.3% of hip fracture subjects (p < 0.0001) or had a

normal BMI (55.9% vs. 25% p < 0.0001) compared to controls. The three controls with a low BMI were all African women.

Only 8.8% of hip fracture subjects had BMI of ≥ 30 compared to 40.5% in the control group. (Figure 4.5 and 4.6). Hip fracture subjects with a BMI of ≥ 30 had a higher survival rate and only one subject died in that group, however there was no gender difference (5 females vs 7 males), but Whites (19%) were more likely to be obese compared to Indians (3.6%) and Africans (7.5%).

When used as a continuous variable, every two unit decrease in BMI increased the odds of a hip fracture by 1.61 (exp (2×0.2409) = exp (0.4818) =1.61) and a 3 unit decrease in BMI increased the odds to 2.06. This needs to be interpreted with caution as BMI was not calculated for all hip fracture subjects.

There was a significant negative correlation between age and weight and between age and BMI in hip fracture subjects (p <0.0001 respectively), but not in control subjects (p = 0.792 and 0.916) respectively.

Co-morbid diseases and secondary medical causes of osteoporosis

Compared to hip fracture subjects, control subjects reported a significantly higher frequency of hypertension (80% vs. 60%; p < 0.0001; OR 3, 95%CI 1.81-4.98), diabetes mellitus (38.5% vs. 28.5%; p = 0.043; OR 0.75, 95%CI 0.44-1.28) arthritis (47.5% vs. 27.5%; p < 0.0001; OR 0.431, 95%CI 0.28-0.67), and chronic backache (17% vs. 7%; p = 0.002; OR 0.379, 95%CI 0.19-0.76) (Table 4.12). Other secondary

medical causes were infrequent in both groups with hip fracture subjects having a greater frequency of cerebrovascular disease (7.5% vs. 2%) while control subjects reported ischemic heart disease (8% vs. 4%); there were no statistical differences between the groups for secondary conditions.

Control subjects with osteoporosis were not enrolled in the study and a prior history of osteoporosis was obtained in 3.5% of hip fracture subjects. Although malignancy (5% vs. 1.5%; p = 0.052) and immobilization (3% vs. 0.5%; p = 0.059) were more common in hip fracture subjects, these did not reach significance possibly due to the small numbers. Rheumatoid arthritis was significantly more common in control subjects (4.5% vs. 1%; p = 0.034; OR 0.22, 95%CI 0.05-1.03) and this may be due to a selection bias.

The use of bone toxic drugs was infrequent in hip fracture subjects and controls. There was no statistical difference in the use of long term glucocorticoids (greater than three months) which were used by 5.5% of hip fracture subjects and 3.5% of controls, anti-epileptics in 5% and 1.5% and antidepressants in 3.5% and 0.5% of hip fracture subjects and controls respectively. Only one subject with hip fractures reported use of long term heparin.

Table 4.12 Baseline socio-demographic characteristics of hip fracture and control subjects (n=200)

	Fracture subjects	Control subjects	p-value	OR	95% CI
Weight (kg) mean ±SD	54.7 ± 13.7 (n=136)	71.0 ± 16.5	*<0.0001	0.906	0.87 - 0.94
Height (cm) mean ± SD	155.4 ± 9 (n=136)	153.7 ± 7.8	0.203	0.998	0.96 - 1.03
BMI (kg/cm^2) mean ± SD	22.6 ± 5.1 (n=136)	30.2 ± 6.4 (n=200)	*<0.0001	0.786	0.71 - 0.87
BMI n (%) 1 Reference category BMI ≥ 30					
BMI < 19	29 (21.3)	3 (1.5)	*<0.0001	43.993	8.78 -220.39
BMI 19 - 24.9	76 (55.9)	49 (24.5)		7.432	3.24 - 17.02
BMI 25 - 29.9	19 (13.9)	67 (33.5)		1.989	0.79 - 5.01
BMI ≥ 30	12 (8.8)	81 (40.5)		1	1
Educational level (n=200) n (%) 1 Reference category Std. 10 plus					
No schooling	74 (37)	25 (12.5)	*<0.0001	11.560	4.38 - 30.49
< Std. 3	65 (32.5)	57 (28.5)		3.890	1.60 - 9.48
Std. 6-7	51 (25.5)	86 (43)		1.810	0.77 - 4.24
Std. 10 plus	10 (5)	32 (16)		1	1
Hypertension	120 (60)	160 (80)	*<0.0001	3.000	1.81 - 4.98
Diabetes mellitus	57 (28.5)	77 (38.5)	*0.043	0.749	0.44 - 1.28
Arthritis	55 (27.5)	95 (47.5)	*<0.0001	0.431	0.28 - 0.67
Chronic back pain	14 (7)	34 (17)	*0.002	0.379	0.19 - 0.76
Osteoporosis	7 (3.5)	0 (0)	n/a	n/a	n/a
Rheumatoid arthritis	2 (1)	9 (4.5)	*0.034	0.222	0.05 - 1.03
Malignancy	10 (5)	3 (1.5)	0.052	3.456	0.94 - 12.75
Prolonged immobilization	6 (3)	1 (0.5)	0.059	0.17	0.020 - 1.38
Glucocorticoids > 3/12	11 (5.5)	7 (3.5)	0.468	0.700	0.27 -1.84

- Results expressed as total numbers with n (%)
- Controls are matched for age gender and ethnicity

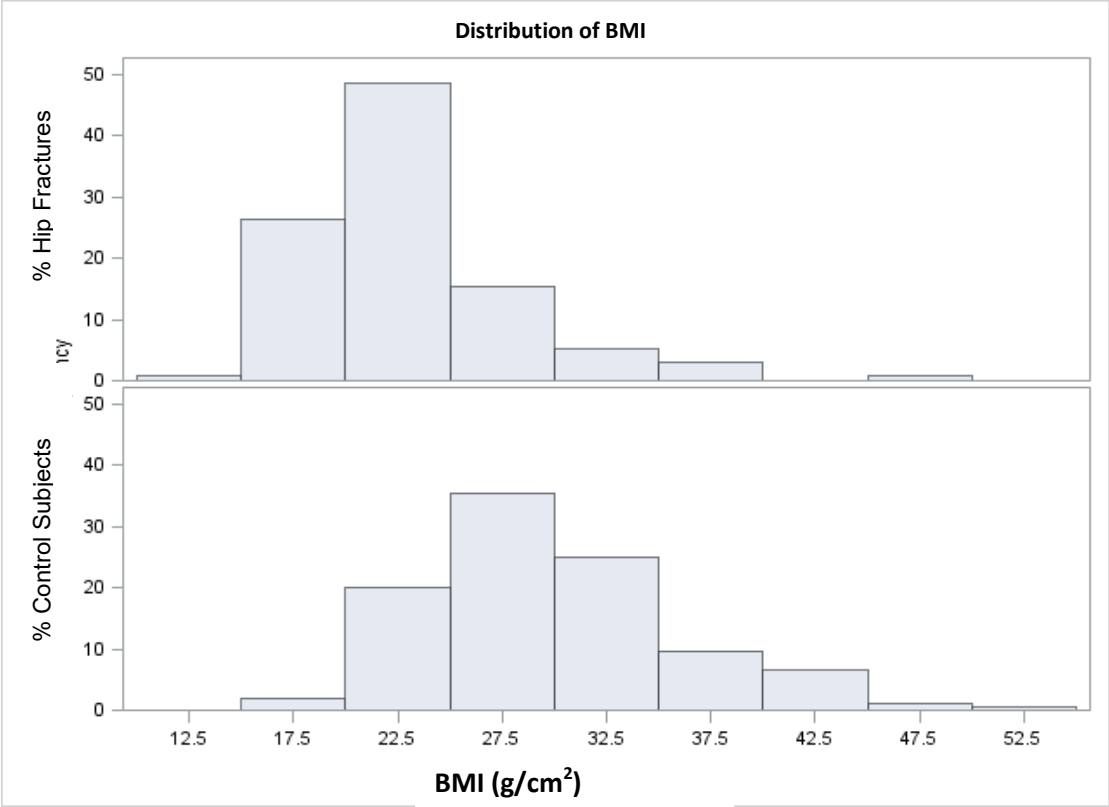

Figure 4.5 Distribution of body mass index in hip fracture and control subjects.

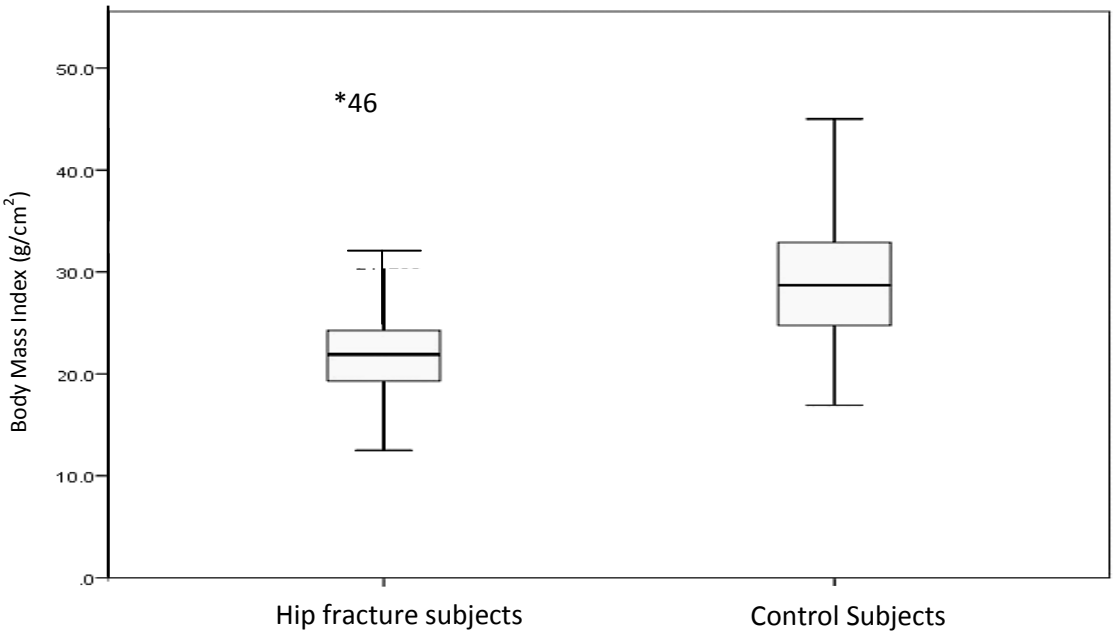

Figure 4.6 Comparison of the mean BMI in hip fracture and control subjects (22.6 ± 5.1 vs 30.2 ± 6.4; p <0.0001)

4.3.1.2 Clinical risk factors for osteoporosis and fractures

The prevalence of established risk factors for osteoporotic hip fractures is shown in Table 4.13. Based on history and examination secondary medical conditions were infrequent and no further analysis was undertaken.

Gynaecological history and use of hormone replacement therapy

Comparing female hip fracture subjects to female controls, no difference was observed in the mean age at menarche (13.7 ± 1.6 years vs. 14.0 ± 1.6 years; p

=0.290; OR 0.902, 95%CI 0.79-1.04) and menopause (47.9 ± 6.2 years vs 47.3 ± 6.8 years; p = 0.992; OR 1.015, 95%CI 0.98-1.05), or the prevalence of premature menopause (23.5% vs 27.5%; p = 0.061). There was no difference in parity between the hip fracture and control groups (3.5 ± 2.4 children vs. 3.7 ± 2.4 children; p =0.964; OR 0.885, 95%CI 0.10-0.25) and the number of subjects with greater than 3 pregnancies was similar in both hip fracture and control subjects.

The use of hormone replacement treatment was significantly less frequent in hip fracture subjects than controls (4.9% vs. 15.3%; p < 0.001; OR 0.201, 95%CI 0.08-0.49). In a conditional logistic regression model for matched data, the non-use of HRT was associated with a 5 times greater odds of sustaining a hip fracture. The use of contraception was not documented.

Cognitive changes

Self-reported poor memory and concern expressed by a family member regarding memory loss were significantly more frequent in hip fracture subjects (39% vs. 22.5%; p < 0.001; OR 2, 95%CI 1.29-3.1) and (34% vs. 18.5%; p < 0.001; OR 2.25, 95%CI 1.39-3.64) respectively. While hip fracture subjects were also more likely to report difficulty in completing familiar tasks, there was no significant difference between the groups. No formal memory assessments were undertaken.

Falls

Although a significant number of both hip fracture and control subjects reported prior falls there was no significant difference between the two groups except that sideways falls were significantly more common in the hip fracture subjects (70% vs. 48.3%; p = 0.016; OR 3.5, 95%CI 1.15-10.63). There was no significant difference in the number of falls (single or multiple) in the previous year or last two years between hip fracture and control subjects. Most of the previous falls occurred more than a year ago and 55% of hip fracture subjects had no prior history of falls before the present fall which resulted in the hip fracture.

Although there was no difference in the number of falls or in the number of multiple falls between hip fracture subjects and control subjects; analysis of risk factors in the EFST surprisingly showed control subjects were more likely to report near falls, would need assistance to stand up after a potential fall and seek medical attention for a fall. Control subjects also reported more visual problems, problems with the lower limbs and gait, limitation of activities and medication problems (Table 4.13).

Past history of fractures

Childhood fractures were uncommon in both hip fracture and control subjects.

Prior fragility fractures were significantly more common in hip fracture subjects (27.5% vs. 8.5%; p < 0.0001; OR 4.083, 95%CI 2.27-7.34). Fifteen (7.5%) of hip fracture subjects had had a previous hip fracture. In both groups the most common

site for a prior fragility fracture was the wrist accounting for 32.7% and 38.9% of fractures in the hip fracture and control groups respectively. Other sites included the ankle, humerus and hand (self-reported after minimal trauma).

Despite the majority of subjects with a prior fracture in the hip fracture group (94.5%) having received acute care for the previous fracture only one subject (1.9%) was screened and treated for osteoporosis. Control subjects who were either screened or treated for osteoporosis were excluded from the study.

Self-reported vertebral fractures

Self-reported VF and kyphosis were uncommon in both hip fracture and control groups (1% vs. 3.8% and 0.5% vs. 2% respectively) and not significantly different.

Family history of osteoporosis and maternal history of hip fracture

A family history of osteoporosis and maternal history of fractures was reported significantly less commonly by hip fracture subjects than by controls; 3.5% vs. 11.5%; p = 0.002; OR 0.266, 95%CI 0.1-0.63 and 5.5% vs. 11.5%; p = 0.034; OR 0.427, 95%CI 0.20-0.90 respectively.

Lifestyle factors

Hip fracture subjects were significantly more likely to report being extremely active than controls (37.5% vs. 12%; $p < 0.0001$; OR 5.118, 95%CI 2.41-10.85) and to report exercising for more than 30 minutes a day (46% vs. 15.5%; $p < 0.0001$; OR 0.218, 95%CI 0.13-0.37).

Although there was a higher mean consumption of caffeine in hip fracture subjects this did not reach statistical significance ($p = 0.059$). There was also no difference in the mean calcium intake, calcium and vitamin D supplementation and sunlight exposure in the two groups.

Hip fracture subjects were significantly more likely to be current smokers (18% vs. 10.5%; $p = 0.047$; OR 1.784, 95%CI 0.10-3.20), to report current alcohol consumption (15.5% vs 4%; $p < 0.0001$; OR 11.00, 95%CI 2.59-46.78) and have a significantly higher average daily consumption (1.1 ± 2.16 drinks per day vs 0.1 ± 6.8 drinks per day; $p = 0.001$).

Table 4.13 Risk factors for osteoporosis in hip fracture and control subjects

	Fracture subjects n=200	Control Subjects n=200	p-value	OR	95%CI
History of falls	90 (45)	87 (43.5)	0.764	1.107	0.75 - 1.64
Sideways falls	63 (70)	42 (48.3)	*0.016	3.500	1.15 - 10.6
Problems with memory	78 (39)	45 (22.5)	*0.001	2.000	1.29 - 3.10
Family report of a memory problem	68 (34)	37 (18.5)	*0.001	2.250	1.39 - 3.64
Childhood fracture	12 (6)	10 (5)	0.533	0.934	0.45 - 1.93
Fragility fracture ≥ 40 years	55 (27.5)	17 (8.5)	*<0.0001	4.083	2.27 - 7.34
Self-reported VF	2 (1)	8 (3.8)	0.132	2.235	0.05 - 1.07
Family history of osteoporosis	7 (3.5)	23 (11.5)	*0.002	0.266	0.11 - 0.63
Maternal history of hip fracture	11 (5.5)	23 (11.5)	*0.034	0.427	0.20 - 0.90
Caffeine (cups/day) mean ± SD	2.3 ± 1.3	2.0 ± 1.6	0.059	1.108	0.96 - 1.28
Sunlight (minutes per day) mean ± SD	28.0 ± 47.7	28.6 ± 55.1	0.911	1.000	1.00
Self-reported activity level **1 Reference category Sedentary**					
Extremely active	75 (37.5)	24 (12)	*<0.0001	5.118	2.42 - 10.85
Moderately active	43 (21.5)	64 (32)	0.120	1.304	0.66 - 2.58
Mildly activity	65 (32.5)	85 (42.5)	0.065	1.203	0.59 - 2.46
Sedentary	17 (8.5)	27 (13.5)	1	1	1
Smoking	36 (18)	21 (10.5)	*0.047	1.784	1.00 - 3.20
Alcohol	31 (15.5)	8 (4)	*<0.0001	11.00	2.59 - 46.78
Calcium intake (mg/day)	432.6± 230.4	473.2± 270.2	0.108	1.000	1.00

- Results expressed as total numbers with n (%)
- Controls are matched for age gender and ethnicity

Table 4.14 The prevalence of risk factors for falls in hip fracture and control subjects

	Fracture subjects (n = 200)	Control subjects (n = 200)	p-value	OR	95% CI
Any near falls	63 (31.5)	110 (55)	*<0.0001	2.600	1.71 – 4.00
Reported any falls	46 (23)	62 (21)	*0.059	1.531	0.98 - 2.39
Sought medical attention for fall	41 (20.5)	66 (33)	*0.003	2.040	1.26 - 3.29
Need help up after a fall	84 (42)	113 (56.5)	*0.007	0.594	0.40 - 0.88
Limited activities	50 (25)	80 (40)	*0.001	0.492	0.32 - 0.752
Visual problems	143 (71.5)	164 (82)	*0.016	1.750	1.1 - 2.78
Seeing different depths	78 (39)	98 (49)	*0.037	1.556	1.02 - 2.36
Sensitivity to light	56 (28)	98 (49)	*<0.0001	0.411	0.27 - 0.63
Numbness or tingling in feet	50 (25)	94 (47)	*<0.0001	0.373	0.24 - 0.58
Uneven footing?	66 (33)	102 (51)	*<0.0001	0.424	0.27 - 0.66
>3 prescription medication	75 (37.5)	132 (66)	*<0.0001	3.528	2.25 - 5.54
Medication to control heart rhythm	14 (7)	35 (17.5)	*0.002	2.750	1.42 - 5.32
Recent changes to medications	13 (6.5)	6 (3)	0.071	2.750	0.88 - 8.64
Activity limited by health problems	32 (16)	64 (32)	*<0.0001	2.571	1.55 - 4.26
Chose not to use a gait aid	21 (10.5)	11 (5.5)	0.106	0.550	0.26 - 1.15
Concerns in transferring	29 (14.5)	48 (24)	*0.007	0.488	0.29 - 0.83
Leg tire easily when walking	79 (39.5)	129 (64.5)	*<0.0001	0.346	0.23 - 0.53
Activity limited by pain	70 (35)	105 (52.5)	*<0.0001	0.418	0.27 - 0.65

- Results expressed as total numbers with n (%)
- Controls are matched for age gender and ethnicity

4.3.1.3 Bone mineral density in hip fracture subjects and controls

A total of 116 hip fracture subjects and 199 control subjects had a DXA scan. Of the 84 hip fracture subjects who did not have a DXA scan 35 died before their 3 month follow up visit, 29 were unable to come to hospital and were followed up telephonically and 14 were lost to follow up. A further 4 subjects did not have a DXA scan due to technical reasons (1 had a recent barium meal, 1 was unable to lie down and two refused).

There was no difference in the age, gender or ethnic distribution between hip fracture subjects who did not have radiology investigations compared to those who did. However a significantly higher mortality rate (45 (53.6%) vs 22 (18.0%); $p < 0.0001$) was seen in fracture subjects who did not do their radiology investigations.

Hip fracture subjects had a significantly lower aBMD measurements compared to controls at the total hip (0.650 ± 0.136 g/cm^2 vs. 0.879 ± 0.163 g/cm^2; $p < 0.0001$), femoral neck (0.518 ± 0.106 g/cm^2 vs. 0.713 ± 0.127 g/cm^2; $p < 0.0001$) and lumbar spine (0.701 ± 0.173 g/cm^2 vs. 0.848 ± 0.183 g/cm^2; $p < 0.0001$), (Figures 4.7 and 4.8 and Table 4.15).

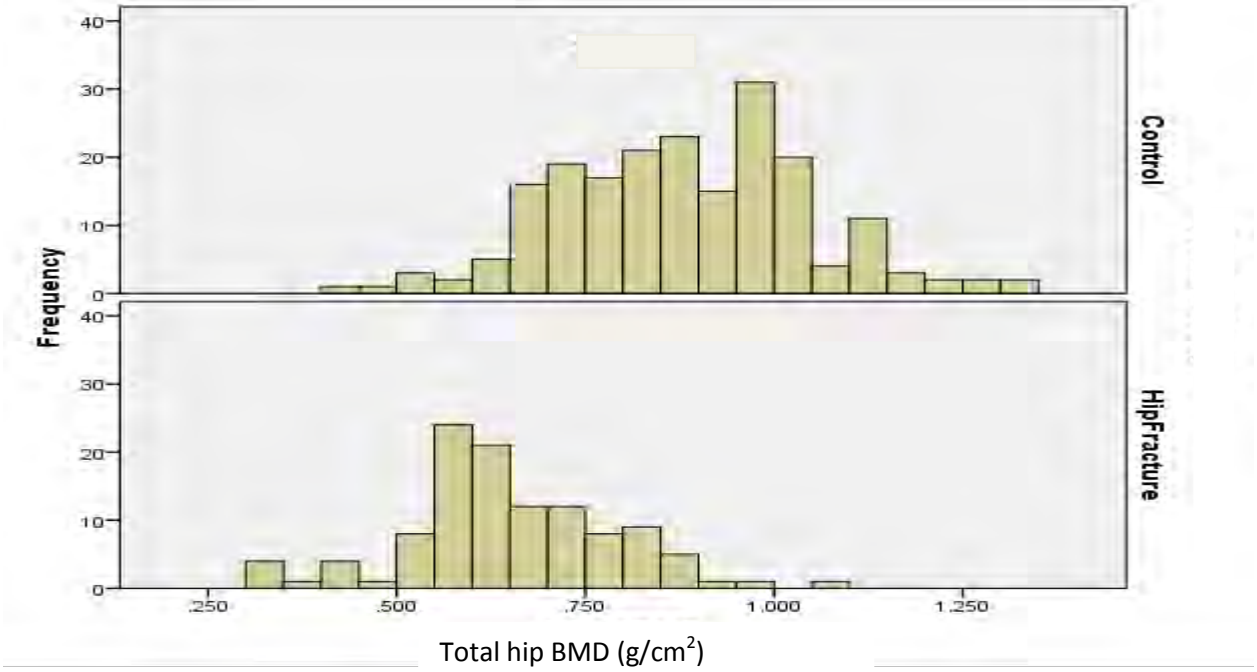

Figure 4.7 Distribution of total hip aBMD in hip fracture subjects (n=112) and control subjects (n=198) (0.650 ± 0.136 g/cm^2 vs. 0.879 ± 0.163 g/cm^2; p < 0.0001)

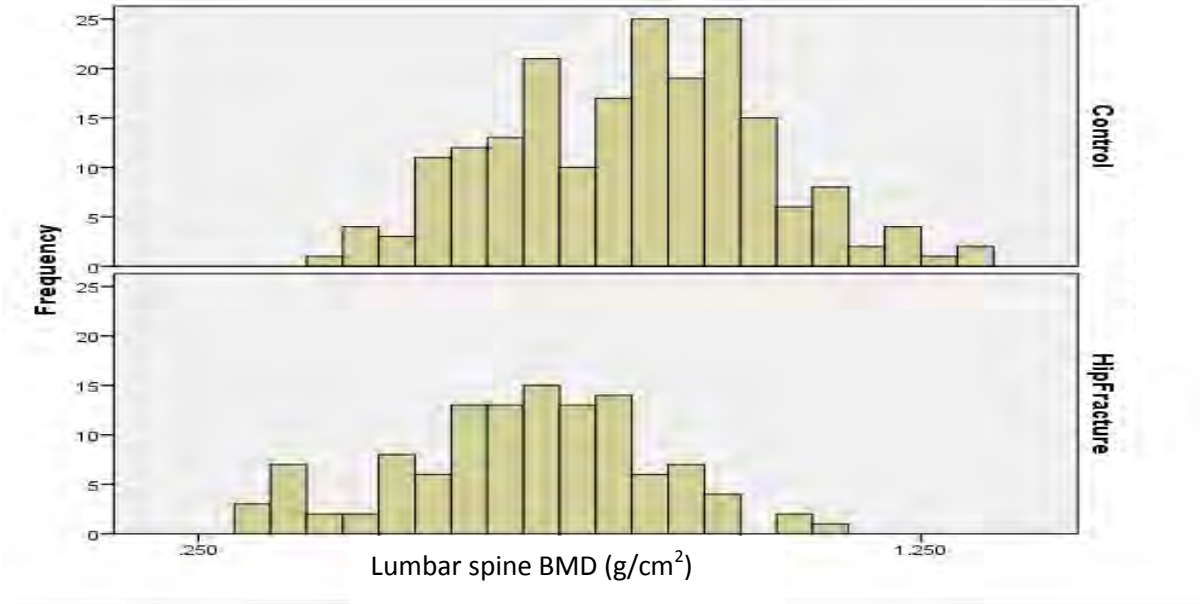

Figure 4.8 Distribution of lumbar spine aBMD in hip fracture subjects (n=116) and control subjects (n=198) (0.701 ± 0.173 g/cm^2 vs. 0.848 ± 0.183 g/cm^2; p < 0.0001)

The calculated mean BMAD at the lumbar spine and total hip remained significantly lower in hip fracture subjects than control subjects; 0.199 ± 0.036 g/cm^3 vs. 0.244 ± 0.041 g/cm^3; $p < 0.0001$ and 0.118 ± 0.092 g/cm^3 vs. 0.143 ± 0.025 g/cm^3; $p < 0.003$, respectively.

The T - score was also significantly lower in hip fracture subjects at the total hip (-2.91 ± 0.85 vs. -1.26 ± 1.25; $p < 0.0001$) and the lumbar spine (-2.99 ± 1.29 vs. -1.26 ± 1.25; $p < 0.0001$).

Table 4.15 Bone mineral density in hip fracture and control subjects

Site	Fracture subjects (n= 116)	Control subjects (n= 199)	p-value
Total spine L1 - L4 (g/cm^2)	0.701 ± 0.173 (n= 116)	0.848 ± 0.183 (n= 199)	*<0.0001
Femoral Neck (g/cm^2)	0.518 ± 0.106 (n= 78)	0.713 ± 0.127 (n= 136)	*<0.0001
Total hip (g/cm^2)	0.650± 0.136 (n= 112)	0.879 ± 0.163 (n= 198)	*<0.0001
Spine BMAD (g/cm^3)	0.199 ± 0.036 (n= 81)	0.244 ± 0.041 (n= 137)	*<0.0001
Hip BMAD (g/cm^3)	0.118 ± 0.092 (n= 73)	0.143 ± 0.025 (n= 136)	*0.003
Spine T - Score	-2.99 ±1.29 (n= 111)	-1.23 ± 1.44 (n= 198)	*<0.0001
Hip T - Score	-2.91 ± 0.85 (n= 107)	-1.26 ± 1.25 (n= 200)	*<0.0001

- BMD reported as mean ± SD

The vast majority of hip fracture subjects had a mean T – score value, according to the WHO, in the osteoporotic range compared to control subjects (85.3% vs 29.1%). The majority of controls (38.7%) had a normal BMD or osteopaenia (32.2%) (Table 4.16). In contrast only three hip fracture subjects had a normal BMD. They were all women, two were Indian and one was African, and all three were alive at one year. No other differentiating or protective features were identified in these three subjects.

Table 4.16 Bone mineral density in hip fracture and control subjects according to WHO classification [168]

Categories	Fracture subjects (n= 116)	Control subjects (n= 199)	p-value
Normal BMD (%)	2.6	38.7	*0.0012
Osteopaenia (%)	12.1	32.2	
Osteoporosis (%)	85.3	29.1	

Age and BMD

There was an inverse correlation between age and hip BMD ($p = 0.025$) and lumbar spine BMD ($p < 0.001$) in the total cohort. However the inverse correlation of BMD with age in fracture subjects was noted only at the hip ($p = < 0.0001$) and not at the lumbar spine ($p = 0.190$). In contrast, in control subjects there was no association between age and hip BMD ($p = 0.324$) but there was a significant inverse correlation between age and lumbar spine BMD ($p < 0.0001$) (Figure 4.9.a, 4.9.b and 4.9.c)

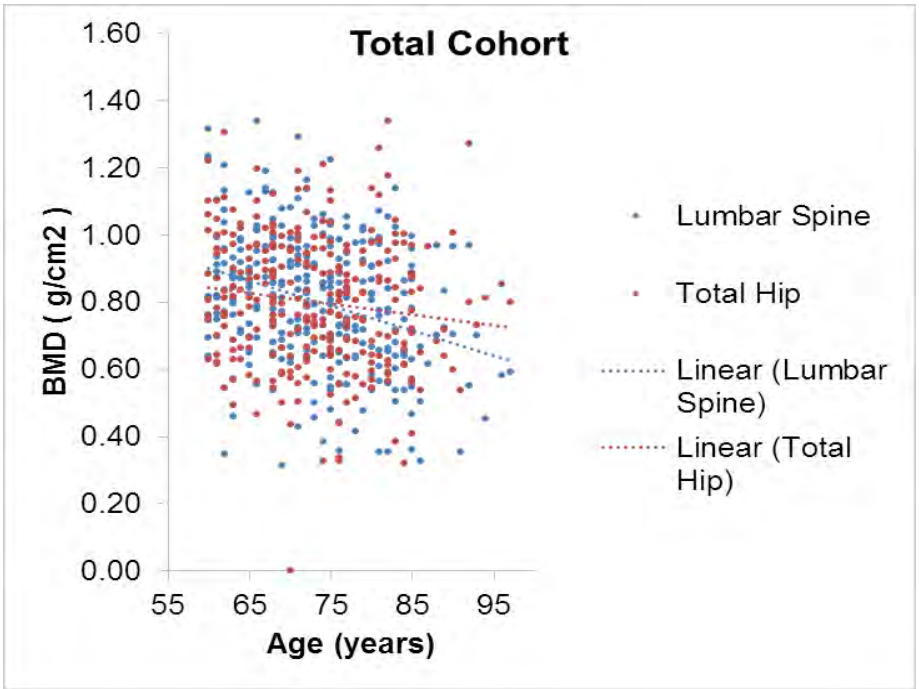

Figure 4.9.a Correlation between age and total hip (p = 0.025) and lumbar spine (p < 0.001) BMD in the total cohort (n = 310).

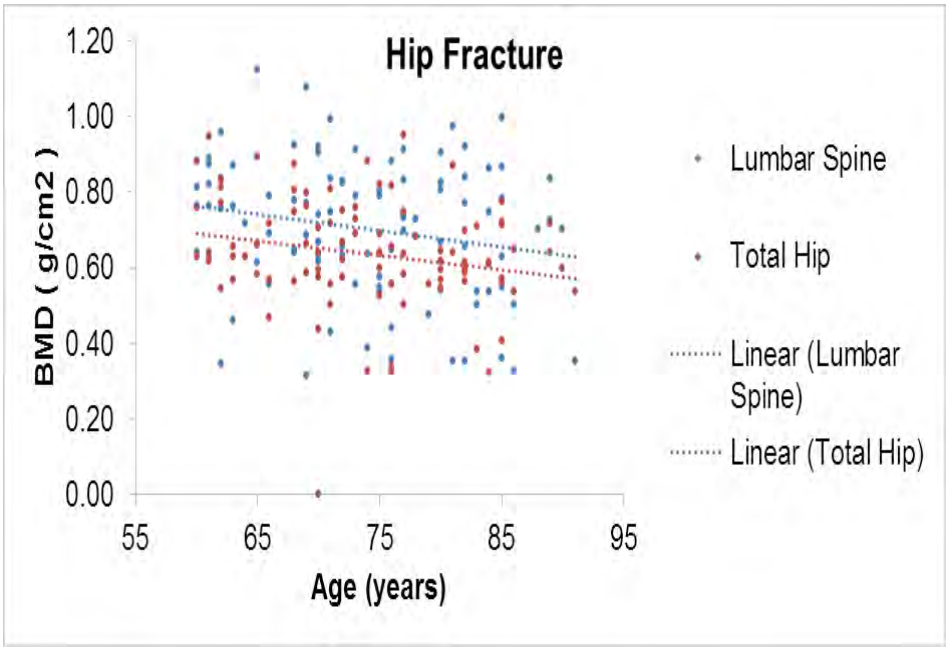

Figure 4.9.b Correlation between age and total hip (p < 0.0001) and lumbar spine BMD (p = 0.190) in hip fracture subjects (n = 112).

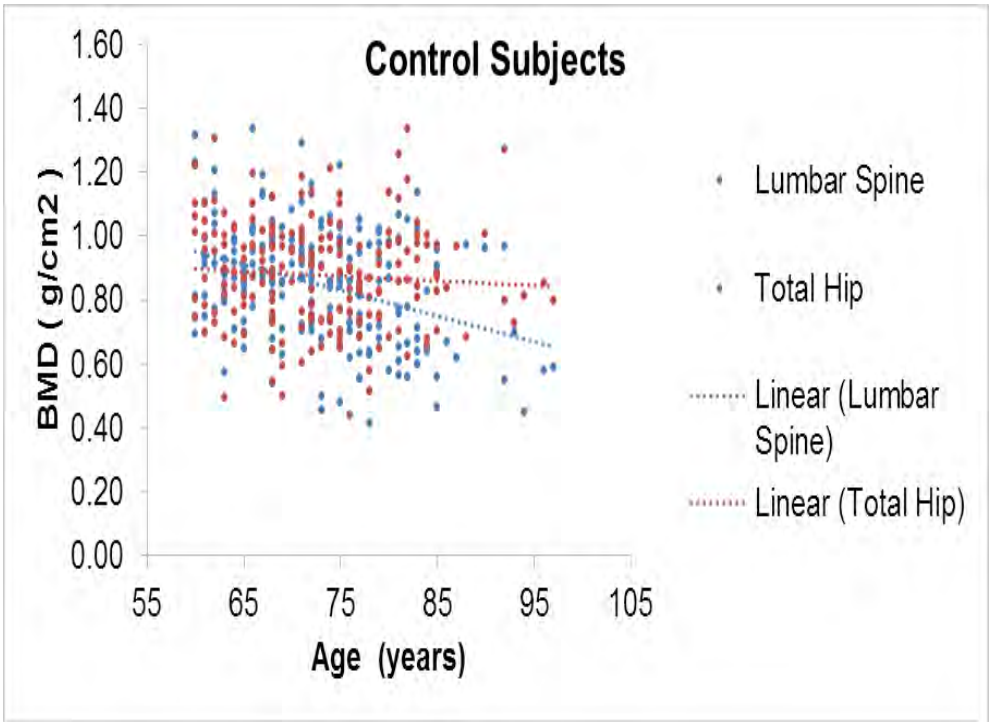

Figure 4.9.c Correlation between age and total hip (p = 0.324) and lumbar spine (p < 0.001) BMD in control subjects (n = 198).

Weight, BMI and BMD

In the total cohort (n=336) and the hip fracture subjects there was an association between weight, BMI and BMD, despite the regression corrected for mean (R^2) not being significant. In the total (n=336) and fracture cohorts (n=116) both weight and BMI correlated with hip (p <0.0001) and lumbar spine BMD (p <0.0001) (Figure 4.10.a, 4.11.a, 4.10.b and 4.11.b). In control subjects there was no association between weight and hip (p =0.160) or lumbar spine BMD (p = 0.792) (Figure 4.10.c) nor was there a correlation between BMI and BMD in control subjects at the hip (p =0.164) or lumbar spine (p =0.916) (Figure 4.11.c).

The correlation of age, weight and BMI to BMD for men and women and different ethnic groups was not conducted as the sample size numbers were too small to draw significant conclusions.

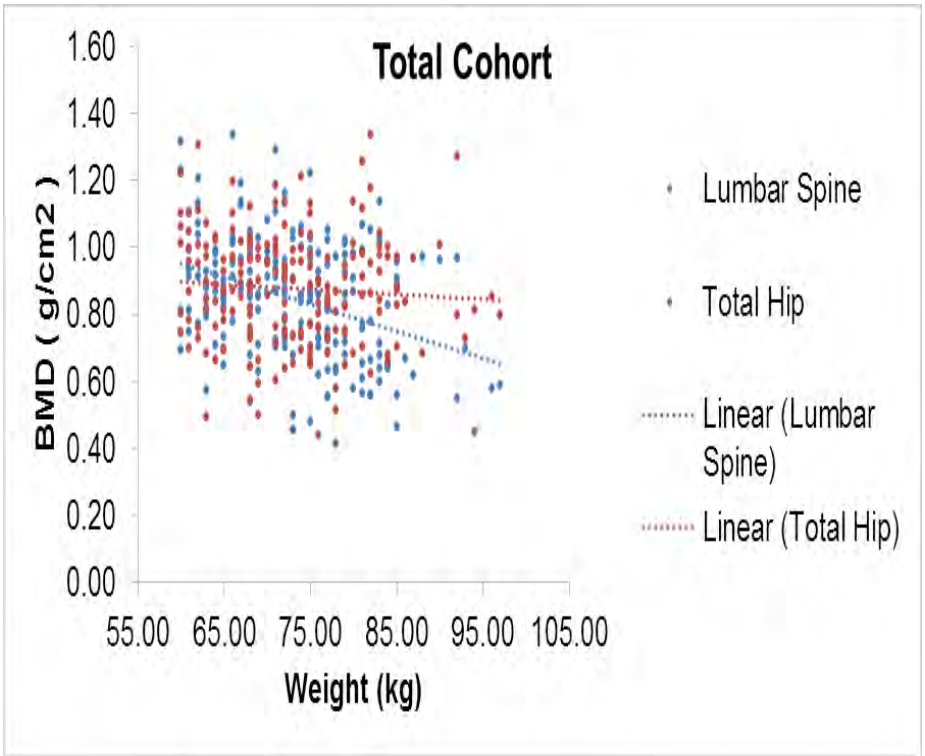

Figure 4.10.a Correlation between weight and total hip ($p < 0.0001$) and lumbar spine ($p < 0.0001$) BMD in total cohort ($n = 310$).

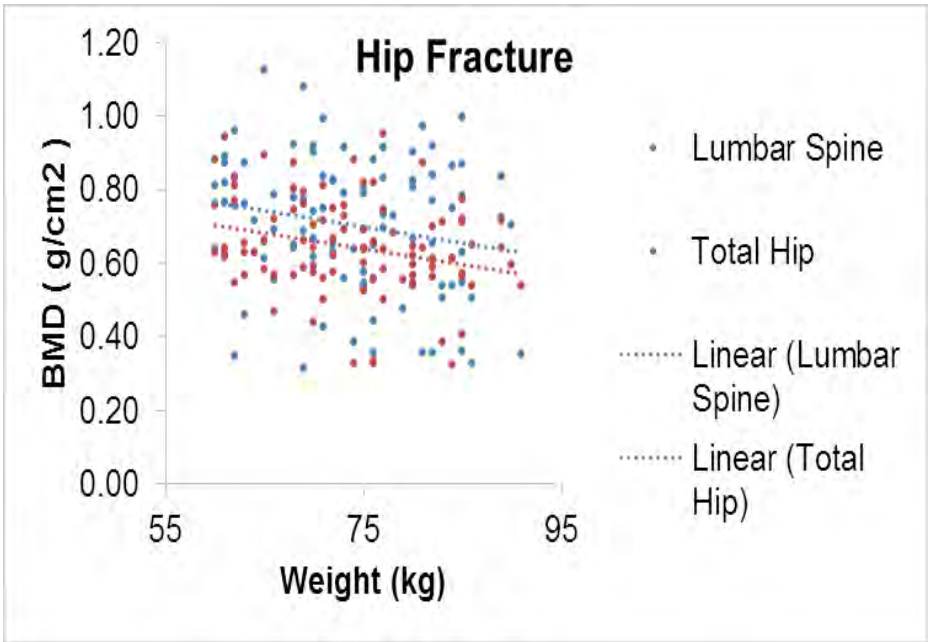

Figure 4.10.b Correlation between weight and total hip ($p < 0.0001$) and lumbar spine ($p < 0.0001$) BMD in hip fracture subjects (n = 112).

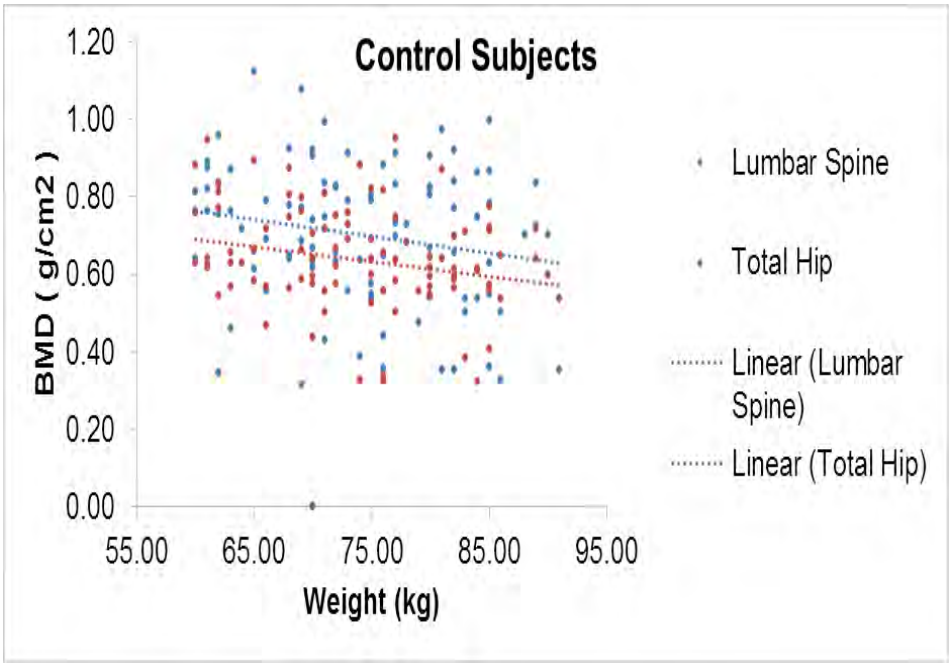

Figure 4.10.c Correlation between weight and total hip ($p = 0.160$) and lumbar spine ($p = 0.792$) BMD in control subjects (n = 198)

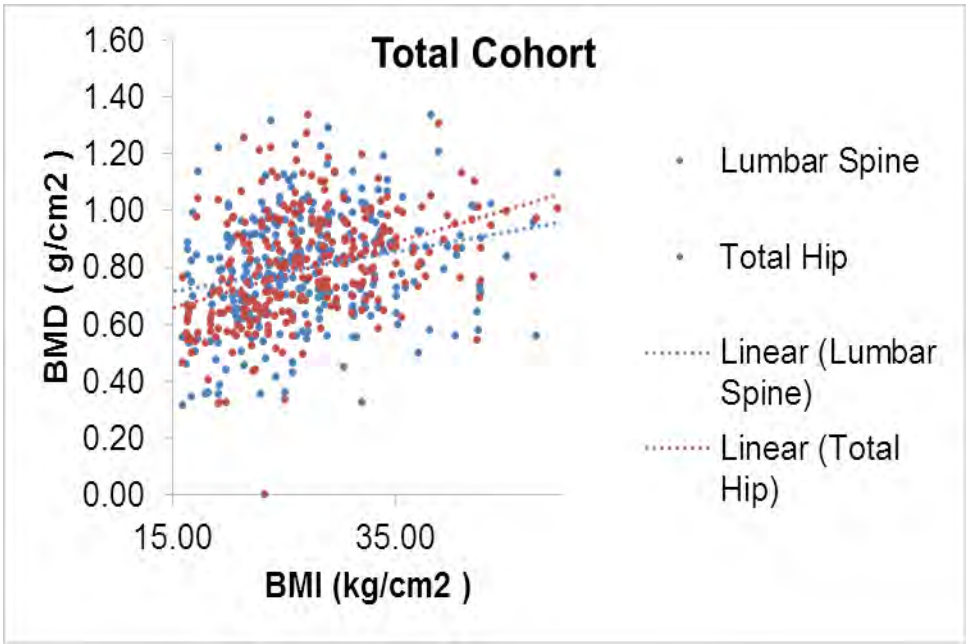

Figure 4.11.a Correlation between BMI and total hip (p <0.0001) and lumbar spine (p < 0.0001) BMD in total cohorts (n = 310)

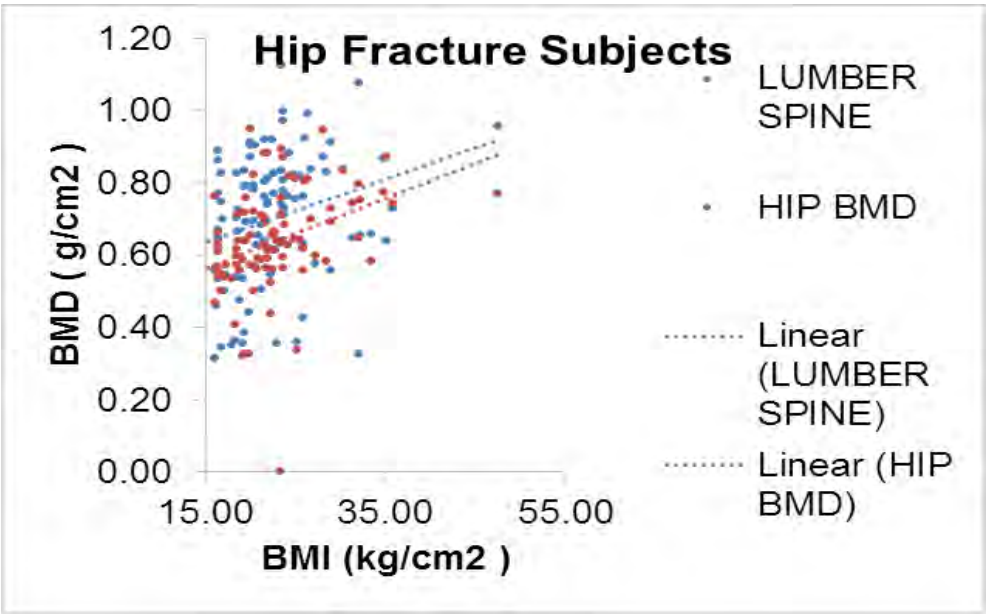

Figure 4.11.b Correlation between BMI and total hip (p <0.0001) and lumbar spine (p < 0.0001) BMD in hip fracture subjects.(n = 112)

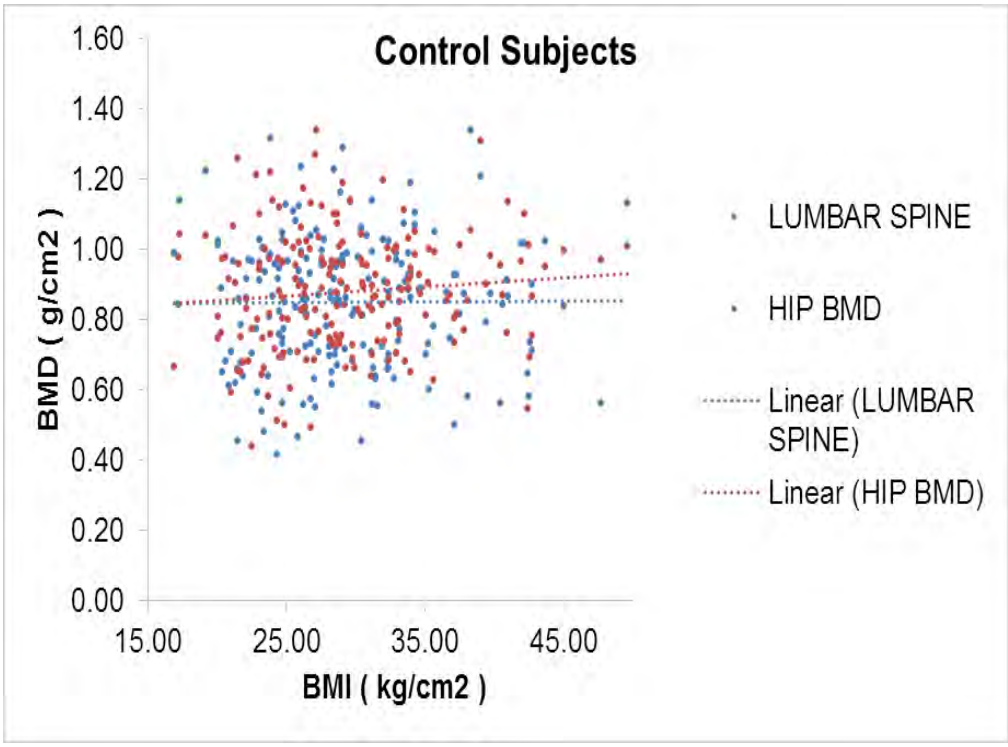

Figure 4.11.c Correlation between BMI and total hip (p =0.164) and lumbar spine (p =0.916) BMD in control subjects (n = 0.198)

4.3.1.4 Morphometric vertebral fractures

Thoracolumbar radiographs in 122 hip fracture and 197 control subjects were analysed. Morphometric VF (defined as a change in height of > 20% of the vertebral body compared to vertebrae above or below) were identified in 81 (25.4%) of the 319 subjects who had radiographs and were significantly more common in hip fracture subjects than control subjects (32.7% vs. 20.3%; $p < 0.0001$) and in women compared to men (27% vs. 21.4%; $p < 0.0001$).

F_Grp

Thirty nine (48.2%) of the VF were seen in Indian subjects, however VF were seen most commonly in the White subjects 44.8%, followed by Africans and Indians, 28.3% and 22% respectively.

Multiple VF's were present in 27 subjects (6.9%), and were more common in subjects with a hip fracture than in those without, but this did not reach statistical significance (12.3% vs. 6.1%; p = 0.057). Indian and African hip fracture were more likely to have multiple fractures than Indian and African control subjects but multiple VF were more likely to occur in White control subjects than White hip fractures subjects. A history of a previous fragility fracture was also more common in the hip fracture subjects with a VF than in control subjects with a VF (32.5% vs. 7.3%, p = 0.005).

The vast majority of vertebral fractures occurred in the lower thoracic and upper lumbar regions [T11 (25%), L1 (22.5%) and T12 (17.5%)] in both groups. In control subjects the highest number of VF were observed at T6 and T11 at 19.5% each, followed by T8 and T12 with 17.1% each (Tables 4.17).

Table 4.17 Distribution of vertebral fracture sites in hip fracture and control subjects

Vertebral level	Hip fracture subjects (n= 41)	Control subjects (n= 41)	Total no. of fractures per site (n= 81)
T5	3	1	4
T6	3	8	11
T7	5	6	11
T8	5	7	12
T9	6	5	11
T10	1	2	3
T11	10	8	18
T12	7	7	14
L1	9	5	14
L2	6	3	9
L3	4	1	5
L4	4	4	8
L5	0	2	2

In the total cohort (hip fracture and control subjects), the majority had moderate vertebral deformities (44.4%), followed by mild vertebral deformities (37.1%) and severe deformities were only seen in 18.5% (Table 4.18). Severe deformities were most likely seen in Indian or African hip fracture subjects.

Due to the small sample size, the ethnic and gender differences in the severity of fractures and distribution was not analysed further, however Africans hip fracture

subjects were more likely to have fractures at T6/7 while Indian and White hip fracture subjects had fractures at T11/12. No difference was noted in control subject fracture distribution.

Table 4.18 Distribution of severity of deformity in vertebral fractures in hip fracture and control subjects

	African hip fracture (n=40)	African control subjects (n=66)	Indian hip fracture (n=70)	Indian control subjects (n=107)	White hip fracture (n=11)	White control subjects (n=13)	Total (n=81)
Mild VF	4	8	5	9	3	1	30
Moderate VF	6	7	6	8	3	6	36
Severe VF	5	0	9	2	0	0	15
Total VF	15	15	20	19	6	7	81

4.3.1.3 Functional assessment in hip fracture subjects (pre-fracture) and controls

Physical self-maintenance scales

Hip fracture subjects had a significantly lower total mean score on the PSMS pre-fracture than control subjects (13.3 ± 1.9 vs. 13.8 ± 1.1; p = 0.001) and were significantly more likely than controls to be unable to perform all basic activities of daily living, except eating, independently (Table 4.19).

Table 4.19 Assessment of physical performance of basic activities of daily living (PSMS) in hip fracture and control subjects

	Fracture subjects (n=200)	Control subjects (n=200)	p-value
Eating (%)	2.5	0.5	0.103
Dressing (%)	9	1.5	*0.001
Grooming (%)	10	2.5	*0.003
Walking (%)	14.5	5	*<0.0001
Transfer to bed (%)	8.5	2.5	*0.010
Bathing (%)	10	3	*0.004
Toileting (%)	9.5	3	*0.006
Total score (mean ± SD)	13.3 ± 1.9	13.8 ± 1.1	*0.001

- Total score calculated out of 17
- (%) of subjects with a score of 0 (unable to perform activity independently)
- Assessment done pre-fracture in hip fracture subjects

Instrumental activity of daily living

Hip fracture subjects were also significantly less likely to be able to complete all the activities in the Lawton IADL (Table 4.) and had a significantly lower total score (22.1 ± 4.8 vs. 25.5 ± 3.4; $p < 0.0001$) (Table 4.20).

Table 4.20 Instrumental activities of daily living and assessment of the performance of instrumental activities of daily living in hip fracture and control subjects

Activity	Fracture subjects (n=200)	Control subjects (n=200)	p-value
Telephone (%)	51	20.5	*<0.0001
Walking a distance (%)	54	18.5	*<0.0001
Shopping (%)	39	9.5	*<0.0001
Cooking (%)	44	14.5	*<0.0001
Housework (%)	59.5	18.5	*<0.0001
Handiwork (%)	51	17.5	*<0.0001
Laundry (%)	18.5	4.5	*<0.0001
Medication (%)	23.5	4	*<0.0001
Finances (%)	26	13.5	*0.002
IADL total score (mean ± SD)	22.1 ± 4.8	25.5 ± 3.4	*<0.0001

- IADL score calculated out of maximum of 27
- (%) of subjects with a score of 0 (unable to perform activity independently)
- Assessment done pre-fracture in hip fracture subjects

Quality of Life

Hip fracture subjects compared to control subjects had significantly higher overall scores (6.3 ± 1.7 vs. 5.9 ± 1.2; p 0.003) and greater difficulty in all domains except daily activities (Table 4.21).

Table 4.21 Quality of life and the assessment of performance of daily activities, mood and pain in hip fracture and control subjects

Domain		Fracture subjects (n = 200)	Control subjects (n= 200)	p-value
Mobility	Unable/needs help	21 (10.5)	4 (2)	*<0.0001
Self-care	Unable/needs help	69 (34.5)	22 (11)	*<0.0001
Daily activities	Unable/needs help	64 (32)	95 (47.5))	*0.002
Pain	Has Pain	29 (14.5)	9 (4.5)	*0.001
Mood	Depressed/Anxious	50 (25)	17(8.5)	*<0.0001
QoL score (mean ± SD)		6.3 ± 1.7	5.9 ± 1.2	*0.003

- QOL score calculated out of 15
- Assessment done pre-fracture in hip fracture subjects
- Number of subjects and n (%)

Oswestry Disability index

A similar mean ODI disability percentage was obtained in the hip fracture and control subjects. Differences in individual parameters i.e. pain, lifting of objects, sleeping, socializing and travelling were noted, with the disability being greater in the fracture subjects (Table 4.22). The final average score was calculated as a percentage of the total number of questions answered, and did not reach statistical significance (30.6 ± 15.2 vs. 28.1 ± 10.8; $p = 0.063$) (Table 4.22).

Visual analogue Scale

Contrary to the ODI, where pain was more common in fracture cases, in the VAS, hip fracture subjects had a significantly lower pain level pre-fracture compared to control subjects (1.4 ± 1.3 vs 3.3 ± 2.6; $p < 0.0001$) (Table 4.22). This is possibly due to difference in pain interpretation between the two questions.

Table 4.22 The Oswestry Disability Index and Visual Analogue Scale and assessment of the performance of the activities and pain in hip fracture and control subjects

Domain		Fracture subjects (n =200)	Control subjects (n = 200)	p-value
Pain	Strong pain/some pain	17 (8.5)	5 (2.5)	*0.008
Personal care	Unable/needs help	109 (54.5)	109 (54.5)	1
Lifting	Unable/needs help	46 (23.0)	14 (7)	*<0.0001
Walking	Unable/needs help	9 (4.5)	3 (1.5)	0.079
Sitting	Unable/needs help	21 (10.5)	33 (16.5)	0.079
Standing	Unable/needs help	7 (3.5)	7 (3.5)	1
Sleeping	Interrupted by pain	28 (14)	15 (7.5)	*0.034
Social life	Unable/difficulty	28 (14)	14 (7)	*0.022
Travelling	Unable/difficulty	28 (14)	14 (7)	*0.022
Oswestry Score (%) (mean ± SD)		30.6 ± 15.2	28.1 ± 10.8	0.063
Visual analogue score (mean ± SD)		1.4 ± 1.3	3.3 ± 2.6	*<0.0001

- Assessment done pre-fracture in hip fracture subjects
- Number of subject's unable/requiring help to perform activity n (%)

4.3.1.5 Haematological and biochemical parameters in hip fracture subjects and controls

Details of the haematological and biochemical tests obtained in subjects with hip fractures at the time of admission and/ or enrolment into the case study and at the time of recruitment in controls are shown in Table 4.23.

Compared to controls, hip fracture subjects had significantly lower haemoglobin, serum sodium, total protein and albumin (Figure 4.13) while the bilirubin, ALT, GGT, and plasma glucose levels were significantly higher. In addition the inflammatory markers; white cell count, CRP and ESR were significantly elevated in hip fracture subjects.

The mean $25(OH)_2$ vitamin D levels were significantly lower in hip fracture subjects and was in the mildly deficient range (24.96 - 49.92 nmol/L).

Serum oestrogen levels were significantly higher in hip fracture subjects but were within the normal range for postmenopausal women. In men there was no difference in testosterone levels between the two groups however the mean values were at the lower end of the normal reference range (8.4 - 28.7 nmol/L).

Table 4.23 Haematological and biochemical results in hip fracture and control subjects

	Fracture subjects	Control subjects	p-value	OR	95% CI
Haemoglobin (g/dl)	11.3 ± 2 (n=200)	12.8 ± 1.7 (n=200)	*<0.0001	1.553	1.31 - 1.85
White cell count ($\times 10^9$/L)	9.8 ± 3.6 (n=200)	7.3 ± 2.1 (n=199)	*<0.0001	0.743	0.66 - 0.83
Sodium (mmol/L)	135.9 ± 4.6 (n=200)	139.6 ± 3.5 (n=199)	*<0.0001	1.219	1.13 - 1.31
Urea (mmol/L)	7.7 ± 4.7 (n=200)	6.6 ± 3.2 (n=199)	0.52	0.936	0.88 - 1.00
Creatinine (umol/L)	96.5 ± 53.5 (n=200)	95 ± 46.5 (n=199)	0.733	0.999	1.00 - 1.00
Total protein (g/L)	71.1 ± 9.3 (n=198)	74.4 ± 5.8 (n=199)	*<0.0001	1.038	1.01 - 1.07
Albumin (g/L)	33.2 ± 7.4 (n=198)	41.4 ± 3.9 (n=199)	*<0.0001	1.246	1.16 - 1.34
Bilirubin (umol/L)	12.8 ± 7.9 (n=198)	10.4 ± 7.2 (n=199)	*0.006	0.962	0.93 - 1.00
Alanine transaminase (IU/L)	28.4 ± 25.5 (n=197)	21.7 ± 14.1 (n=198)	*0.008	0.985	0.97 - 1.0
Gamma glutamyl transferase (IU/L)	45.9 ± 45 (n=198)	28.2 ± 20.3 (n=199)	*<0.0001	0.979	0.97 - 0.99
Glucose (mmol/L)	6.9 ± 3.5 (n=175)	5.9 ± 1.8 (n=199)	*0.001	0.813	0.71 - 0.93
Calcium (mmol/L)	2.3 ± 0.1 (n=185)	2.3 ± 0.1 (n=188)	0.236	0.37	0.07 - 1.92
Thyroid stimulating hormone (mIU/L)	3.4 ± 6.3 (n=155)	3.7 ± 9.3 (n=197)	0.671	1.008	0.98 - 1.04
25(OH) vitamin D (nmol/L)	38.9 ± 22.4 (n=171)	51.4 ± 24.2	*<0.0001	1.03	1.02 - 1.05
Parathyroid hormone (pg/ml)	6.7 ± 3.7) (n=158)	7.6 ± 5.4	0.101	1.008	0.95 - 1.07
C-Reactive protein (mg/L)	24.3 ± 31.8 (n=182)	8.8 ± 10.3	*<0.0001	0.952	0.93 - 0.98
Erythrocyte sedimentation rate (mm/hr)	42.3 ± 28.4 (n=162)	25.5 ± 26.7	*<0.0001	0.977	0.97 - 0.99
Oestrogen (pmol/L) (women only)	68.9 ± 43.8 (n=123)	49.9 ± 19.6 (n=144)	*<0.0001	0.985	0.97 - 1.00
Testosterone (men only) (nmol/L)	10.2 ± 4.8 (n=34)	10.5 ± 4.9 (n=56)	0.46	1.087	0.92 - 1.28

- All results reported as a mean ± SD
- All controls subjects age, gender and ethnic matched.

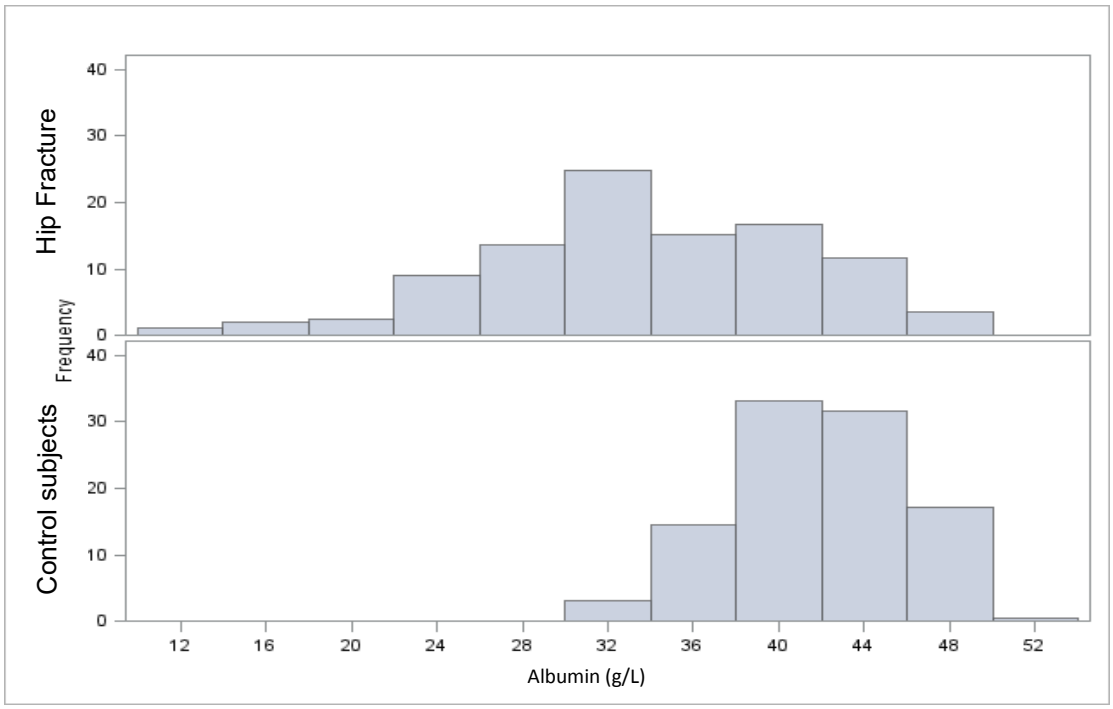

Figure 4.12 Comparison of mean albumin levels in hip fracture (n=198) and matched control (n=199) subjects on enrolment (p <0.001)

4.3.1.5 Multivariate analysis of variables associated with osteoporotic fractures

The variables with significant associations were identified in the univariate analysis and were entered into a COX regression model. The variables that remained significant in the step wise backwards logistic regression in hip fracture subjects compared to controls were a prior fragility fractures, pre- fracture self-reported physical activity levels, BMI, education level, IADL and QoL total scores, and the haemoglobin, albumin, white blood cell count and C-reactive protein at time of admission/enrolment (Table 4.24)

Table 4.24 Multivariate analysis of variables with significant association in hip fractures subjects

Variable		p-value
Step 10	Mean body mass index	*<0.0001
	Education no schooling	*<0.0001
	Education < Standard 3	*0.002
	Education < Standard 6 - 7	*0.013
	Education Standard 10 plus	0.583
	Self-reported activity level	
	extremely active	*0.002
	Moderately active	*0.015
	Mild activity	0.873
	Sedentary	0.978
	Prior fragility fracture >40 years old	*0.001
	Instrumental activity of daily living score	*0.002
	Quality of life score	*0.038
	Low haemoglobin	*0.011
	Elevated white blood cell count	*<0.0001
	Low albumin level	*<0.0001
	Elevated C-reactive protein	*0.005

4.3.2 Risk factor assessment in male and female hip fracture subjects

4.3.2.1 Socio-demographic characteristics

Age, gender and ethnicity

Of the 200 hip fracture subjects, there were 56 men and 144 women. Men were significantly younger; 70.7 ± 8.7 years vs. 75.7 ± 8.5 years; $p < 0.0001$ than women with hip fractures (Table 4.25).

Social Status: employment, housing and education

There was no difference in housing or employment between men and women fracture subjects.

Women with hip fractures were significantly more likely than men to have had no formal education (40.3% vs. 28.6%; $p = 0.006$) or less than five years of education (35.4% vs. 25%; $p = 0.006$) whereas men were likely to have had at least a high school education (42.9% vs. 18.8%; $p = 0.006$) (Table 4.25).

Anthropometric measures

Although men with hip fractures were significantly taller than women with hip fractures, there was no significant difference in weight or BMI between men and women hip fracture subjects. In contrast, both men and women with hip fractures

weighed significantly less than their matched control subjects (56.4 ± 12.9 kg vs. 74.7 ± 15 3 kg; $p < 0.0001$) for men and (54.1 ± 14.1 kg vs. 71.0 ± 16.5 kg; $p < 0.0001$) for women respectively (Table 4.25).

There was no difference in the mean BMI value between men and women hip fracture subjects. Men and women with hip fractures compared to their matched control subjects had a significantly lower BMI values; (21.7 ± 4.5 kg/cm^2 vs. 27.3 ± 5.1 kg/cm^2; $p < 0.0001$; OR 0.739, 95%CI 0.58-0.95) for men and (23.1 ± 6.0 kg/cm^2 vs. 29.9 ± 6.2 kg/cm^2; $p < 0.0001$; OR 0.797, 95%CI 0.72-0.89) for women.

Table 4.25 Baseline demographic characteristics in men and women with hip fractures

	Men (n=56)	Women (n=144)	p-value
Age (years) mean ± SD	70.7 ± 8.7	75.7 ± 8.5	*<0.0001
Weight (kg) mean ± SD	56.4 ± 12.9 (n= 40)	54.1 ± 14.1 (n= 96)	0.392
Height (cm) mean ± SD	160.3 ± 9.3 (n= 40)	153.7 ± 8.4 (n= 96)	*<0.0001
BMI (Kg/cm^2) mean ± SD	21.7 ± 4.5 (n= 40)	23.1 ± 6.0 (n= 96)	0.709
Education level n (%)			
No schooling	16 (28.6)	58 (40.3)	*0.006
< Std. 3	14 (25)	51 (35.4)	
Std. 6-7	24 (42.9)	27 (18.8)	
Std. 10 plus	2 (3.6)	8 (5.6)	
Hypertension n (%)	26 (46.4)	94 (65.3)	*0.018
Diabetes mellitus n (%)	10 (17.9)	47 (32.6)	*0.024
Arthritis n (%)	6 (10.7)	49 (34)	*0.001
Chronic back pain n (%)	3 (5.4)	11 (7.6)	0.572
Osteoporosis n (%)	0 (0.0)	7 (4.9)	n/a
Rheumatoid arthritis n (%)	0 (0.0)	2 (1.4)	n/a
Malignancy n (%)	1 (1.8)	9 (6.3)	0.193
Prolonged immobilization n (%)	1 (1.8)	5 (3.5)	0.53
Glucocorticoids > 3/12 n (%)	2 (3.6)	9 (6.3)	0.456

4.3.2.2 Clinical risk factors

Co-morbid diseases and secondary medical causes of osteoporosis

Hypertension, diabetes and arthritis were significantly more common in women than men with hip fractures (Table 4.25). A similar trend was seen with rheumatoid arthritis, malignancy, prolonged immobilization and the use of glucocorticoids, however this was not significantly different from men and the sample size was extremely small limiting the interpretation of results.

Female control subjects compared to female hip fracture subjects had a significantly higher risk of hypertension (79.2% vs 65.3%; p = 0.004) and chronic back pain (19% vs 7.6%; p = 0.028) whereas malignancy was more common in hip fracture women than control women (6.3% vs 1.2%; p = 0.034), however the sample size numbers were too small to draw any significant conclusion.

Cognitive changes

While there was no difference in memory between men and women with hip fractures, women hip fracture subjects had greater memory concerns than matched women controls (36.8% vs 20.4%; p 0.003).

Falls

Although the number of falls was similar in men and women with hip fractures, sideways falls were significantly more frequent in women fracture subjects than men (33.3 vs. 26.8%; p = 0.022) (Table 4.26). The fall risk assessment however showed no significant differences in number of previous falls, visual or sensory disturbances, gait and balance, activity limitation due to fear of falling or painful joints between men and women hip fracture subjects.

Similar to the main study, men and women control subjects were more likely to report near falls, needing help getting up after a potential fall, seeking medical attention after a fall, visual problems, problems with the lower limbs, gait, limitation of activities and medication problems than men and women hip fracture subjects. Additionally men hip fracture subjects were more likely not to use a walking aid than matched control men.

Past history of fractures

Although no difference was seen in the number or prior fragility fractures between men and women hip fracture subjects (Table 4. 26), women with hip fractures reported previous fragility fractures significantly more than women control subjects (29.9% vs. 11.8%; p < 0.0001; OR 2.857, 95%CI 1.56-5.25). While 21.4% of men with hip fractures reported a previous fragility fracture, no male control subject had a

previous fragility fracture. The sites of prior fractures were not different between men and women.

Self-reported vertebral fractures

There was no significant difference in men and women in previous self-reported VF.

Family history of osteoporosis and maternal history of hip fractures

A family history of osteoporosis or maternal history of fracture was only reported in women and not in men with hip fractures. Seven women (4.9%) reported a family history of osteoporosis and 11 (7.6%) a maternal history of hip fracture.

Lifestyle factors

There was no difference in the duration of sunlight exposure, calcium intake or caffeine intake between men hip fracture subjects compared to woman hip fracture subjects.

In the hip fracture group, men were significantly more likely than women to smoke (53.6% vs. 4.2%; $p < 0.0001$) and to be current consumers of alcohol (41.1% vs. 5.6%; $p < 0.0001$) (Table 4.26).

Male hip fracture subjects were also more likely to smoke and consume alcohol compared to their matched control subjects (53.6% vs. 21.1%; $p < 0.0001$) and (41.1% vs.10.5%; $p < 0.0001$; OR 11.0, 95%CI 2.56-46.78) respectively.

In the female group the total number who smoked or consumed alcohol was very small and there was no difference between the hip fracture and matched control subjects.

Table 4.26 Clinical risk factors for osteoporosis and fractures in men and women hip fracture subjects

Risk factor	Male (n=56)	Female (n=144)	p-value
Prior history of falls	26 (46.4)	64 (44.4)	0.8
Sideways fall	15 (26.8)	48 (33.3)	*0.022
Fragility fracture >40 year	12 (21.4)	43 (29.9)	0.23
Self-reported vertebral fracture	1 (1.8)	1 (.7)	0.486
Self-reported activity level			
Extremely active	19 (33.9)	56 (38.9)	*<0.0001
Moderately active	13 (23.2)	30 (20.8)	*<0.0001
Mildly active	21 (37.5)	44 (30.6)	*<0.0001
Sedentary	3 (5.4)	14 (9.7)	*<0.0001
Smoking	20 (53.6)	6 (4.2)	*<0.0001
Alcohol	23 (41.1)	8 (5.6)	*<0.0001
Calcium intake (mg/day) mean ± SD	447.1 $\pm$ 241.6	426.9 $\pm$ 226.5	0.200
Sunlight (minutes) mean ± SD	40.5 $\pm$ 75.1	28$\pm$47.6	0.100

- Number of subjects n (%)

4.3.2.3 Bone mineral density

There was no difference in the areal BMD, BMAD and T - scores at both the spine and hip between men and women fracture cases. Surprisingly, given the expected finding of a higher BMD in males, all parameters of bone mass except hip BMAD were also comparable to the control cohort. (Table 4.27).

Table 4.27 Bone mineral density in men and women hip fracture subjects

Risk factor	Male	Female	p-value
Spine aBMD (g/cm^2) mean ± SD	0.733 ± 0.144 (n=31)	0.689 ± 0.182 (n=85)	0.234
Femoral neck aBMD (g/cm^2) mean ± SD	0.516 ± 0.100 (n=31)	0.519 ± 0.109 (n=83)	0.896
Total hip aBMD (g/cm^2) mean ± SD	0.680 ± 0.134 (n=31)	0.640 ± 0.136 (n=84)	0.168
Spine BMAD (g/cm^3) mean ± SD	0.198 ± 0.031 (n=31)	0.200 ± 0.038 (n=85)	0.455
Hip BMAD (g/cm^3) mean ± SD	0.105 ± 0.02 (n=31)	0.123 ± 0.109 (n=84)	0.841
Hip T – Score mean ± SD	-2.81 ± 0.82 (n=31)	-2.95 ± 0.86 (n=84)	0.464
Spine T – Score mean ± SD	-2.93 ± 1.24 (n=31)	-3.01 ± 1.32 (n=85)	0.782

Compared to their matched controls, male hip fracture subjects had a significantly lower BMD at all sites (Table 4.28). Similarly in women hip fracture subjects compared to their matched controls, the BMD was lower at all sites except for the hip BMAD. (Table 4.29).

Table 4.28 Bone mineral density in male hip fracture and male control subjects

Risk factor	Male hip fracture	Male control subjects	p-value
Spine aBMD (g/cm^2) mean ± SD	0.733 ± 0.144 (n=31)	0.919 ± 0.182 (n=56)	*<0.0001
Femoral neck aBMD (g/cm^2) mean ± SD	0.516 ± 0.100 (n=31)	0.745 ± 0.144 (n=55)	*<0.0001
Total hip aBMD (g/cm^2) mean ± SD	0.680 ± 0.134 (n=31)	0.907 ± 0.161 (n=56)	*<0.0001
Spine BMAD (g/cm^3) mean ± SD	0.198 ± 0.031 (n=31)	0.248 ± 0.048 (n=55)	*<0.0001
Hip BMAD (g/cm^3) mean ± SD	0.105 ± 0.02 (n=31)	0.146 ± 0.026 (n=56)	*<0.0001
Hip T – Score mean ± SD	-2.81 ± 0.82 (n=31)	-1.14 ± 1.23 (n=55)	*<0.0001
Spine T – Score mean ± SD	-2.93 ± 1.24 (n=31)	-1.05 ± 1.41 (n=55)	*<0.0001

Table 4.29 Bone mineral density in women hip fracture and women control subjects

Risk factor	Female hip fracture	Female Control	p-value
Spine aBMD (g/cm^2) mean ± SD	0.689 ± 0.182 (n=85)	0.821 ± 0.177 (n=144)	*<0.0001
Femoral neck aBMD (g/cm^2) mean ± SD	0.519 ± 0.109 (n=83)	0.699 ± 0.117 (n=95)	*<0.0001
Total hip aBMD (g/cm^2) mean ± SD	0.640 ± 0.136 (n=84)	0.868 ± 0.163 (n=144)	*<0.0001
Spine BMAD (g/cm^3) mean ± SD	0.200 ± 0.038 (n=85)	0.242 ± 0.038 (n=144)	*<0.0001
Hip BMAD (g/cm^3) mean ± SD	0.123 ± 0.109 (n=84)	0.142 ± 0.024 (n=144)	0.106
Hip T – Score mean ± SD	-2.95 ± 0.86 (n=84)	-1.31 ± 1.26 (n=144)	*<0.0001
Spine T – Score mean ± SD	-3.01 ± 1.32 (n=85)	-1.29 ± 1.45 (n=85)	*<0.0001

4.3.2.4 Morphometric vertebral fractures

There was no difference in the number of morphometric VF between men and women hip fracture subjects. Due to the small numbers the severity or site of fractures between the two groups was not compared.

4.3.2.4 Functional assessment

Physical self-maintenance scale

No significant differences were noted in the performance of daily activities between men and women hip fracture subjects, except that men were more likely to be unable to eat independently prior to having had the hip fracture (7.1% vs. 0.7%; p = 0.009). Male fracture subjects compared to their matched control subjects had greater difficulty with eating and dressing. In contrast women hip fracture subjects pre-fracture compared to their matched controls had greater difficulty in all the domains of PSMS apart from eating and transferring (Appendix 4.A, Table 4.A.1).

Instrumental activity of daily living

There was no difference in the ability to perform individual activities or in the total score of the Lawton's IADL between men and women hip fracture subjects. However when compared to their matched controls, both men and women hip

fracture subjects were significantly more likely to be unable to complete all IADL tasks independently and had lower scores (Appendix 4.A, Table 4.A.2).

Quality of Life

There was no significant difference in the QoL total score between men and women subjects with hip fractures, but both men and women with hip fractures compared to their respective matched cohort had a lower QoL score. Both men and women hip fracture subjects had greater difficulty with mobility and self-care compared to their matched control subjects. In addition male fracture subjects compared to their matched controls were more likely to have a depressed mood, whilst female hip fracture subjects reported greater pain compared to women control subjects (Appendix 4.A, Table 4.A.1).

Oswestry disability index

Women with hip fractures were more likely to be unable to lift objects (77.8% vs. 57.1%; p = 0.004) and walk a distance (58.3% vs. 39.3%; p = 0.015) compared to men with hip fractures, but there was no difference in their total percentage score.

Women fracture subjects had greater difficulty compared to women control subjects in all parameters apart from personal care, walking distance and standing. Men hip fractures subjects had greater difficulty with lifting objects only (Appendix 4.A, Table 4.A.4).

Visual analogue scale

There was no difference in the VAS score between men and women with hip fractures but the pre-fracture VAS score was lower in both male and female hip fracture subjects compared to their matched control subjects (Appendix 4.A, Table 4.A.4).

4.3.2.6 Haematological and Biochemical Comparison

Similarly the haematological and biochemical results were also not remarkably different in men and women with hip fractures except for the haemoglobin level and GGT which although within the normal range, was significantly higher in men (11.9 ± 2.4 g/dl vs. 11.1 ± 1.7 g/dl; p = 0.026) and (60.5 ± 60 IU/L vs. 40.2 ± 36.4 IU/L, p = 0.021) respectively (Table 4.30).

Table 4.30 Haematological and biochemical results in men and women hip fracture subjects

	Male	Female	p-value
Haemoglobin (g/dl)	11.9 ± 2.4 (n=56)	11.1 ± 1.7 (n=144)	*0.026
25 (OH) Vitamin D (nmol/L)	34.7 ± 21.3 (n=48)	40.5 ± 22.7 (n=123)	0.123
Gamma Glutamyl transferase (IU/L)	60.5 ± 60 (n=55)	40.2 ± 36.4 (n=143)	*0.021
Glucose (nmol/L)	6.3 ± 1.9 (n=43)	7.2 ± 3.8 (n=132)	0.135

- All results reported as mean + SD

The mean glucose was significantly higher in hip fracture women than control women, but no difference was seen in male subjects. These were random blood glucose values and the relevance of the difference in the means is uncertain given that were a number of subjects with diabetes. Both men and women hip fracture subjects had a higher GGT than matched control subjects, and no difference was seen in vitamin D or PTH levels (Table 4.31).

Table 4.31 Biochemical results in men and women fracture and matched controls

	Male Subjects			Female subjects		
	Hip fracture	**Control**	**p-value**	**Hip fracture**	**Control**	**p-value**
Gamma glutamyl transferase (IU/L)	60.5 ± 60 (n=55)	31.8 ± 24 (n=56)	*0.001	40.2 ± 36.4 (n=143)	26.9 ± 18.5 (n=143)	*<0.0001
Glucose (nmol/L)	6.3 ± 1.9 (n=43)	5.8 ± 1.9 (n=56)	0.244	7.2 ± 3.8 (n=132)	5.9 ± 1.8 (n=143)	*0.002
25 (OH) Vitamin D (nmol/L)	34.7 ± 21.3 (n=48)	51.7 ± 21.7 (n=56)	*0.003	40.5 ± 22.7 (n=123)	51.3 ± 25.2 (n=144)	*<0.0001
Parathyroid hormone (pg/ml)	5.8 ± 3.7 (n=43)	7.6 ± 6.7 (n=56)	*0.084	7.1 ± 3.7 (n=115)	7.6± 4.8 (n=144)	0.67

- All results reported as mean + SD

4.3.3 Risk assessment in African and Indian hip fracture subjects.

Of the 200 hip fracture subjects, 66 were African and 110 Indian. Their socio-demographic characteristics, CRF, fall risk, BMD and laboratory measurements were compared. In view of their small number, White (n= 21) and Coloured (n= 3) patients with hip fractures were not included in the comparison.

4.3.3.1 Socio-demographic characteristics

Age, gender, housing, employment and education

There was no significant difference in housing, employment, age, gender ratio or education levels between Indians and African hip fracture subjects, despite a higher number of Africans having no schooling compared to Indians (50% vs. 35.5%; p = 0.12). Indian and African control subjects had a significantly higher level of education compared to matched hip fracture subjects.

Anthropometric measures

Although Indian hip fracture subjects had a significantly lower mean body weight compared to African hip fracture subjects (51.9 ± 11.4 kg vs. 56.8 ± 13.3 kg; p = 0.034), there was no difference in height or BMI between Indians and Africans (Table 4.32). Both Indian and African subjects with hip fractures weighed significantly less than their matched control cohorts (51.9 ± 11.4kg vs. 67.0 ±14.1kg; p < 0.0001; OR

0.893; 95%CI 0.84-0.95) and (56.8 ± 13.3 kg vs. 80.7 ± 16.8 kg; p < 0.0001; OR 0.916; 95%CI 0.86-0.97) respectively.

Table 4.32 Baseline characteristic in African and Indian hip fracture subjects

	African (n=66)	**Indian (n=110)**	**p value**
Age (years) mean ± SD	74.5 ± 9.9 (n=45)	73.4 ± 7.9 (n= 76)	0.416
Weight (kg) mean ± SD	56.8 ± 13.3 (n= 45)	51.9 ± 11.4 (n= 76)	*0.034
Height (cm) mean ± SD	157.1 ± 8.1 (n= 45)	153.6 ± 9.9 (n= 76)	0.072
BMI (kg/cm^2) mean ± SD	23.2 ± 5.7	21.9 ± 4.2	0.317
Diabetes mellitus n (%)	14 (21.2)	40 (36.4)	*0.028
Arthritis n (%)	12 (18.2)	38 (34.5)	*0.014

Similarly Indian and African hip fracture subjects had a lower BMI than their matched control subjects (21.9 ± 4.2 kg/cm^2 vs 27.6 ± 5.0 kg/cm^2; p < 0.0001) and (23.2 ± 5.1 kg/cm^2 vs. 27.4 ± 5.1 kg/cm^2; p < 0.0001) respectively. While there was no difference in height between Africans, Indian fracture subjects were significantly shorter than their matched Indian controls (153.6 ± 9.9 cm vs. 155.8 ± 10.2 cm; p = 0.009) (Table 4.33).

Table 4.33 Baseline characteristic in African and Indian hip fracture subjects compared to matched control subjects

	African hip fractures (n=45)	African control subjects (n=66)	p value	Indian hip fractures (n=76)	Indian control subjects (n=110)	p value
Weight (kg)	56.8 ± 13.3	80.7 ± 16.8	*<0.0001	51.9 ± 11.4	67 ± 14.1	*<0.0001
Height (cm)	157.1 ± 8.1	158.2 ± 8	0.335	153.6± 9.9	155.8 ± 10.2	*0.009
Mean BMI (kg/cm^2)	23.2 ± 5.7	32.6 ± 6.4	*<0.0001	21.9 ± 4.2	27.6 ± 5	*<0.0001

- **All results reported as mean**

4.3.3.2 Clinical risk factors

Comorbid diseases and secondary medical causes of osteoporosis

Diabetes mellitus and arthritis were significantly more common in Indian fracture subjects compared to African fracture subjects. Although African fracture subjects had a higher frequency of hypertension compared to Indian fracture subjects this was not significant. There were no other significant differences in secondary medical conditions between Indian and African hip fracture subjects. The profile of chronic and secondary medical conditions in matched Africans was similar to the main study

findings but in Indians only diabetes mellitus and chronic back pain were significantly more common in control subjects than Indian fracture subjects.

Gynaecological history and use of hormone replacement therapy

There was no significant difference between Indian and African fracture subjects regarding age of menarche, menopause or parity and no difference in the use of hormone replacement between Indian and African hip fracture subjects, however the numbers were very small for meaningful comparison.

Cognitive changes

Although there was no difference in memory between Indian and African hip fracture subjects, Indian hip fracture subjects had greater memory concerns than matched Indian controls.

Falls

On history there was a higher number of self-reported falls in Indian compared to African hip fracture subjects (Table 4.34), but no difference in the number of sideways falls. In the EFST, Indian fracture subjects were more likely to report falls, seek medical attention for a fall, use medication more frequently and have activity

limitation due to pain. However, there was no significant difference in the number of near falls, visual or sensory disturbances and gait and balance abnormalities.

Both Indian and African control subjects compared to their matched hip fracture subjects reported a greater number of near falls, activity limitation due to a fear of falling, concerns about uneven footing, use of higher number of prescription medications and easily fatigability. In addition African control subjects compared to African hip fracture subjects were significantly more likely to have reported a fall, sought health care after a fall, have had more pain and concerns regarding transfer. Indian control subjects compared to Indian hip fracture subjects reported greater visual impairment and were more likely to report that they would need assistance to stand if they fell.

Past history of fractures

Childhood fractures were more common in Indian than African hip fracture subjects (Table 4.34); however there was no difference in number of previous fragility fractures. Additionally Indian and African hip fracture subjects reported previous fragility fractures significantly more commonly than their matched controls (25.5% vs. 7.78%; $p < 0.0001$; OR 3.375, 95%CI 1.53-7.43) and (22.7% vs. 9.6%; $p = 0.038$; OR 3.0, 95%CI 1.09-8.25) respectively.

Self-reported vertebral fractures

There was no difference in the number of self-reported VF.

Family history of osteoporosis and maternal history of hip fractures

A family history of osteoporosis or fracture was not different between Indian or African hip fracture cases but Indian control subjects had a significantly greater history of both conditions than Indian fracture subjects.

Lifestyle factors

Hip fracture subjects, Indians and Africans, were significantly more active than their matched control subjects (38.2% vs. 12.5%; $p < 0.0001$; OR 8.679, 95%CI 2.45-30.73) and (34.8% vs. 11%; $p < 0.0001$; OR 4.949, 95%CI 1.34-18.31), and Indian hip fracture subjects were more likely to exercise for more than 30 minutes a day compared to African hip fracture subjects (47.3% vs. 14.4%; $p < 0.0001$) (Table 4.34).

Calcium intake was significantly lower in African than in Indian hip fracture subjects (346.4 ± 209.3 mg/day vs. 458.6 ± 214.2 mg/day; $p = 0.005$) (Table 4.34). African hip fracture subjects also had significantly lower calcium intake than their matched control subjects (346.4 ± 209.3 mg/day vs. 498.6 ± 279.2 mg/day; $p < 0.0001$).

Although there was no difference between Indian and African hip fracture subjects with regards to sunlight exposure, alcohol consumption or smoking, Indian fracture subjects were more likely to consume alcohol compared to Indian control subjects (18.2% vs. 4.8%; p = 0.004; OR 7.0, 95%CI 1.59-30.8).

Table 4.34 Clinical risk factors for osteoporosis and fractures in African and Indian hip fracture subjects.

	African (n=66)	**Indian (n=110)**	**p value**
History of falls	21 (31.8)	56 (50.9)	*0.013
Sideways falls	15 (22.7)	40 (36.3)	0.594
Childhood fracture	21 (31.8)	56 (50.9)	*0.013
Fragility fracture >40 year	15 (22.7)	40 (36.4)	0.967
Self-reported vertebral fracture	3 (4.5)	2 (1.8)	0.292
Self-reported physical activity level			
Extremely active	23 (34.8)	42 (38.2)	*<0.0001
Moderately active	23 (34.8)	32 (29.1)	*<0.0001
Mild activity	13 (19.7)	27 (24.5)	*<0.0001
Sedentary	7 (10.6)	9 (8.2)	*<0.0001
Smoking	10 (15.2)	22 (20)	0.522
Alcohol	8 (12.1)	20 (18.2)	0.087
Calcium (mg) mean ± SD	346.4 ± 209.3	458.6 ± 214.2	*0.005

- **Number of subjects n (%)**

4.3.3.3 Bone mineral density

Areal BMD measurements tended to be higher in African fracture cases, but reached statistical significance for total hip measurement only (Table 4.35). Interestingly, the BMAD finding in the two ethnic groups was similar.

Table 4.35 Bone mineral density in African and Indian hip fracture subjects.

	African fracture subjects	**Indian fracture subjects**	**p value**
Spine BMD (g/cm^2)	**0.715 ± 0.166 (n=39)**	**0.686 ± 0.176 (n=67)**	**0.413**
Femoral neck BMD (g/cm^2)	0.545 ± 0.104 (n=41)	0.505 ± 0.104 (n=63)	0.120
Total hip BMD (g/cm^2)	0.692 ± 0.147 (n=41)	0.630 ± 0.129 (n=63)	*0.025
Spine BMAD (g/cm^3)	0.192 ± 0.034 (n=39)	0.202 ± 0.038 (n=67)	0.611
Hip BMAD (g/cm^3)	0.113 ± 0.019 (n=41)	0.126 ± 0.122 (n=63)	0.286
Hip T - Score	-2.73 ± 0.61 (n=41)	-2.96 ± 0.92 (n=63)	0.185
Spine T - Score	-3.10 ± 1.43 (n=39)	-3.03 ± 1.24 (n=67)	0.800

- All result reported as mean ± SD

Both African and Indian fracture subjects when compared to their matched control groups had a lower BMD at all sites measured. In Indians however there was no

significant difference in the hip BMAD measurements between fracture and control subjects (Table 4.36).

Table 4.36 Bone mineral density in African and Indian hip fracture and matched control subjects

	African Fracture	African control	p value	Indian fracture	Indian Control	p value
Lumbar spine BMD	0.715 ± 0.166 (n=39)	0.885±0.165 (n=65)	*<0.0001	0.686 ± 0.176 (n=67)	0.834 ± 0.185 (n=110)	*<0.0001
Femoral neck BMD	0.545 ± 0.104 (n=41)	0.731 ± 0.13 (n=65)	*<0.0001	0.505 ± 0.104 (n=63)	0.701 ± 0.124 (n=109)	*<0.0001
Total hip BMD	0.692 ± 0.147 (n=41)	0.893 ± 0.154 (n=66)	*<0.0001	0.63 ± 0.129 (n=63)	0.861 ± 0.156 (n=109)	*<0.0001
Spine-BMAD	0.192 ± 0.034 (n=39)	0.244 ±±0.442 (n=65)	*<0.0001	0.202± 0.038 (n=67)	0.244 ± 0.038 (n=110)	*<0.0001
Hip-BMAD	0.113 ± 0.019 (n=41)	0.145 ± 0.023 (n=64)	*<0.0001	0.126 ± 0.122 (n=63)	0.143 ± 0.026 (n=109)	0.229
Hip T score	-2.73 ± 0.61 (n=41)	-1.2 ± 1.31 (n=66)	*<0.0001	-2.96 ± 0.92 (n=63)	-1.28 ± 1.22 (n=110)	*<0.0001
Spine T score	-3.10 ± 1.43 (n=39)	-1.19 ± 1.64 (n=66)	*<0.0001	-3.03 ± 1.24 (n=67)	-1.45 ±1.4 (n=110)	*<0.0001

- All results reported as mean ± SD

4.3.3.4. Morphometric vertebral fractures

Morphometric VFs were significantly greater in African than Indian hip fracture subjects (37.5% vs. 28.6%; $p < 0.0001$). Both Indian and African hip fracture subjects had significantly greater number of morphometric fractures than matched controls (28.6% vs. 17.8%; $p < 0.0001$) and (37.5% vs. 22.7%; $p = 0.002$) respectively.

4.3.3.5 Functional Assessment

Physical self-maintenance scale and Instrumental activity of daily living

There was no significant difference between Indian and African hip fracture subjects in the individual basic activities of daily living or the total scores for PSMS or IADL. However Indian hip fracture subjects compared to African hip fracture subjects were more likely to have difficulty with using a telephone, walking a distance, cooking and handiwork (Table 4.37).

Both Indian and African hip fracture subjects had significantly poorer overall total PSMS and IADL cores compared to their matched control subjects. Indian fracture subjects, although reported being more active than matched control subjects, had significantly greater difficulties with most physical activities except for eating and in all the IADL parameters (Appendix 4.B, Table 4.B.1). Whereas African hip fracture subjects had similar IADL activities compared to control subjects except for cooking, handiwork, and managing finances (Appendix 4.B, Table 4.B.2).

Table 4.37 Independent performance of instrumental activities of daily living in African and Indian hip fracture subjects.

IADL	African (n= 66)	Indian (n 110)	p value
Telephone (%)	42.4	59.1	*0.032
Walking a distance (%)	45.5	60.9	*0.046
Shopping (%)	21.8	44.5	0.095
Cooking (%)	31.8	50.9	*0.013
Housework (%)	51.5	65.5	0.067
Handiwork (%)	40.9	58.2	*0.026
Laundry (%)	21.2	18.2	0.593
Medication (%)	22.7	225.5	0.684
Finance (%)	15	32	0.356
Total score mean ± SD	22.7 ± 5	21.6 ± 4.7	0.148

- Percent of subjects with 0 (unable to perform activity)
- Pre-fracture evaluation

Quality of Life

The only difference between Indian and African hip fracture subjects was Indians were less likely to be able to complete daily activities independently (40.9% vs 25.8%; p = 0.042).

Indian hip fracture subjects had a higher QoL total score, depressed mood, pain, difficulty with mobility and self-care than Indian control subjects. In contrast African hip fracture subjects had a better total score than African control subjects, but the

latter were more likely to require assistance with daily tasks (Appendix 4.B, Table 4.B.3).

Oswestry Disability Index and Visual Analogue Score

Indian hip fracture subjects had a higher percentage ODI score (p= 0.043) and had greater difficulty with personal care (59.1% vs 42.4%; p = 0.032) compared to African subjects The VAS score pre or post fracture for pain was not significantly different between Indian and African fracture subjects.

African hip fracture subjects had a lower ODI and VAS score than African controls. Indian hip fracture subjects compared to Indian control cases however had significantly higher ODI score (p =0.006), but also lower VAS pain score. They also needed help with lifting, had a disturbed sleep pattern and difficulty with socializing and travel pre-fracture compared to their matched controls (Appendix 4.B, Table 4.B.4).

4.3.3.6 Haematological and biochemical comparison

African fracture subjects had significantly higher mean sodium (however this was within the normal range), mean urea and mean random glucose levels compared to Indian fracture subjects. While Indian fracture subjects had a higher CRP level (Table 4.38). There was no significant difference in vitamin D, PTH or hormonal levels between the two fracture cohorts.

Table 4.38 Biochemical results in African and Indian hip fracture subjects

	African (n=66)	Indian (n=110)	p-value
Sodium (mmol/L)	137 ± 5.3	135.3 ± 4.2)	*0.017
Urea (mmol/L)	8.6 ± 5.8	6.8 ± 4.2	*0.033
Glucose (mmol/L)	7.3 ± 4.3 (n=55)	6.3 ± 1.6 (n=108)	*0.031
C-Reactive protein (mg/L)	19.2 ± 25.9 (n=59)	30.7 ± 36.8 (n=101)	*0.022
Vitamin (OH) D (nmol/L)	39.7 ± 22.6 (n=56)	38.9 ± 24 (n=95)	0.823

- All results reported as mean ± SD

There was a significantly lower mean total protein (71.9 ± 12.8 g/L vs. 74.7 ± 5.2 g/L; p = 0.001) and higher mean random plasma glucose (6.3 ± 1.6mmol/L vs. 5.9 ± 1.9mmol/L; p = 0.004) in Indian fracture subjects compared to their matched control subjects (table 4.39).

Table 4.39 Biochemical results in African and Indian hip fracture and matched control subjects.

	African hip fracture (n=66)	African control (n=66)	p-value	Indian hip fracture (n=110)	Indian control (n=110)	p-value
Total protein (g/L)	71.3 ± 8.6)	75.2 ± 5.9 (n=65)	0.151	71.9 ± 12.8 (n=108)	74.7 ± 5.2	*<0.0001
Gamma Glutamyl transferase (IU/L)	42.8 ± 45.8	26.8 ± 19.4 (n=65)	*0.002	48.4 ± 42.7 (n=108)	32.1 ± 22.4	*0.001
Glucose (nmol/L)	7.3 ± 4.3 (n=55)	5.9 ± 1.9 (n=65)	0.367	6.3 ± 1.6 (n=101)	5.9 ± 1.9	*0.004
25 (OH) Vitamin D (nmol/L)	39.7 ± 22.6 (n=56)	49.2 ± 23.7	*0.004	38.9 ± 24 (n=95)	51.7 22.7	*0.002
Parathyroid hormone (pg/ml)	6.3 ± 3.9 (n=51)	7.3 ± 7.8 (0.8-74)	0.081	7.5 ± 3.7 (n=108)	9.5 ± 6.9	0.407

- All results reported as mean ±SD

4.4 Outcomes post hip fracture

Of the 200 subjects who participated in the one year prospective study, by the end of the study period 67 subjects (36.4%) had died and 16 (8%) were lost to follow up, either because they had opted out of the study or could not be contacted. The remaining 117 subjects (58. 5%) completed the one year follow up.

4.4.1 Acute hip fracture management

The majority of the subjects (72%) had presented directly to one of the regional level hospitals after a fall. Of the remainder, 9.5% presented to a local district hospital or a clinic and 9% to their primary care physician before being referred to the regional hospital.

Indian and White subjects were more likely to go directly to a regional hospital, 75.5% and 71.4% respectively or to have gone initially to a private health care provider, 8.2% and 23.8% respectively. Africans subjects presented either to the regional hospital (65.2%), or to a public health sector clinic (19.7%).

There was a wide variance in the time to admission after the hip fracture with a mean of 4.2 ± 2 days (range 0 - 122 days). Similarly the mean time to surgery was 11.3 ± 9.2 days (range 1 – 75 days) and the mean length of stay was 21.9 ± 14.8 days (range 5 - 116 days).

All subjects received skin traction and pre-operative physiotherapy. Surgical management was undertaken in 173 subjects (86.5%) with spinal anaesthesia being most commonly used.

The choice of prosthesis was determined by fracture type and the attending surgeon's choice and there is no restriction placed on choice. Most commonly used were a pin and plate in 64 subjects (37%) and a bipolar prosthesis in 60 subjects (34.7%). The rest had either a Thompson's prosthesis (15.6%) or a femoral nail (12.7%) inserted. One subject died during surgery and data was not available for three subjects.

Twenty seven subjects (13.5%) were considered unfit for surgery based on underlying medical conditions and not fracture severity and managed conservatively.

4.4.2 Mortality rate

At the end of one the year study period 67 subjects (36.4%) had died. The mortality rate was highest in the first month with 26 deaths (13%) which accounted for 38.8% of all mortality. At three months and six months a further 9 (4.5%) and 17 (8.5%) subjects died respectively and from months seven to 12, a further 15 (7.5%) had died (Figure 4.13).

A tendency towards a higher overall mortality was noted in men compared to women (41.1% vs. 30.6%; $p = 0.34$) but this did not reach statistical significance. African

fracture subjects had significantly higher mortality than Indians during the one year study period (Figures 4.14 and 4.15).

The highest percentage of deaths was seen in African women 20 (46.5%), followed by Indian men 14 (45.1%), African men 7 (36.8%), White women 5 (31.3%) and 14 (26.8%) in Indian women.

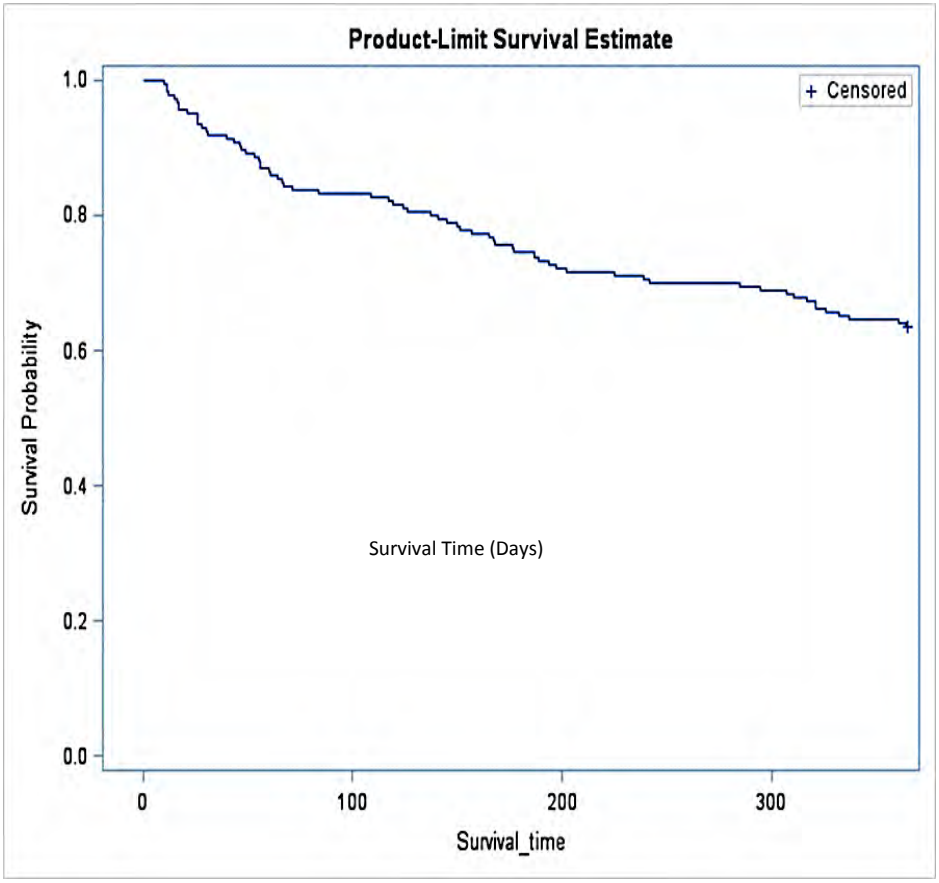

Figure 4.13 Kaplan Meier curve showing a decrease in survival with time in the total hip fracture subjects over a twelve month period (n=184)

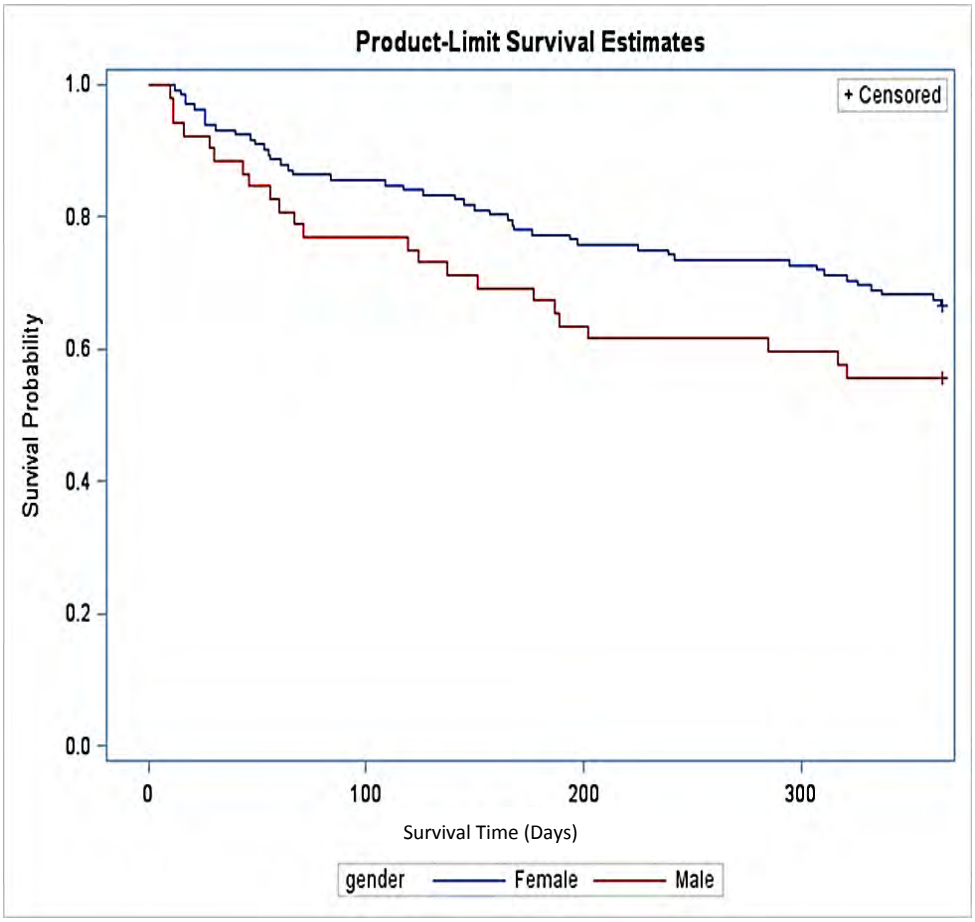

Figure 4.14 Kaplan Meier curve for survival in men (n = 49) and women (n = 135) hip fracture subjects over a twelve month period

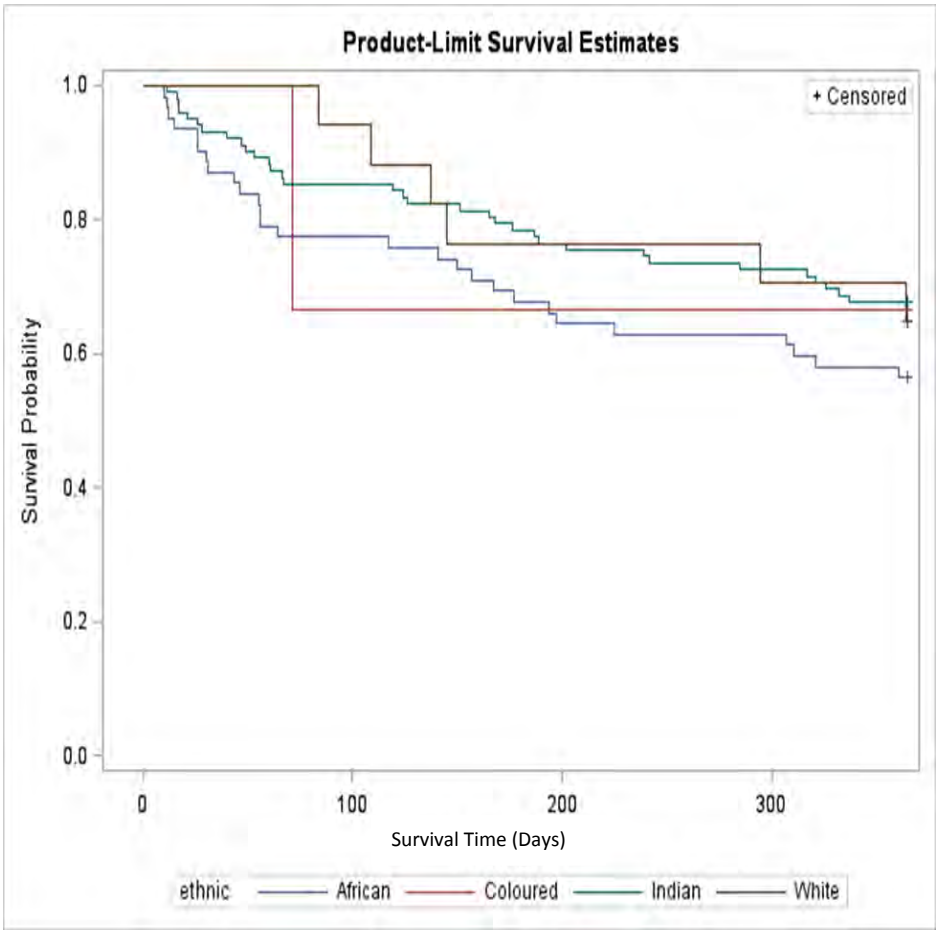

Figure 4.15 Kaplan Meier curve for survival in African (n = 62), Indian (n = 136), Coloured (n = 3) and White (n = 17) hip fracture subjects over a twelve month period

4.4.2.1 Demographic and clinical characteristics of deaths in hip fracture subjects.

In univariate analysis, deaths at one year were older (76.2 ± 9.7 years vs. 73.4 ± 8.2 years; p = 0.048), had a significantly lower mean body weight (51.0 ± 10.8 kg vs. 56.7± 14.9 kg; p = 0.036; OR 1.036 CI 1.0-1.21) and mean BMI (21.2 ± 4.2 kg/cm^2 vs. 23.2 ± 5.1 kg/cm^2; p = 0.037; OR 1.101 CI 1.0-1.21) compared to survivors (Table 4.30). It is noteworthy that of the 67 hip fracture subjects who died, weight could not be measured in 30 (44.8%) subjects due to severity of hip fracture and inability to stand unassisted at the time of discharge. There is therefore a significant association between missing weight and the outcome death (p = 0.001). Furthermore weight was not measured in 28 (23.9%) of the survivors.

Although hip fracture subjects had a lower education level than control subjects, deaths at one year were more likely to have a better education level compared to those who survived. No differences were noted in housing or employment status

No significant difference was observed in the prevalence of chronic cardiovascular disease (hypertension and DM) amongst deaths at one year and survivors. Although only 7 subjects had a prior history of osteoporosis, 5 of these subjects died (p = 0.052; OR 9.355, 95%CI 1.07-81.85), this did not reach statistical significance.

There was no significant association between mortality and other secondary causes of osteoporosis (RA, chronic gastro intestinal disease, hyperthyroidism, hyperparathyroidism, malignancy, prolonged immobilization, hypogonadism or

chronic renal failure). The use of bone toxic drugs including GC was not significantly different amongst the two groups.

Hip fracture subjects with a higher self-reported physical activity levels were more likely to survive compared to those who were mildly active or sedentary. There were no significant differences in hormonal or lifestyle factors.

Table 4.40 Characteristics of hip fracture subjects who died or survived at 12 months

	Survivors n (n=117)	Deaths (n= 67)	p value	OR	95% CI
Age(years) mean ± SD	73.6 ± 8.0	75.3 ± 8.6	*0.048	n/a	
Weight (kg) mean ± SD	56.7 ± 14.9 (n= 92)	51.0 ± 10.8 (n=37)	*0.036	1.036	1.00 - 1.07
BMI (kg/cm^2) mean ± SD	23.3 ± 5.4	21.2 ± 4.2	0.037	1.102	1.00 - 1.21
Education level n (%) 1:Reference category Std. 10 plus					
No schooling	41 (35%)	26 (38.8%)	*<0.0001	6.308	1.24 - 32.05
Std. 3 or lower	43 (36.8%)	20 (29.9%)	*<0.0001	8.6	1.67 - 44.24
Std. 6-7	31 (26.5%)	13 (19.4%)	*<0.0001	9.538	1.78 - 51.15
Std. 10 plus	2 (1.7%)	8 (11.9%)	0.168	1	1
Self-reported activity level n (%) 1 :Reference category sedentary					
Extremely active	47 (40.2%)	22 (32.8%)	*<0.0001	2.403	0.82 - 7.07
Moderately active	28 (23.9%)	14 (20.9%)	*<0.0001	2.25	0.71 - 7.09
Mildly active	34 (29.1%)	22 (32.8%)	*<0.0001	1.739	0.58 - 5.19
Sedentary	8 (6.8%)	9 (13.4%)	*0.002	1	1
Morphometric VF	24 (20.5%)	18 (26.9%)	*<0.0001	n/a	

4.4.2.2 Functioning level

Compared to survivors, subjects who died had significantly greater difficulty with performing most of the basic activities of daily living (PSMS) and a lower total PSMS score (Table 4.41), but the difference only neared significance (p=0.062).

Table 4.41 Independent performance of basic activities of daily living in PSMS in survivors and deaths in hip fracture subjects at 12 months

Activity	Survivors (n=117)	Deaths (n=67)	p value
Eating (%)	0.0	7.5	*0.003
Dressing (%)	6.8	14.9	0.076
Grooming (%)	6.8	17.9	*0.020
Walking (%)	11.1	22.4	0.076
Transfer bed (%)	4.3	17.9	*0.002
Bathing (%)	7.7	16.4	0.067
Toileting (%)	8.5	3.4	0.295
Total score mean ± SD	13.5 ± 1.6	12.9 ± 2.5	0.062

- Total score calculated out of 17
- (%) of subjects with a score of 0 (unable to perform activity independently)
- Assessment done pre-fracture in hip fracture subjects

The total IADL score was significantly in hip fracture cases that survived than those who died at 12 months. Hip fracture subjects who died had greater difficulty with

walking distance, shopping, cooking, taking medication and managing finances independently (Table 4.42).

Table 4.42 Independent performance of instrumental activities of daily living in survivors and deaths in hip fracture subjects at 12 months

IADL	Survivors (n=117)	Deaths (n 67)	p value
Telephone (%)	48.7	61.2	0.103
Walking distance (%)	48.7	67.2	*0.015
Shopping (%)	34.2	52.2	*0.016
Cooking (%)	39.3	56.7	*0.023
Housework (%)	58.1	67.2	0.225
Handiwork (%)	48.7	59.7	0.151
Laundry (%)	15.4	26.9	0.052
Medication (%)	18.8	32.8	*0.032
Finances (%)	21.4	35.8	*0.033
IADL Score mean ± SD	22.5 ± 4.6	20.9 ± 5.1	*0.036

- Total score calculated out of 27
- (%) of subjects with a score of 0 (unable to perform activity independently)
- Assessment done pre-fracture in hip fracture subjects

The total ,QoL, ODI and VAS scores were similar between hip fracture cases that survived and those who died at 12 months, except survivors had better mobility (p = 0.01) and lifting ability (p = 0.045) (Table 4.43 and 4.44).

Table 4.42 Independent performance of QoL activities in survivors and deaths in hip fracture subjects at 12 months

Quality of life	Survivors (n= 117)	Deaths (n=67)	p value
Mobility (%)	6.8	19.4	*0.010
Self-care (%)	32.5	41.8	0.205
Daily activities (%)	31.6	32.8	0.865
Pain (%)	14.5	14.9	0.942
Mood (%)	23.9	16.9	0.658
QOL Score mean ± SD	6.2 ± 1.7	6.5 ± 1.7	0.15

- Total score calculated out of 15
- (%) of subjects with a score of 0 (unable to perform activity independently)
- Assessment done pre-fracture in hip fracture subjects

Table 4.43 Independent performance of ODI activities and VAS for pain in survivors and deaths in hip fracture subjects at 12 months

	Survivors (n=117)	Deaths (n=67)	p value
Pain (%)	7.7	11.9	0.338
Personal care	52.1	61.2	0.234
Lifting (%)	19.7	32.8	*0.045
Walking (> 1km) (%)	2.6	9	0.053
Sitting (>1 hour) (%)	10.3	13.4	0.514
Standing (%)	2.6	4.5	0.482
Sleeping (%)	12.0	19.4	0.178
Social life (%)	13.7	17.9	0.442
Travelling (%)	13.7	17.9	0.442
Oswestry Disability Score (%) mean ± SD	33.5 ± 17.1	29.7 ± 14.4	0.107
VAS pre-fracture mean ± SD	1.4 ± 1.3	1.4 ± 1.3	0.711
VAS immediately post-fracture mean ± SD	5.5 ± 1.9	5.7 ± 1.8	0.619

- VAS calculated out of 10
- (%) of subjects with a score of 0 (unable to perform activity independently)
- Assessment done pre-fracture in hip fracture subjects

4.4.4.3 Haematological and biochemical differences in survivors and deaths at 12 months post hip fracture

Subjects who died (investigations at time of fracture) had a significantly higher serum urea, creatinine levels and GGT levels while their serum total protein, albumin and vitamin D levels were significantly lower. (Table 4.45)

In addition the inflammatory markers, CRP and ESR were significantly higher in the subjects who died (Table 4.45).

Table 4.45 Biochemical parameters in survivors and deaths in hip fracture subjects at 12 months

	Survivors (n=117)	Deaths (n=67)	p-value	OR	95% CI
Sodium (mmol/L)	136.4 ± 3.8	135.9 ± 4.8	*0.027	1.083	1.01 - 1.16
Urea (mmol)	7.0 ± 3.9	9.1 ± 6	*0.010	0.917	0.86 - 0.98
Creatinine (umol)	90.6 ± 47.9	107.8 ± 65.1	0.062	0.994	0.99 - 1.00
Total protein (g/dl)	72.4 ± 8.4 (n=116)	68.9 ± 10.5	*0.014	1.043	1.01 - 1.08
Albumin (g/dl)	36.1 ± 6.4 (n=116)	28.8 ± 7.9	*<0.0001	1.187	1.12 - 1.26
Gamma glutamyl transferase (IU/L)	39.7 ± 41.5 (n=116)	55.8 ± 49.7	*0.020	0.992	0.99 - 1.00
25 (OH) vitamin D (nmol/L)	41.6 ± 23.4 (n=110)	33.0 ± 20.5 (n=50)	*0.025	1.02	1.00 - 1.04
C-Reactive protein (mg/L)	17.4 ± 28.1 (n=113)	39.4 ± 36.1 (n=58)	*<0.0001	0.977	0.97 - 0.99
Erythrocyte sedimentation rate (mm/hr)	39.2 ± 27.2 (n=105)	52.1 ± 30.4 (n=47)	*0.010	0.985	0.97 - 1.00

- All results reported as a mean ± SD

4.4.2.4 Management

Surgery was performed significantly more frequently in survivors than in deaths at one year (90.6% vs. 80.6%; p = 0.045; OR 2.320 CI 0.98-5.52) and hip fracture subjects managed conservatively had a significantly higher mortality (59.3% vs. 40.7%; p = 0.004).

There was significant greater delay in time to surgery in demised subjects (13.9 ± 12.6 days vs. 10.1 ± 6.8 days; p = 0.039) whilst time to admission (4.0 ± 7 days vs. 4.4 ± 14.7; p = 0.828) or duration of hospital stay (24.5 ± 16.8 days vs. 20.7 ± 13.5 days; p = 0.131) was not significant in the univariate analysis.

4.4.2.5 Predictors of mortality

In a backward conditional logistic regression model ethnicity (Africans), lower body weight or BMI, higher education status, difficulty with cooking, taking medications or managing finances, decreased mobility, decreased albumin or raised C-reactive protein and longer mean hospital stay (Table 4.46) were found to be significant.

Table 4.46 Multivariate model for predictors of mortality

		SE	Wald	p-value.
Step 12	Ethnicity		8.815	*0.012
	African	1.129	4.671	*0.031
	Mean body weight	0.086	8.095	*0.004
	Mean body mass index	0.189	5.171	*0.023
	Education > Std. 10		14.063	*0.003
	Education Std. 7 level	1.537	8.555	*0.003
	Education –primary school	1.397	8.875	*0.003
	Education no schooling	1.181	.029	0.865
	Ability to cooking	1.027	8.487	*0.004
	Ability to take medications	1.055	7.576	*0.006
	Manage finances	0.888	7.438	*0.006
	Mobility	0.939	7.355	*0.007
	Low albumin	0.073	6.930	*0.008
	Elevated C-reactive protein	0.012	8.735	*0.003
	Days to surgery	0.017	6.297	*0.012

4.4.3 Morbidity: One year outcome in hip fracture survivors

The functional assessments (BADL, IADL, QoL, ODI and VAS), performed at baseline, three, six and twelve months in 117 hip fracture survivors were compared using the McNemar test (Figures 4.16 – 4. and Appendix 4.C).

Physical Self Maintenance scale

A significant deterioration in all basic activities of daily living was noted from pre-fracture to three months. Subsequently most but not all parameters showed improvement but the negative change from baseline remained significant at one year for all parameters.

The percentage of subjects who were unable to dress or groom independently increased from 6.8% to 21.4% by twelve months ($p < 0.0001$). Prior to the hip fracture, 11.1% subjects were unable to walk independently, but at three months 78.6% and at one year 43.5% of survivors needed assistance or were unable to walk. A similar trend was seen with bathing and toileting. At each time point the overall score was significantly lower compared to baseline score. (Figure 4.16).

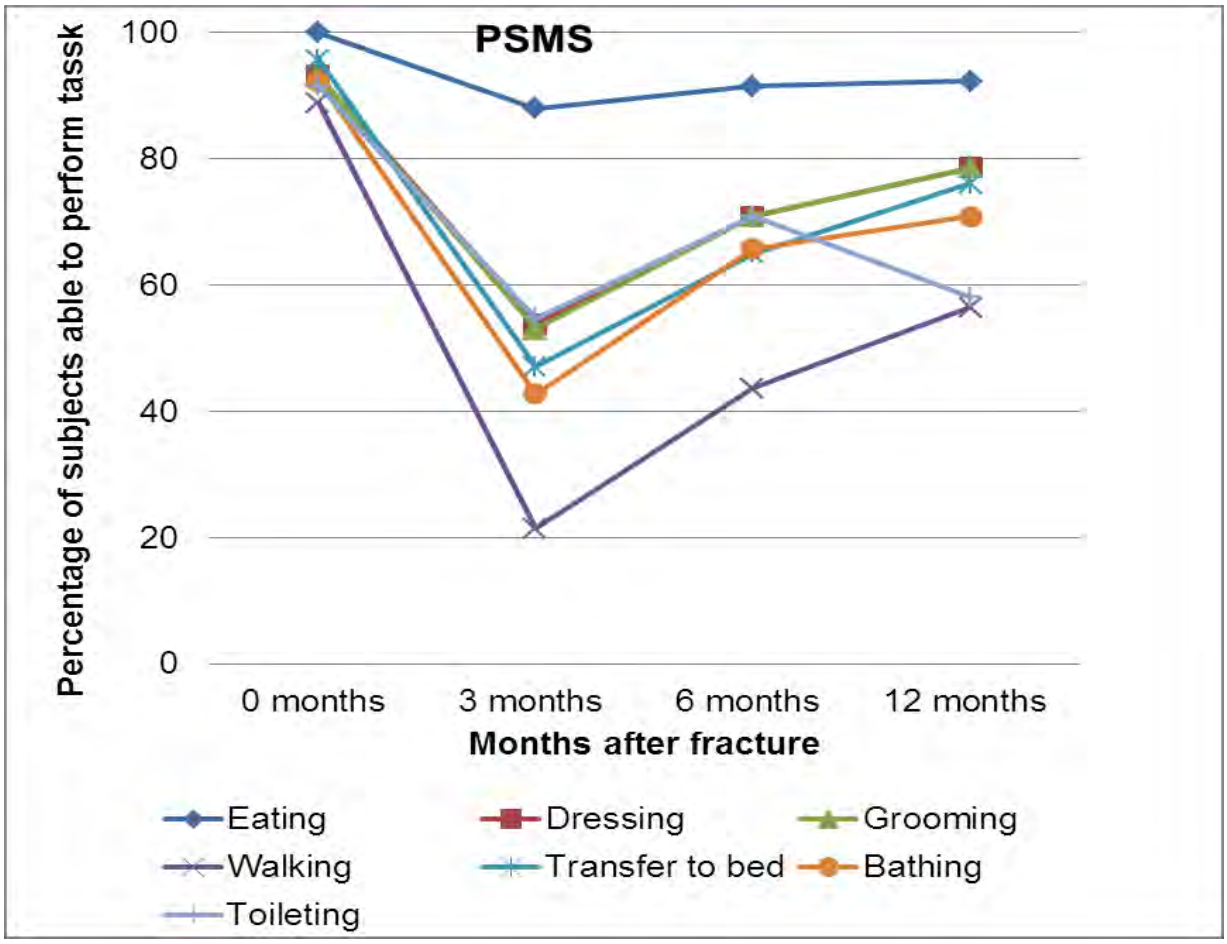

Figure 4.16 Comparison of percentage change in activities of daily living in survivors post hip fracture over a twelve month period (n=117). All parameters were significant p < 0.0001 at three months, six months and one year compared to baseline.

Instrumental activity of daily living

The ability in survivors to perform IADL also significantly declined at three months post hip fracture and although recovery was noted, at one year and this remained significantly lower than baseline at all-time points. (Figures 4.17

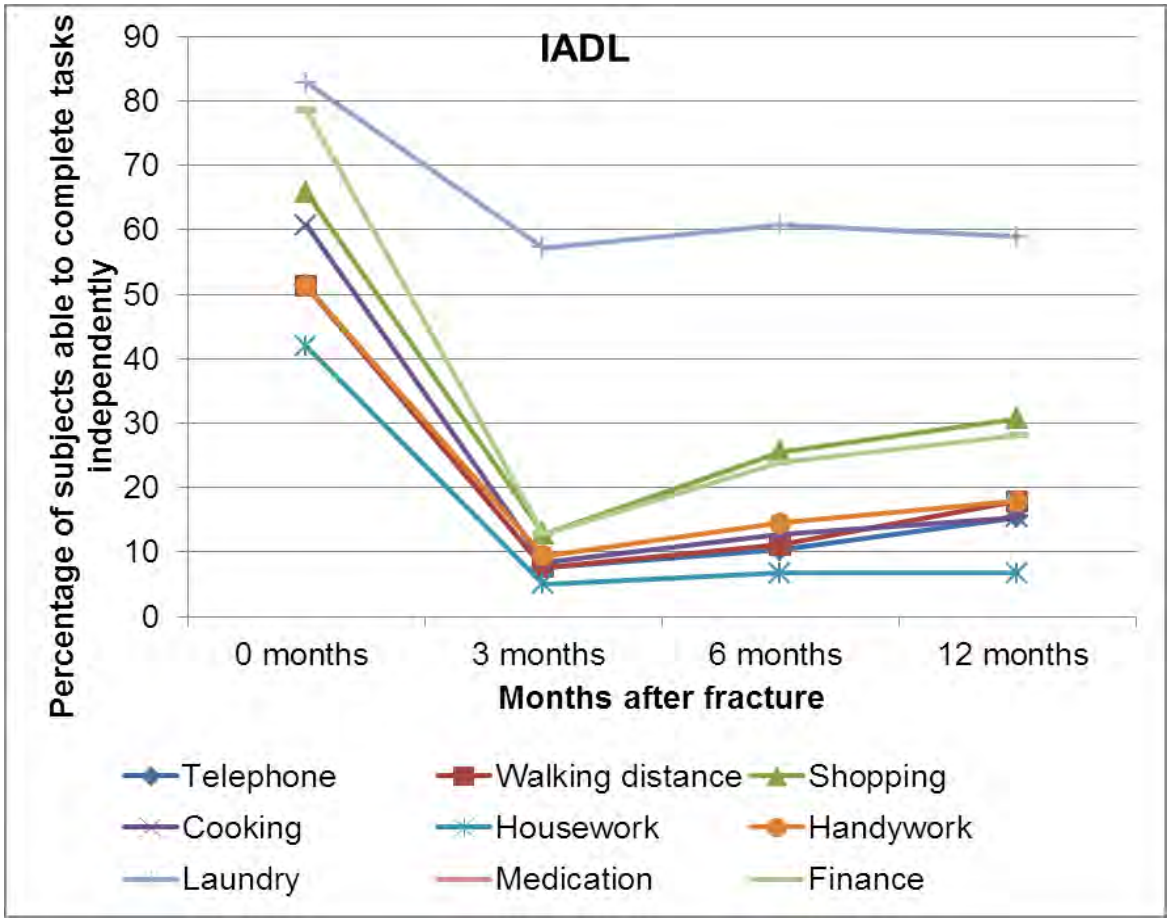

Figure 4.17 Comparison of percentage change in IADL in survivors post hip fracture over a twelve month period (n=117). All parameters were significant ($p < 0.0001$) at three months, six months one year compared to baseline.

Quality of life

At one year 33.3% were bed ridden or had problems with walking compared to 6.8% pre-fracture. This trend was seen in all aspects assessed; only 19.7% were able to complete basic self-care activities, 34.2% had no difficulty with daily activities and pain increased significantly from 14.5% to 35% at the end of one year. The total score was significantly higher compared to baseline at each time point (Figure 4.18)

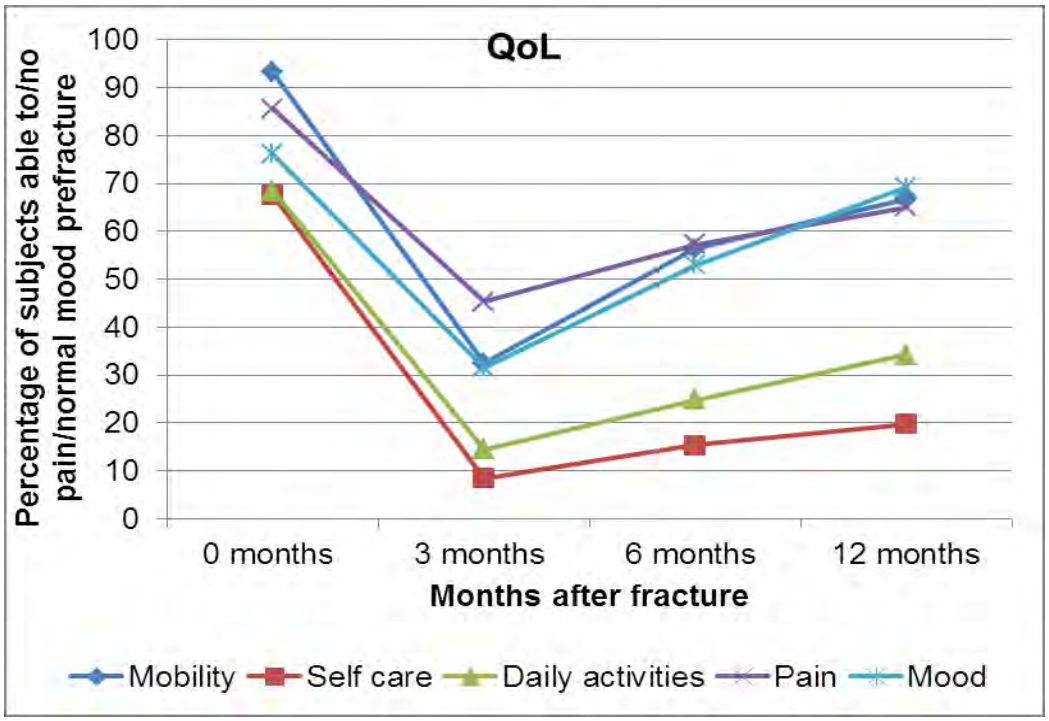

Figure 4.18 Comparison of percentage change in QoL activities, pain and mood in survivors post hip fracture over a twelve month period (n=117). All parameters were significant ($p < 0.0001$) at three and six months and at one year compared to baseline, except pain which at one year showed no significance difference ($p = 0.312$)

Oswestry disability index

There was a significant decline in all domains assessed including, personal care, lifting, walking, sitting, standing and sleeping which was still significant at one year. There was marked limitation in social activities and travel with a decline from 86.3% to 19.7% at three months and at one year only 27.4% could independently travel or socialize (Figure 4.19).

Visual Analogue Scale

The visual analogue scale remained significantly higher post fracture ($p < 0.0001$) (Appendix 4.C)

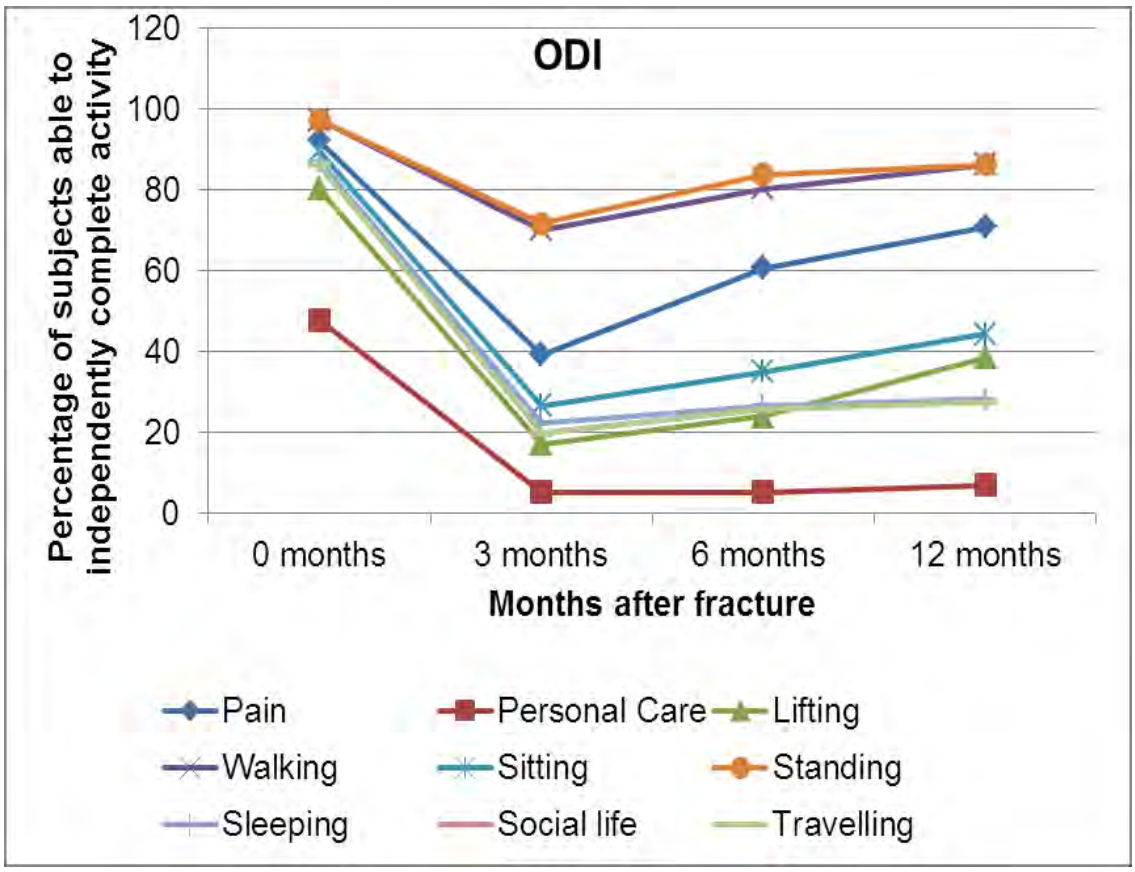

Figure 4.19 Comparison of percentage change in ODI activities in survivors post hip fracture over a twelve month period (n=117). All parameters were significant ($p < 0.0001$) at three and six months and at one year compared to baseline, except walking which although significant was ($p= 0.001$) at one year and standing ($p = 0.002$).

4.5 Health care costs associated with acute hip fracture management in the public sector

The costs of acute hip fracture were calculated in the modified bottom up approach for the admission and management of the 200 subjects enrolled in the prospective study. The cost of treatment was sub-divided into its major components: acute ward costs, theatre costs and investigations performed. The cost of prosthesis was determined.

The average cost per patient who was surgically managed was R62 891.65. (Table 4.47)

Table 4.47 Direct costs of hip fracture treatment in surgically managed hip fracture subjects

		Total cost in Rands	Percentage Cost (%)
Acute Ward Costs			
Ward costs (n=173)		11 056 073.64	87.9
Staff costs		10 373 693.52	82.5
Total Medications		190 904.73	1.5
Ward costs / consumables		481 912.80	3.8
Distance - Paramedic	64 Patients	5 562.59	
Stationary (ZAR /patient	20.00	4 000.00	
Theatre costs			
Surgical costs (n=173)			
Theatre Meds / consumables		291 862.56	2.3
Theatre Other		349 044.00	2.8
Investigations			
Radiology costs		304 495.00	2.4
Other: Electrocardiogram/ Echocardiogram		38 105.00	0.3
Haematological and biochemical tests		218 270.27	1.7
Prosthesis (n=169)*		320 480.00	2.5
Miscellaneous			
Private Doctor Referrals	5 Patients	1 250.00	
Total Cost		12 578 330.48	
Cost per patient		62 891.65	100

- *One patient died intraoperatively

Ward expenses were computed, with the aid of the Finance department (DOH), using the average cost per day as determined for the financial year 2010 / 2011 and the KZN DOH Hospital fees manual 2011.

Costs related to other resources were established from actual individual use. The length of stay in orthopaedic wards was recorded. In addition, number of days to surgery was documented for each patient and the total number of delayed days, with resultant costs, was calculated. The average daily cost of in-hospital ward was R 2560.06. The average number of days before surgery was 10.7 days. The number of days of delay for surgery was 1851 hospital bed days at a cost of R4 738 816 (n=173 surgically managed subjects).

The surgical procedure, operation, duration in minutes and type of implant used were reviewed. The average cost incurred for one hour of operating time was calculated. This estimate accounts for staff time in theatre and patient recovery area, use of equipment, sterile services and expendable items including, those employed by the anaesthetic team. The cost for the different types of implant was calculated and incorporated separately into the costing.

All pathology, microbiology and radiological investigations performed were documented for each patient and frequency recorded. Using this data the individual total cost incurred in the treatment of each patient was calculated.

The normative cost of treating a hip fracture was calculated as per flow diagram in methodology (Section 3.13) based on ideal management of hip fracture subjects. The difference in costing based on a 7 day hospital stay using the same type of prosthesis was R 22 996.65 per patient.

The detailed normative costing framework is attached in Appendix 3H.

4.5.1 Comparative analysis normative versus actual costs

Normative Costing

Sample size	Total Cost (R)	Cost per patient (R)
169	R 6 742 227.00	R 39 895.00

Actual Costing

Sample	Total Cost (R)	Cost per patient (R)
169	R 10 628 688.85	R 62 891.65

Treatment with anti-osteoporotic drugs decrease hip fractures approximately by 36% [500]. The treatment could potentially have resulted in only 110 subjects having a hip fracture. If we estimate that Zoledronic acid a yearly infusion costs R1534.00 then treatment of the 173 subjects who had surgery with Zoledronic acid would have resulted in an approximate saving of R 3 .7 million.

4.6 Summary of Results

The main findings of this study were:

- Of the 277 consecutive subjects admitted during the study period, the mean age was 75.9 ± 9.2 years and the female: male ratio was 2.8:1 with men being significantly younger than women (75.2 ± 9.3 years vs. 77.2 ± 8.8 years; p< 0.001).

- The highest number of hip fractures were seen in Indians (52.7%), followed by African (31.4%), Whites (13.4%) and lowest Coloureds (2.5%).

- The crude incidence rate for minimal trauma hip fractures in the eThekwini public sector hospitals was 97.4/100 00. The incidence rate for hip fractures increased with age in both men and women and a similar trend was seen in African, Indian and White women subjects.

- In the univariate analysis the risk factors identified for hip fractures were a lower educational level, low body weight and body mass index, prior fragility fractures, sideways fall, memory impairment, morphometric vertebral fractures, higher physical activity levels, smoking alcohol consumption, poorer functional activity level, low vitamin D levels and low BMD. The haematological and biochemical investigation showed hip fracture subjects had a lower haemoglobin, total protein and albumin, with raised inflammatory markers.

- In the stepwise backwards Cox logistic regression model a prior fragility fracture (p = 0.001), higher pre- fracture physical activity levels (p = 0.002), lower BMI (p < 0.0001), higher education level (p < 0.0001), lADL (p = 0.002) and QOL (p =

0.038) scores, haemoglobin ($p = 0.011$), albumin ($p < 0.0001$), white blood cell count ($p < 0.0001$) and C-reactive protein ($p = 0.005$) remained significant.

- The majority of hip fracture subjects were managed surgically and the mean time to surgery was 11.3 ± 9.2 days (range 1 – 75 days).

- A high mortality rate of 36.4% was recorded at one year.

- In the univariate analysis, risk factors for mortality at one year included increasing age, lower body weight and BMI, higher educational level, lower physical activity levels, greater difficulty with functional activities and laboratory test found a higher serum urea, creatinine and GGT levels and inflammatory markers, CRP and ESR, while their serum total protein, albumin and vitamin D levels were significantly lower.

- The predictors for mortality in the backwards stepwise multivariate logistic regression model included ethnicity, education, mobility, ability to cook, take their medication, manage finances independently, length of hospitalization, lower albumin and elevated C-Reactive protein levels.

- In survivors there was a significant decline in basic and instrumental activities of daily and quality of life in the first three months which persisted at one year.

- Direct health costs were approximated to be R 62 891.65 per patient who was surgically managed with ward costs contributing to >85% of total expenditure.

Chapter 5 Discussion

5.1 Introduction

Over the latter half of the 20th century there has been a rapid demographic transition, especially in developed countries. With decreased fertility and death rates and increased longevity, the proportion of older persons has risen dramatically. This has been largely due to an improvement in socio-economic conditions and public health care and advances in medicine. However, this has also resulted in an increase in the prevalence and burden of NCDs, including osteoporosis. Currently developed countries bear the osteoporosis burden and have the highest incidence of osteoporotic hip fractures. Although hip fractures account for less than 20% of all fractures, they are an important barometer of the osteoporosis burden as they diminish quality of life and have the highest mortality rate [3]. The pathology, epidemiology and risk factors of osteoporosis have been extensively studied in developed countries, and the introduction of cost-effective intervention thresholds [343] have resulted in the stabilization or decline in age adjusted hip fractures rates in White postmenopausal women [312, 501].

Developing countries, which still have a relatively low LE, have little data or emphasis on osteoporosis or fractures [28]. However, with urbanization and secular changes the LE is increasing, and it is projected that the burden of hip fractures will move to developing nations of Asia, Latin America and Africa [90]. It is expected by the year 2050, 50% of all osteoporotic fractures will occur in Asia; while Africa will experience the highest proportionate increase in hip fracture rates [28, 90].

South Africa is classified as an upper middle income country and spends approximately 8.8% of its gross domestic product (GDP) on health care [502]. In its dual health care system, however, less than one in five households have medical insurance with the majority of individuals dependent on state health care [497, 503]. There are limited epidemiological and health economic studies and accessing data from both sectors is challenging due to incorrect International Classification of Diseases (ICD) and procedure coding. In addition, the vast majority of public hospitals are under resourced, paper based and tracing of records retrospectively is a difficult and onerous task.

The South African multi-ethnic society, termed the “rainbow nation”, differs in many aspects including disease profiles. It has been postulated that the risk for osteoporosis varies in the different ethnic groups due to differences in BMD, bone turnover rates and skeletal geometry [67, 69, 387]. Lower spine BMD, but higher femoral BMD has been reported in Africans compared to Whites [56, 68], while BMD has been reported to be similar in Whites and Coloureds [387]. More recently a lower BMD has been reported in Indian men and women compared to their African counterparts [71]. However there has only been one study on the incidence of hip fractures over 40 years ago which reported an extremely low incidence of hip fractures in Africans compared to Whites [39].

In view of the lack of data this study was undertaken to determine the incidence, demographic profile, risk factors, outcomes and health care costs in patients aged 60 years and over with minimal trauma hip fractures in the public health sector of eThekwini area, South Africa.

5.2 Demographic profile

5.2.1 Age, gender and ethnicity

This is the first study to report the demographic profile of multi-ethnic subjects with hip fractures presenting to the public sector in the eThekwini region of KwaZulu-Natal. Of the 277 subjects with hip fractures, 146 (52.7%) were of Indian descent, 87 (31.4%) African, 37 (13.4%) Whites and 7 (2.5%) classified themselves as Coloureds (i.e. of mixed descent).

The mean age of the total group was 75.9 ± 9.2 years; with the lowest mean age in Indian subjects (74.2 ± 8.08 years), followed by African subjects (76.5 ± 10.5 years) and the highest in Whites (80.2 ± 8.5 years). The lower mean age in Indians subjects is consistent with an earlier study which showed that fractures in immigrant Indians in the UK occurred 10 - 15 years earlier than Whites [44, 370]. Studies from India have also reported a lower mean age [43]. Although Indians in SA and India may share genetic similarities, there are may be significant differences between Indians in residing in India and SA, due changes in diet from a predominantly vegetarian diet to a diet higher in animal protein, climate, and possible differences in physical activity levels, however there are no studies directly comparing the two population groups.

Life expectancy in SA, is lower than developed countries, estimated to be 50.1 years for men and 52.1 years for women [504] (for the period to 2009 -2012) compared to 77.3 years and 81 years for men and women respectively in the UK. The lower mean age for hip fractures, is possibly due to a lower LE. Another possible reason is that this study was undertaken in an urban area and traditionally older Africans,

especially women, return to rural areas to care for younger family members while economically active individuals remain in cities.

The average age of the fracture subjects in this study was higher than other developing countries such as India, Latin America and rest of Africa where the mean age is usually less than 75 years [43, 47, 505]. The reasons for this are not clear as the population of eThekwini is predominantly young, with only 6.8% of the population being above the age of 60 years old, and the LE is lower than in India (62.8 years and 65.7 years for men and women, respectively) but similar to Latin America and other African countries [506]. There are limited hip fracture studies from Africa and most the recent published studies are from Morocco [47]. A similar average age has been reported from Morocco for hip fracture subjects (75.0 ± 10.7 years for women and 73.3 ± 11.0 years for men) [47], however it must be emphasized that there are significant differences in ethnicity, culture, diet, dress and lifestyles between Morocco and SA. The reasons previously postulated for the lower mean age in the few studies from Africa include under-reporting of cases, conservative management at home of older frail individuals, lack of access to health care and greater use of traditional healers may not apply in an urban environment in possibly a relatively better developed SA [37, 48, 50].

The younger age of men in the total hip fracture cohort (75.2 ± 9.3 years vs. 77.2 ± 8.8 years; $p < 0.0001$), largely due to the predominance of Indian men in this cohort who were younger (70.1 ± 6.7 years vs. 75.8 ± 8.1 years; $p < 0.0001$), was highly significant. Men were more likely to have a fracture before the age of 75 years than women (64.4%% vs. 35.3%; $p < 0.0001$). The latter difference although significant in the Indian fracture subjects (72.1% vs. 41.7%; $p = 0.001$) did not reach statistical

significance in the African fracture cohort (56% vs. 33.9%; p = 0.058). Although it is traditionally believed that men are more likely to fracture at an older age, this study supports recent studies that have shown that men fracture three to six years before women [507, 508].

There are no recent studies from SA to compare differences in age in men and women with hip fractures. The mean age for Africans with hip fractures in this study was higher than in the landmark Solomon study [39] and the smaller study by Schnaid et al., [53], however these studies enrolled subjects from the age of 30 and 45 years respectively and cannot be used for comparison. The latter study also excluded subjects with osteoporosis, so possibly older subjects with hip fractures were excluded [53].

The total number of Coloured and Whites subjects were small and the study was not powered to draw any conclusions regarding age differences, however White women had the highest mean age at 80.6 ± 8.4 years which is comparable to White women in Europe [508].

In this study, the gender ratio of female to male at 2.8:1, was similar to that in developed countries, were 70 - 75% of hip fracture are seen in women [3]. This ratio may however be exaggerated by the absence of White men in this study. The gender ratio for the Indian and African subjects is higher than that described in the Indian subcontinent or other African countries [37, 43, 48]. Compared to the Solomon study [29] the gender ratio in African subjects has changed significantly from a male predominance (male: female ratio of 1.5:1) to a female predominance with a female to male of 2.5:1 in this study. A potential reason for the lower number

of African women in the earlier study was that at that time (1960's), SA pass laws restricted access of Africans, especially women, into city centres [509]. Subsequently, however urban and peri-urban townships were developed for African families. In addition, the rapid urbanization post-apartheid, associated dietary changes [391] and increase in sedentary lifestyle may also be responsible for an increased fracture risk. However due to the HIV/AIDS epidemic, LE has not changed significantly from 1960, when the mean LE was 49.2 years and 47.4 years and 51 years in men and women, respectively [510]. Studies in other developing countries including the AOS, Nigeria and Morocco have seen a similar change in gender ratio with a higher increase in the fracture risk in women than men [47, 81, 384]. In contrast, recent studies from the Indian subcontinent have observed only a slight increase in women compared to men [43, 511] and the gender ratio in African Americans remains unchanged and much lower at 1.5:1 [507].

A higher PBM and a higher BMD than women through most of life stages, decreased longevity, the lack of abrupt hormonal changes and the lower risk of falls are cited as reasons for the lower hip fracture rate in men in developed countries [218].

5.3 Incidence of osteoporotic hip fractures

The ethnic and racial makeup of a country plays an important role in determining the number of hip fractures, and the pattern of fractures seen in a country with a mixed population is often similar to the country of initial origin of that population group as observed from studies in Canada, Mexico and Spain where fracture rates are similar to UK, Spain and Europe respectively [343, 505, 512]. The majority of persons aged

60 years and over in eThekwini are African (45.9%), with Indians and Whites comprising 26.3% and 25.1% respectively and Coloureds the small minority at 2.7% [467]. The population of eThekwini represents only 4.3% of the total elderly population of Africans, 7.2% of Whites and 2.1% of Coloureds but 55% of Indians in SA.

In the incidence study the majority of hip fracture subjects were Indian (54.3%). The study may still be a potential under-representation of this group as approximately 46.1% and 66.1% of the Indian population have a medical aid or utilize private health care facilities respectively [498]. It is more likely to be accurate for Africans as only 10.8% of Africans have a medical aid. The low number of Whites subjects in this study was contradictory to expectations as hip fractures have consistently been reported more commonly in Whites [39, 61, 65, 343]. The low numbers of White subjects is most likely due to an under-representation, with White subjects more likely to use the private health care sector in SA compared to the other ethnic groups. Whites due to historical advantages are still the highest earners in SA and have a mean household monthly income of R9000 (approximately USD 850) while Africans have the least at R 2 167.00 (approximately USD 205) per month [513]. In addition White males especially, have had the highest employment rates and are most likely to have medical insurance [503]. In contrast, in 2007, only 6.9% of Africans and 6.5% of elderly were estimated to have medical aid. It is unlikely that Whites subjects did not seek medical care or were not referred for further management as health awareness and education levels are assumed equivalent if not better in Whites than in Indian and African individuals [514]. The small numbers

in the Coloured population is not unexpected as Coloureds comprise 1.3% of the at risk population only.

5.3.1 Crude incidence

In this study the crude incidence rate in person over the age of 60 years for the eThekwini area was 97.4 per 100 000 and the age adjusted rate for SA was 109 per 100 000. The crude incidence rate may possibly be higher as White men were not represented in the sample size, however despite this, the rate is almost 20 fold higher when compared to the incidence rate of 5.2 per 100 000 reported in urban Africans aged 40 years and older from Johannesburg in 1968 [39] and 9 fold higher than the 12 per 100 000 reported in a subsequent study in African men and women from Natalspruit [53]. Possible reasons for the increase in incidence rates are methodological issues, significant changes in SA population dynamics from a younger to older population. The population of persons aged 65 years and over was constant between the period 1965 (3.9%) to 2000 (3.7%), however in the last ten years it has increased to 4.6% [515] and further a substantial increase in the number of persons aged 50 years and over from 15.3% in 2010 to 24.1% by the year 2050 is expected. Until recently LE had not increased significantly due to the HIV epidemic [515]; however with the introduction of antiretroviral treatment LE is projected to increase in the future [28]. Urbanization and lifestyle changes may also contribute to an increase in the risk of osteoporosis and fractures.

This is the first study in the SA multi-ethnic population and specifically in South African Indians. The study confirms that hip fractures rates are increasing in

developing countries as predicted, while a decline or stabilization in hip fracture ASR is being observed in developed countries. The main reasons for the decline in developed countries is improved perinatal nutrition [26], change in lifestyle factors including diet, cigarette smoking [158] and alcohol intake, an increase in body weight from a sedentary lifestyle [33, 232, 340, 341], a change in the number of reproductive years, increased exposure to exogenous oestrogens [151, 342] and increased osteoporosis screening and treatment due to a higher awareness levels [339, 516]. The number of total hip fractures however in developed countries continues to increase due to an increased total number of older people and increased longevity in men [26, 90, 174].

The incidence rate in this study in eThekwini although higher than previously reported may be an under-representation as this study was conducted in an urban area only and does not represent all ethnic groups, rural and perhaps older Africans. The incidence rate however is higher than previously reported from SA but remains much lower than developed countries of Europe [517], North America [33, 61], Australia [151], and developing countries such as Jordan (158 per 100 000), China (140 per 100 000) [43], Mexico (173 per 100 000) [505] and India (129 per 100 000) [43]. The incidence rate is however higher than in Venezuela (100 per 100 000) [518] and other countries in Africa such as Morocco (85.9 per 100 000 in women and 72.7 per 100 000 in men) [47], Tunisia (50 per 100 000) [28], Nigeria (57.8 and 46.3 in men and women) [37] and Cameroon at 4.1 per 100 000 [48].

The crude incidence rate of hip fractures, although higher than the rest of Africa is most likely still an under estimation due to the low numbers of Whites and absence of subjects using the private health care facilities in SA. However, possible reasons

for the higher rate in SA compared to rest of Africa, include the geographic gradient with SA being further south of the equator than North and West Africa; having a multi-ethnic population (high proportion of Indian subjects with hip fractures) and possibly SA is better developed with better access to health care than the rest of Africa. The SES of the SA population is higher than most other African states with only SA, Botswana, Gabon and Mauritius being categorized as upper middle economic countries in Africa [504]. Furthermore, incidence rates from North and West Africa cannot necessarily be compared to that of SA as differences in anthropometry, culture, lifestyle and nutrition may exist [67] and no formal studies have been conducted comparing BMD or osteoporotic fracture incidences between the different populations. In addition, despite the sunny climate, vitamin D levels fluctuate across Africa due to increased skin pigmentation, calcium deficiency and cultural practices [28, 240, 241] and there is a north to south gradient with lower levels in countries furthest away from the equator. There is agreement however, that fracture rates in Africa are increasing with the increasing longevity and the presence of other risk factors such as a low calcium intake, multiple pregnancies, prolonged breastfeeding, decreasing physical activity levels and increasing urbanization [47, 48].

Urbanization has been associated with higher fracture rates in Asian countries such as Hong Kong, Singapore and Japan [35, 55]. It is possible that the incidence rate in this study may have been lower if a rural SA population was included. However an earlier study, albeit small, found a low incidence of lumbar osteoporosis and VFs in both urban and rural African women, suggesting that there are no marked differences between the two populations [385]. There are however no recent studies

in the SA rural community. Similarly, recent studies from Africa are from large urban centres, and the only study in rural women in Gambia found that despite a lower BMD than matched White women in the UK, there was no increase in age related hip fractures [45].

5.3.2 Gender specific rates

Similar to developed and many developing countries, the crude incidence rate in women at 133 per 100 000 was almost twice that in men (68.5 per 100 000). The incidence rates however are significantly lower than in developed countries [4, 75] and are in the low risk category, defined as less than 150 per 100 000 [4]. The gender specific rates in this study are also lower than other developing countries including in the AOS study, India and from Mexico [35, 43, 505]. The highest rate in men is found in Denmark (290 per 100 000) and lowest rate is reported from Ecuador (35 per 100 000) [518].

The incidence rate in men at <150 per 100 000 is similar to that in Latin America, Jordan, Saudi Arabia, India, China, Indonesia, Philippines, Croatia and Romania [312] but higher than in Morocco and Nigeria [37, 47]. The precise reasons for the variations in hip fracture incidence are not known and environmental and genetic factors may play a role. The higher fracture rates in Chinese in Hong Kong and Singapore than in China [81] support the role of environmental factors in determining fracture risk. Similarly, studies suggest that differences exist in the fracture risk between American Africans and the indigenous populations in Africa [39, 61], however this has not been systematically studied or confirmed

5.3.3 Age adjusted incidence rates

In accordance with other studies, an age related increase in hip fracture rates was noted with an almost 10 fold increase in hip fracture rates from 36.1 per 100 000 in the 60 – 65 years age group to 322.4 per 100 000in the 80 - 84 years age group. Similarly, the SOF research group found a 40% increase in fracture risk for every five year increment in age due to an increase in comorbid illness and falls, independent of bone mass [147]. The age adjusted fracture rates in the study are similar in men and women until age 75 years; however women in the 80 - 84 year age group had a 3.3 times higher fracture risk compared to men (138.5 and 451.2 per 100 000 in men and women respectively). This is most likely due to the increased longevity in women compared to men as seen in both developed and developing countries [26].

5.3.4 Ethnicity adjusted incidence rates

The age adjusted rate for SA Indians was 2.8 fold greater than their African counterparts (207.2 per 100 000 compared to 73.3 per 100 000). Higher rates have also been reported in Asian Indians compared to African Americans in the USA [128, 373] and were postulated to be due to a lower BMD [220, 336]. In this study the gender specific rates for Indian men and women was not reported due to the small numbers however the combined incidence rate for men and women in SA Indians is higher than that reported from India (105 and 159 per 100 000 in men and women) and similar to Singaporean Indians (128 per 100 000 and 264 per 100 000 for men and women, respectively) [35]. The lower BMD at the hip and spine recently

reported in Indians compared to Africans in SA [71] may in part account for the difference in incidence rates in this study. This study supports this finding as Indian hip fracture subjects compared to African hip fracture subjects had a significantly lower BMD at the hip but similar BMD at the lumbar spine. However in the Indian and African fracture subjects compared to their matched control groups, hip fracture subjects had lower scores at all sites, except for the hip BMAD which was similar in Indian hip fracture and control subjects. These findings confirm that BMD is an important in both Africans and Indians and that other factors contribute to the higher incidence in Indians.

The age adjusted incidence rate was highest in Indian subjects aged 85 years and older at 855.8 per 100 000 and is comparable to India were the incidence rate is 638 per 100 000 in older men (85 - 90 year age group) and women (962 per 100 000 in the 90 - 95 years age group) [43].

The crude and age adjusted incidence of hip fractures in Africans was 63.8 per 100 000 and 73.3 per 100 000, respectively. This is almost 14 fold higher when compared to the incidence rate of 5.2 per 100 000 reported in urban Africans aged 40 years and older from Johannesburg in 1968 [39] and 6 fold higher than the 12 per 100 000 reported in a subsequent study in African men and women from Natalspruit [53].

Similar to Indians, the age adjusted incidence rate was highest in the 85 years and older age group at 305.8 per 100 000. The rate remains significantly lower than developed countries and African Americans [61, 519] but higher than that seen in Nigeria (57.8 and 46.3 for men and women respectively >80 year age group) [384]

and Morocco (85.9 per 100 000 in women and 72.7 per 100 000 in men) in persons 50 years and older [47].

In the White hip fracture group, incidence rate was only calculated for White women as only one White man had been enrolled in the study. The age adjusted rate for White women at 91.6 per 100 000, is significantly less than expected and is most likely an under estimation due to under representation of White subjects in this study.

These findings and the expected increase in LE and proportion of older persons in SA, support the prediction that there will be a significant increase in number of hip fracture [26]. A major limitation of the original prediction is that the estimates for Africa were based on two studies only; one of which was conducted in 1960's in urban Johannesburg Africans only and excluded rural dwellers, miners and migratory individuals and therefore represented only 27% of the African population who lived in defined urban area of Johannesburg. The study further included all subjects presenting with fracture irrespective of degree of trauma, but excluded pathological fractures. It is therefore likely that individuals with non-osteoporotic fractures are included in this sample as the men in the sample were manual labourers. Despite these significant limitations an age related increase in fracture rates was seen in African subjects [39]. The second study from Nigeria may be an under-representation of actual osteoporotic hip rates due to under-reporting [4]. Both these studies found extremely low rates and showed a greater than 10% variation compared to studies from the rest of the world [312].

The higher incidence found in this study needs to be considered in the prediction of the future hip fracture burden in SA and the rest of Africa.

5.4 Clinical risk factors for osteoporotic hip fractures

The FRAX® assessment tool based on an analysis of 12 study populations is now recommended by the WHO and IOF to predict major and hip osteoporotic fracture risk [83]. The tool uses age, gender, weight, height, parental history of osteoporotic hip fracture, prior fragility fracture, smoking, alcohol (> three units a day), rheumatoid arthritis, long term (> 3 months) use of systemic GC and secondary medical conditions with or without a BMD to predict the 10 year probability of a major or hip fracture [31, 310]. The strength of the model lies in the additive effect of the clinical risk factors, however it has limitations as it does not incorporate other important risk factors e.g. bone quality and falls which are significant independent risk factors. In addition, country specific hip fracture incidence rates, all-cause mortality rates and a cost efficacy analysis are required to determine intervention thresholds. The tool cannot be used in persons less than 40 years old, premenopausal women, persons on osteoporosis treatment and importantly only uses hip BMD and not vertebral BMD [88]. Due to a lack of data on the incidence of hip fractures in SA and all-cause mortality data, the FRAX® tool is not available for SA. In addition, the multi-ethnic population precludes the use of a surrogate country.

No studies in SA have specifically looked at risk factors in subjects with hip fractures. Studies have however, investigated and compared the risk factors for the differences in BMD in the different ethnic groups [71]. This study is the first to systematically assess for risk factors in a case control study of multi-ethnic subjects with hip fractures.

In the case control study, a lower educational level, low body weight and body mass index, prior fragility fractures, sideways fall, memory impairment, morphometric VF, higher physical activity levels, smoking alcohol consumption, poorer functional activity level, low vitamin D levels, low BMD, a lower haemoglobin, total protein and albumin, with raised inflammatory markers were identified as risk factors for hip fractures on univariate analysis. After a step wise backwards logistic regression, educational level, a prior fragility fracture, BMI, pre- fracture physical activity levels, IADL activity level and QoL scores, haemoglobin and white blood cell counts and serum albumin and C-reactive protein levels remained as significant associations with hip fracture.

5.4.1 Age and gender

Osteoporotic hip fractures increase with age and are more frequent in women. Age and gender are well established risk factors and are strong independent markers of fracture risk [90, 95, 147, 216, 520]. The incidence of hip fractures in this study rose exponentially with age and was higher in women than men. In addition to the decreasing BMD with age, other reasons for the increased incidence with age include an increase in comorbid diseases and a higher fall risk [147, 300, 521]. In contrast the lower incidence rate in men is probably due to the decreased longevity in men and a lower rate of bone loss [218].

Interestingly, the incidence rate in men and women younger than 74 years old was similar but after age 75 years, the increment increase was far greater in women. This may be explained by the absence of White male subjects and rural subjects

who may have been older. Other factors such as a lower BMD in older women, differences in fall risk and other clinical risk factors may contribute to the gender differences with age. This study however did not specifically compare CRF or BMD in men and women younger and older than 74 years. The study was conducted over fourteen months and the younger age in men is unlikely to be due to sampling error.

5.4.2 Housing, employment and education

The association between SES and hip fractures has been well described as an indirect marker for other risk factors. A low SES has been found in several hip fracture studies and is an indicator for a poor nutritional state, low calcium intake and decreased access to health care [34, 66, 140, 511] and correlates with hip fracture rates. In the first NHANES report, a poor nutritional status due to poor dietary intake, was associated with a low body mass and serum albumin and independently increased hip fracture risk [522]. In contrast, and other studies have shown a linear relationship between increasing GDP and ten year hip fracture risk, with hip fracture probability increasing by 1.3% for every US $10 000 increase in GDP per capita [75]. The general consensus is that with increasing prosperity, physical activity levels decrease and surface hardness (pavement and brick buildings) improves resulting in a higher risk of severe injury. Furthermore, the higher number of hip fractures in urban compared to rural dwellers [226] is thought to be due to differences in physical activity levels associated with farming, living circumstances and environmental factors, however the exact reasons remain unclear. The data regarding the association between hip fracture risk and SES however is conflicting.

This study was conducted in a peri-urban population living in KZN and no significant differences in housing or employment status between control subjects or gender and ethnic groups was observed. The majority of subjects lived in formal housing and were pensioners, receiving a state old age pension. An assumption was made that they belonged to a similar SES status (lower and middle income) as individuals qualify for the government pension based on economic status after reaching the age of 60 years [523]. However, this may be an insensitive marker of SES and may not adequately reflect the true SES of individuals and their financial responsibilities.

Despite the similar SES, educational level differed significantly and education was an independent risk factor in hip fractures subjects, irrespective of gender and ethnicity. Hip fracture subjects compared to control subjects were significantly more likely to have had no schooling (37% vs. 12.5%, $p < 0.0001$) and less likely to have had a tertiary education (5% vs. 16%, $p < 0.0001$). Women with hip fractures were more likely not to have had any schooling compared to men (40.3% vs. 28.6%, $p < 0.0001$). Possible reasons for this is that older women, especially of Indian descent, may have not received schooling for cultural reasons and secondly, due to apartheid access to higher education was denied to many African and Indian persons [509].

A lower level of education in hip fracture subjects has been confirmed in several studies from Iran, India and Turkey, where a low level of literacy and less than 12 years of schooling after adjustment for age, height and weight was a significant risk factor [140, 327]. The studies postulate that a low education level is an indirect indicator of early economic and nutritional status including possibly health care access and subsequent failure to achieve the genetic potential for PBM. Lower education status is often associated with a decreased health awareness and health

care seeking behaviour. In this study an additional explanation for the control cohort having a better education may be due to a sample bias as it is possible that individuals with a higher education level were better able to understand the risk of osteoporosis fractures and therefore were more likely to volunteer to participate in the study.

5.4.3 Weight, height and body mass index

Perhaps after age and prior fractures, body weight and BMI are the most important CRF for hip fractures in both men and women and different ethnic groups [33, 76, 140, 147, 232, 511, 524]. Body weight, height and BMI influence hip fracture risk via BMD or independently.

In SA, a significant a strong association has been reported between total body weight and all BMD parameters in African women [69]. In addition, in premenopausal African and White women, fat free soft tissue mass, although lower in African women, was the most significant contributor to BMD at all sites in African women and the hip in White [67]

In this study of older men and women, there was a significant negative correlation between body weight and BMD at the lumbar spine ($p < 0.0001$) and total hip ($p = 0.001$) in the total cohort and total hip fracture cohort but not in the total control group. This supports the association between body weight and bone mass, especially in hip fracture subjects.

The positive relationship between body weight and BMD is mediated via mechanical and hormonal factors [117, 228, 311]. Obesity results in a higher bone mass due to increased weight bearing, and slower bone loss rates due to a primary increase in oestrogen levels. In addition, the fat pads provide cushioning in the event of a fall [127, 147, 228, 229]. In converse, a low body weight and weight loss are potentially indirect measurements of general ill health [443], and weight loss is also associated with decrease in growth factors including insulin and increase corticosteroid levels which increase the rate of bone loss [192].

Several epidemiological studies have however failed to show a relationship between weight and BMD including the BRAZOS, WHI and EPIDOS. Possible explanations for the failure to show a positive associations in these studies, include a younger cohort and that these studies were not designed to assess hip fracture risk specifically [233, 525]. .

A low mean body weight was an independent risk factor for hip fractures in the total fracture cohort (OR 0.906, 95% CI 0.87-0.94) and in both Indian and African hip fracture subjects compared to matched control subjects (OR 0.893; 95%CI 0.84-0.95) and (OR 0.916; 95%CI 0.86-0.97) respectively. Of note, is that the difference in body weight between hip fracture subjects and controls was greater in the African cohort compared to the Indian cohort.

In addition, the mean total body weight in both Indians and Africans, and in men and women fracture subjects was less than 57 kg, the cut-off value used in the FRAX® tool [31, 80].

The ethnic difference in skeletal size has been well established. In the SA population, African subjects have the heaviest skeletons and African women are heavier than Indian women but Indian men are heavier than African men [79]. In this study African subjects with hip fractures were significantly heavier than their Indian counterparts who may in part be due to differences in skeletal size, however skeletal mass only contributes to 12-15% [69, 526] of total body weight and difference in soft tissue mass is the more likely explanation for the weight differences.

An increased In view of the influence of weight and height on hip fracture it is intuitive that BMI would have a similar effect. In this study the mean BMI was significantly lower in hip fracture subjects compared to controls (22.7 ± 5.7 kg/m^2 vs. 29.2 ± 6.0 kg/m^2; $p < 0.0001$; OR 0.786, 95%CI 0.7-0.87), and only 3 control subjects (all African women) had a low BMI and interestingly, despite having no other clinical risk factors for osteoporosis, two of these subjects had morphometric VF and a low BMD emphasizing the association between low BMI and fracture risk, albeit vertebral. The majority of hip fracture subjects had either a normal (55.9%) or low BMI (21.3%) while control subjects were more likely to be overweight (33.5%) or obese (40.5%). In addition, when BMI was used as a continuous variable, every two unit decrease in BMI increased the odds of a hip fracture by 1.61 and a 3 unit decrease in BMI increased the odds to 2.06.

The increase in hip fracture risk with a low BMI has been shown in a recent study, where a BMI of less than 26 kg/cm^2 was associated with an increased risk of osteoporosis [140]. The relationship between BMI and fracture risk is strongest for BMI in the underweight category as was reported in the meta-analysis of 12 prospective studies [232]

Further in the 12 hip fracture subjects who had a BMI of greater 30kg/cm^2, 41% were African and 58.3% were men (58.3%). There were no other differences in this group, except that only one of these 12 subjects died in the study period.

The significantly higher BMI in control subjects is in keeping with findings in a community study where the mean BMI was 24.8 kg/cm^2 and 28.8 kg/cm^2 in the 60 - 69 years and 24.4 kg/cm^2 and 27.7 kg/cm^2 in the 70 - 79 year age groups, in men and women, respectively [527].

A possible reason for low body weight and BMI in the hip fracture subjects could be malnutrition in early life resulting in underweight adults and a failure to achieve PBM, and an increase in fracture risk. The association between SES and nutritional status with BMD is supported by the finding in India that 29% of 30 - 60 years old women from a low economic group with a poor nutritional status, based on dietary assessment, and lower calcium intake had osteoporosis based on the WHO criteria [66]. However this study failed to show a relationship between body weight and BMD and did not interrogate early nutrition or SES in childhood. The low serum albumin and haemoglobin levels in hip fracture subjects; in addition to the low body weight and BMI do however suggest that hip fracture subjects had a poorer nutritional status than did control subjects. The association between a low albumin and ageing and femoral neck fractures has previously been reported in comparative study in women [459].

Another potential cause for a low body weight is general medical illnesses; however in this study, control subjects had a higher burden of hypertension and DM. Perhaps this higher prevalence, sometimes loosely referred to as disease of affluence, may

be a surrogate marker of better SES and better nutritional status. However as discussed previously, this study was unable to show any difference in SES between hip fracture subjects and controls.

An increased hip fracture risk has also been documented in taller individuals, and several studies report height as important as weight in determining fracture risk [33, 147]. Taller subjects have an increased hip fracture risk [192, 521] due to a longer HAL [196] and/or fall from a greater height increasing the potential for an injury [298]. Height was not significantly different between fracture and matched control subjects in the total and African and Indian cohorts. However, men were shorter than their matched controls while women with hip fractures were taller than matched control subjects. It is therefore difficult to explain the significance of height in our sample population subgroups and it's possible that morphometric VF secondary to osteoporosis may have resulted in a decrease in height in our subjects.

5.4.4 Co-morbid diseases and secondary causes of osteoporosis

Several medical conditions and drugs predispose to secondary osteoporosis and especially important in men and young patients presenting with fractures [26, 88, 346]. In addition, comorbid diseases in older persons contribute to frailty and an increased fall risk [192, 265, 270, 528]. In a case control study of 124 655 hip fracture subjects, hypertension and stroke were the only significant risk factors while myocardial ischaemia, deep vein thrombosis, peripheral vascular disease and atrial fibrillation were associated with a transient (less than three month) risk [406]. A high prevalence of hypertension has also been reported in Indian subjects with hip

fractures [511]. Hypertension is probably only indirectly associated with hip fractures secondary to treatment side effects [96]. In this study while hip fracture subjects were more likely to have had a stroke (7.5% vs. 2%), the numbers were too small to draw any association. The risk of fractures in stroke is multifactorial and due to loss of mobility and decreased load bearing on parts of skeleton, and an increased fall risk [270].

In this study, the sample size was too small to show significant differences in the prevalence of chronic diseases between hip fracture and controls.

Paradoxically, however hypertension, DM and RA known to be risk factors for hip fractures, were found more commonly in the control subjects. This is considered to be most likely due to a sample bias, as some of the controls were outpatients at the selected hospitals or were more aware of osteoporosis and therefore preferentially entered the study. However in fracture subjects, hypertension and DM was more common in women compared to men, and Indians were more likely to have DM than Africans. The latter is probably due to the high prevalence of DM in SA Indians [529, 530].

In contrast, self-reported osteoarthritis and the associated obesity are considered to be protective against hip fractures [226, 527]. Consistent with this there was a significantly higher prevalence of self-reported arthritis in control subjects compared to hip fracture subjects (47.5% vs. 27.5%, $p < 0.0001$). Control subjects were also heavier (71.0 ± 16.5 kg vs. 54.7 ± 13.7 kg, $p < 0.0001$) and complained more of chronic back pain (37% vs. 7%, $p = 0.002$; OR 0.379, 95% CI 0.19-0.76).

Although infrequent, an underlying malignancy was more common in hip fracture than controls (5% vs. 1.5%; p = 0.052) but did not quite reach significance. Malignancy was significantly more common in women with hip fractures compared to women controls, whereas in men there was equal low prevalence in men of 0.5% in those with and without hip fractures.

Consistent with previous findings of the association between memory impairment and fracture risk [76], self-reported poor memory and concern expressed by a family member regarding memory loss were significantly more frequent in hip fracture subjects compared to controls (39% vs. 22.5%, p < 0.001; OR 2.0, 95%CI 1.29-3.1) and (34% vs. 18.5%, p < 0.001; OR 2.25, 95%CI 1.39-3.64), respectively. While hip fracture subjects were also more likely to report difficulty in completing familiar tasks, there was no significant difference between the groups. The positive association between memory complaints was found despite only enrolling subjects able to give consent. By excluding those who were not able to give consent this study may have excluded subjects with more significant cognitive impairment. It is therefore likely that association between cognitive impairment and fracture may be stronger than found in this study. The increased fracture risk with cognitive impairment is due to a combination of factors that include neuromuscular, fall and gait factors [147, 531, 532]. Although memory loss and difficulty in completing tasks was greater in matched women and Indians than men and Africans the reasons for this were not clear.

Other secondary causes (chronic renal failure, cirrhosis, IBD) are well documented in the literature [119] but were found in low numbers in this study in both cohorts and no significant difference was noted. Hip fracture subjects self-reported a greater

frequency of gastric ulcers (4.5% vs. 2%), and epilepsy and schizophrenia at 1.5% respectively which are associated risk factors [147, 192, 263, 264] but no associations could be drawn in view of the small numbers.

Although several studies have found decreased vision, poor depth perception and decreased contrast sensitivity increase fall and fracture risk [147, 271, 511], this study failed to show any associations and in contrast, these impairments were significantly more common in control subjects. It is possible that due to these impairments control subjects may be more careful and therefore have a lower fall risk.

Despite the higher frequency of chronic diseases in control subjects, potentially bone toxic drugs were used more frequently by hip fracture subjects however the number of subjects using the drugs was low and use was not significantly different between the two cohorts. The long term usage (three months) of GC in hip fracture subjects was 5.5% vs. 3.5% ($p = 0.468$) and while the use of other bone toxic drugs, although more common in hip fracture subjects than controls was not significant including anti-epileptics, antidepressants and long term heparin which in other studies have been associated increased fracture risk [147, 255].

5.4.5 Hormonal factors

The loss of oestrogen with menopause is the most common recognized cause of osteoporosis [98, 140]. The primary reason for the rapid bone loss in post-menopausal women is the decline in oestrogen levels resulting in an imbalance in

bone remodelling [191, 533]. While there are established differences in bone mass in different ethnic groups, the rate of bone loss and bone turnover rates are similar at menopause in Indians from India [140], African-Americans and US White women [534]. There are site specific differences in bone loss patterns over menopause. Similar loss at the spine, higher femoral loss and is in general better maintenance with ageing explaining the better BMD in elderly African women in SA [69]

In SA, bone loss is similar in pre-menopausal African and White women, and increases in Whites at menopause but not in Africans [69]. The rate increases later in older post-menopausal Africans most likely due to a negative calcium balance and secondary hyperparathyroidism resulting in an increased bone loss at the femoral head.

The amount of time the body is exposed to oestrogen is critical in determining osteoporosis risk and this is dependent on several factors including time of menarche, age of menopause, periods of amenorrhoea, breast feeding duration, parity and use of exogenous oestrogen [82, 147]. Delayed puberty or hypogonadism results in a failure to attain PBM and hypogonadism in adulthood is associated with accelerated bone loss. It is estimated 20% of elderly and 50% of men with hip fractures may have hypogonadism [535].

In this study, there was no difference in age at menarche and menopause, parity, (including a higher parity i.e. >3), and hormonal levels between hip fracture subjects and controls. There are however conflicting reports on the influence of parity on fracture risk. Some studies, including a study on osteoporosis risk factors from SA [68], suggest that greater than 3 pregnancies may be associated with a decrease in

pelvis and lumbar spine density of between 1 - 4% with each birth, while in other studies higher parity (>3 children) has been associated with decreased fracture risk as pregnancy is associated with increased oestrogen exposure, weight gain, and increased calcium absorption [536]. While yet others, similar to this study, have noted no significant difference in number of pregnancies and fracture risk [225, 226].

The benefits of HRT in maintaining bone mass are well established and the effect of HRT was confirmed in the WHI study were HRT use decreased hip fracture risk by 50% [537]. The use of HRT is however limited in older women due to its side effect profile. The risk reduction however, is greatest during HRT use and lasts up to 5 years after HRT is stopped [76, 224, 538]. The beneficial effect of HRT was confirmed in this study and any use was significantly less in hip fracture subjects compared to controls (4.9% vs. 15.3%; $p < 0.001$; OR 0.201, 95%CI 0.08-0.49). However, hormone replacement was infrequent, even in the control group, and there was no difference between Indian and African hip fracture subjects.

5.4.6 Falls

The risk of falls increases progressively with ageing and along with the associated increased skeletal fragility accounts for the significantly increased risk of hip fractures seen in the elderly [33, 123]. The type of fall, surface hardness, neuromuscular factors and protective arm movements all play a contributory role. [33, 304, 305, 539]. While most studies have found a positive association between falls and hip fractures [28], other studies have found conflicting results. Cummings et al., found the risk of a fracture rose by 30% for each additional fall but after

adjusting for health status and ability to rise from a chair, falls were no longer a significant risk factor [147, 192].

Interestingly, this study found no association between numbers of prior falls, number of falls or time of last fall in hip fracture compared to control subjects. Further 55% of hip fracture subjects had no previous falls. Postulated reasons for the conflicting results for falls are that only 5% of falls result in fracture and that co-existent illnesses, psychotropic medication, cardiovascular medications all influence fall risk [540]. Although this study was unable to show any difference in the number of falls, hip fracture subjects, particularly women, had a significantly higher number of sideways falls. Several studies have shown that the type of fall differs between gender and ethnic groups and plays an important role in determining injury [298]. A sideways fall on an outstretched hand results in a significant higher impact on the greater trochanter and is particularly associated with hip fractures [304, 305]. An additional reason for the failure to identify differences in the number of falls between hip fracture and control subjects is that control subjects may have been more likely to participate in the study in anticipation of being screened for osteoporosis and to prevent a fracture if they had future falls. The study may potentially have under-estimated the risk of falls in fracture subjects.

Furthermore, while there was no diference in the fall assessment between men and women with hip fractures, compared to African subjects with hip fractures, Indian fracture subjects were more likely to report falls and sought care and limited their activities due to a fear of falling despite the fact there was no difference in total number of falls. Its seems possible that Indians may have higher health seeking

behaviour. This may possibly be related to ease of access to health care but the study did not look for this and further research is required in this area.

The role of physical activity in decreasing fall risk is controversial and while few studies have failed to show a benefit [152, 541], others have found that an improvement in strength and balance results in a 10% reduction in fall risk [303]. Most authors agree that gait, balance and lower extremity strength play a critical role in falls and hip fracture risk, independent of BMD [33, 147]. The findings in this study of higher activity levels in fracture subjects and the equivalent number of falls in hip fracture and control subjects is surprising and reinforces the multifactorial aetiology of hip fractures.

Interestingly, the study also found that control subjects were more likely to have had near falls; this may have resulted in greater psychological fear of falling. The fear of falling may result in decreased physical activity and can lead to dependence and decreased function and paradoxically increase risk of falling [542]. This fear may have prompted them to participate in a study assessing their risk of serious injury following a fall. Controls also had greater concern regarding falling and needed more assistance after a fall. Additionally they had greater concerns with regards to transfer in the bathroom or bedroom, painful legs, visual problems, difficulty with depth perception and activity limitation due to fear of falling. In contrast, hip fracture subjects were more likely not to choose to use a walking aid, significant in men but not in women, and although not significant had a higher frequency of medication changes. It is possible that despite a similar number of falls, control subjects due to pain, higher prevalence of co-morbid diseases and lower activity levels are more careful than fracture subjects. Further they had a higher BMI and BMD and

therefore possibly better cushioning and stronger bones to decrease the impact of a fall. Hip fracture subjects were more likely to fall outside where surface are harder resulting in possible greater trauma. The association of these factors with fractures have been previously reported [20, 49, [271].

5.4.7 Prior fragility fractures

Wrist fractures usually precede hip fractures by 15 years [5, 543, 544] and present an ideal opportunity to assess for osteoporosis. Following a wrist fracture there is a three-fold increase in a future wrist fracture and a doubling of the risk for any fracture, which may occur within 1-3 years [545]. Furthermore after a hip fracture, the risk of a second hip fracture varies between 2 - 10% and although highest in the first year, can occur up to number of years later with a mean duration of four years [30, 443].

A major concern however is that despite this < 50% and < 10% of subjects after a wrist and hip fracture, respectively [545-547] are investigated and treated for osteoporosis even in countries with a high incidence of hip fractures.

In this study, only 3.5% of subjects had a diagnosis of osteoporosis prior to their hip fracture. These were all female subjects highlighting the lack of awareness, especially in men. Despite the low finding of an established diagnosis of osteoporosis in the fracture group, 27.5% of hip fracture subjects reported a prior fracture which was a significant risk factor in both gender and ethnic matched groups (OR 4.083; 95%CI 2.27-7.34). This finding is in keeping with the literature that a

significant number of individuals post fragility fracture are not screened or treated appropriately for osteoporosis, and that a prior fragility fracture confers a high risk of a second fracture. The risk of subsequent fracture occurs in men and women and is influenced by age, number and sites of the previous fracture [295, 548], with the highest risk commonly reported after a VF.

In this study, the most common site for a self-reported prior fracture was the forearm which is similar to CaMos study [192] where a morphometric VF predicted risk for future VF but not for non-VF. A possible reason for this is VFs are often due to primary bone fragility while the aetiology of hip fractures is multifactorial including fall risk and clinical factors [192]

Surprisingly, a prior hip fracture was found in 7.5% of hip fracture subjects. Post hip fracture, the risk of a second fracture is increased as there is rapid bone loss in the contralateral hip due to increased bone turnover, loss of lean body mass and increased fat mass associated with the first hip fracture [433]. The risk of second hip fracture was 10.3% in the USA in the following three years after a hip fracture with the risk being the highest in the first year at 51% [434].

5.4.8 Family history of osteoporosis

Genetic factors strongly correlate with bone mass [95, 203, 204] and the relationship between fracture risk and family history is independent of BMD [147, 525]. A maternal history of fracture especially before the age of 80 years doubles the fracture risk in both men and women and different ethnic groups[128, 157, 160, 429].

Counterintuitively, hip fracture subjects were less likely than control subjects to report a family history of osteoporosis (3.5% vs. 11.5%, p = 0.002, OR 0.266, 95%CI 0.11-0.63) and a maternal history of hip fracture (5.5% vs. 11.5%, p = 0.034; OR 0.427, 95%CI 0.20 - 0.90). In addition, no male fracture subjects reported either a family history of osteoporosis or fracture. These findings support the notion that there is a low awareness of osteoporosis and hip fractures in this population and that the controls may well be more aware and were therefore more likely to participate in the study. Thus the risk associated with a positive family history may be under-estimated in this study. Alternatively, these findings may reflect a true increase in the incidence of hip fractures either due to an increased LE or a change in risk factor profile. The CaMos study also failed to show any positive correlation between family history and fracture risk, but the possible reason for this was that a general family history for osteoporosis and fracture was obtained rather than a maternal history [192]

5.4.9 Lifestyle factors

Although environmental factors are thought to play a smaller role in determining PBM than genetic factors, they play an important role in maintaining bone mass and determining subsequent rate of bone loss [95]. Amongst the most studied are caffeine, smoking, alcohol consumption, physical activity levels sunlight exposure, calcium intake and vitamin D levels.

Physical activity

Decreased physical activity correlates with increased hip fracture risk in both genders and different ethnic groups [76, 81, 511, 525]. Conversely, weight bearing exercises increase bone density at the spine and simple exercises like walking strengthen tone and muscles [549].

Contrary to these findings, the self-reported activity levels were significantly higher in hip fracture subjects compared to controls in this study. Hip fracture subjects also exercised significantly more often than did control subjects. A similar finding was also reported form India by Keramat et al., who found that walking distance or level of activity level was not protective for osteoporosis [140]. In this study the control cohort had a higher number of co-morbid diseases and visual difficulties which may have resulted in lower level of physical activity.

Caffeine intake

In this study no association was found between the intake of caffeine and fracture risk, in keeping with current literature. Caffeine has a potentially negative effect on bone by [550] decreasing intestinal calcium absorption [147] and acts on the VDR in women with the *tt* genotype are more susceptible to the negative effects of caffeine[550]. Although caffeine was thought to have a deleterious effect on bone mass, several subsequent studies found no direct association between fracture risk and caffeine use [284]. The conflicting findings are dependent on the type of coffee and the impact of adding milk. In a meta-analysis the negative effects in coffee

drinkers was shown to be due a low calcium intake rather than a direct effect of caffeine [284]. In contrast, some studies still continue to show an increased risk with caffeine [76, 511].

Sunlight exposure and vitamin D levels

Reduced sunlight exposure (UVB) has been associated with vitamin D deficiency in several studies. This study was undertaken in eThekwini which has a sunny climate and not surprisingly there were no differences in sunlight exposure between fracture or control subjects. Furthermore, unlike in Europe and USA where the majority of hip fractures occur during the winter months, there was no seasonal variation in this study, similar to other studies from Africa [37, 47]. The increase risk of fracture in winter in the Northern hemisphere is thought to be due to an increase in neuromuscular dysfunction secondary to the cold temperature and vitamin D deficiency [75, 95, 231]. The seasonal variation in incidence however is found usually with greater latitude changes from the equator [75].

The role of sunlight exposure in SA is not well defined. Vitamin D deficiency was found in elderly Coloureds in Cape Town, however this was a cross sectional study and there was no correlation with bone health [551]. An earlier study in Johannesburg found a seasonal variation in vitamin D levels in Johannesburg with environmental temperature and not with number of hours of sunlight [245]. Later studies showed seasonal variation in sunlight only in Cape Town with the previously observed variation in Johannesburg explained on individuals wearing more clothes in winter rather than a geographic variation in UVB exposure [244]. No studies have

been conducted in eThekwini which has a more tropical climate than either Johannesburg or Cape Town.

Despite the fact that there was no difference in sunlight exposure, a significantly lower mean 25 (OH) vitamin D level was noted in hip fracture subjects compared to controls (38.9 ± 22.4 nmol/l vs. 51.4 ± 24.2 nmol/l, $p < 0.0001$). The mean 25 (OH) vitamin D level in hip fracture subjects was in mildly deficient category (24.96 - 49.92 nmol/L) as seen in several studies [525]. In the hip fracture subjects there was no difference in the mean vitamin D levels between African and Indian or male and female subjects. Vitamin D levels however were significantly lower in both men and women fracture subjects compared to their matched controls ($p = 0.003$) and ($p < 0.0001$) respectively. This significant difference was also observed in Indian and African fracture subjects compared to their matched controls ($p = 0.004$) and ($p = 0.002$) respectively. Vitamin D levels were not analysed in White women due to the small sample size but the mean vitamin D level in White fracture subjects was only marginally higher than that of African or Indian fracture subjects. This implies that factors apart from ethnicity, gender and sunlight exposure affect vitamin D levels.

Calcium

Low vitamin D levels are associated with a decreased calcium absorption resulting in secondary hyperparathyroidism and increased bone resorption. With increasing age, the ability of the skin to synthesize vitamin D decreases and the decreased synthesis combined with a decrease in intestinal calcium response to vitamin D [553]

results in calcium and vitamin D deficiency in the elderly and exacerbates bone loss [176].

In this study, a low calcium intake was documented in both fracture and control subjects with a mean calcium intake of less than 500 mg/day. Calcium intake was lowest in African fracture subjects, with a significantly lower daily calcium intake compared to their matched controls and compared to Indian fracture subjects ($p = 0.005$). The low calcium intake noted in Africans fracture cases may suggest poorer nutrition and a lower SES.

The low calcium intake and low vitamin D levels in this study are in keeping with global studies, including developing countries, which show that a low calcium intake and hypovitaminosis in the elderly result in a higher fracture risk [76, 81, 511]. In an Indian study, 52% of subjects had vitamin D insufficiency mainly due to a diet in poor in calcium and high in phytates [555]. A review of vitamin D levels across several countries found that obesity (BMI >30), residing in a non-equatorial country, Asian ethnicity, poor health, poor vitamin D supplementation, and no recent travel to sunny areas all increased risk of vitamin D insufficiency [553].

In contrast, this study found that fracture subjects, despite having a lower BMI, residing in a sunny climate and having a lower incidence of chronic diseases compared to controls, had lower vitamin D status.

In SA, a lower calcium intake and vitamin D levels have been reported in postmenopausal Africans compared to Whites [69] and in Indians compared to African women [71]. This study, despite finding a significantly lower calcium intake in Africans, found no difference in vitamin D levels between African and Indian hip

fracture subjects. Possible reasons may be similar skin colour, exposure to sunlight or polymorphisms of the VDR receptor.

A possible reason for the low calcium intake in this study is that calcium rich foods are expensive and may have been not affordable as most of the study subjects are dependent on their social pensions which were approximately R 1000 (USD 80) in 2010/11 (personal observation by investigator). Other studies from Africa have also implicated low calcium as a possible risk factor for osteoporotic fractures, however it is suggested that Africans have better calcium utilisation than Whites as despite a lower mean intake, they have lower a fracture rate [38, 39, 221, 268].

Additionally, in African Americans a relative skeletal resistance to the actions of PTH, which possibly protects them against the effects of a low calcium intake, has been reported. [222] The resistance is, however relative and secondary hyperparathyroidism has been shown in African Americans from a low SES and an inadequate intake of calcium.

Calcium and vitamin D are widely recommended in the treatment of osteoporosis as an adjunct to more specific anti-osteoporosis medication. Calcium supplementation has been shown to increase BMD at the lumbar spine, hip and femoral neck by 4 - 6% [248], however its role in fracture reduction is less well defined [235]. Vitamin D in a dose of 700 - 800 IU decreases hip fracture risk by 25% in elderly individuals, however this risk reduction has been shown in subjects using concomitant calcium [554].

In an attempt to clarify the role of calcium and Vitamin D in hip fracture reduction, Boonen et al., [246] reviewed the literature including results of the Randomized

Evaluation of Calcium Or Vitamin D (RECORD) and WHI [250] and in the meta-analysis found that in all the studies except the RECORD, a combination of Vitamin D and calcium significantly reduced hip fracture risk by 18%. This finding supports an earlier Cochrane review in 2005 that calcium or vitamin D alone do not decrease fracture risk [246]. The RECORD trial showed no additional benefit of combined supplementation, however the RECORD subjects were younger, the study was underpowered and compliance with trial medication was only 60%, whilst compliance in the WHI was 80%. Despite the conflicting results, supplementation is effective provided subjects are compliant and should be restricted to select subjects with low levels rather than widespread community supplementation [246]. In this study the use of additional calcium or vitamin D was not significantly different and found in less than 15% of both cohorts and therefore given the low dietary intake subjects would most likely benefit from supplementation.

Smoking

Smoking increases bone loss in post-menopausal women, but its effect on bone mass in pre-menopausal women smokers is conflicting [273]. Studies in pre-menopausal discordant twins reported a lower bone mass in smokers, possibly due to decreased oestrogen [274] while other studies have found no relationship between smoking and bone loss in pre-menopausal women [556].

The metabolic, hormonal and nutritional changes associated with smoking result in smokers being thinner and reaching menopause earlier due to a higher metabolism of oestrogen [96].

In this study there was a significant association of current smoking in hip fracture subjects compared to control subjects. This is consistent with findings from several studies which have shown that smoking is an independent risk factor for osteoporotic fractures [147, 273, 525, 562]. Men with hip fractures were more likely to smoke than women as reported in the AOS study [81].

Although smoking increases the risk for any fracture, it is specifically associated with a higher hip fracture risk [158, 562]. In contrast, Cummings et al., found that after adjustment for weight loss, poor health status, decrease activity and difficulty in arising from chair, smoking was not a significant risk factor in White women [147].

Alcohol

Excessive alcohol consumption decreases bone mass directly and indirectly by suppressing bone osteoblastic activity [276, 277]. Alcohol decreases osteocalcin levels resulting in decreased bone volume and trabecular thickness with associated mild demineralization. The indirect effects of alcohol are mediated via liver damage, nutritional deficiencies and associated hypogonadism [276, 277].

Moderate use on the other hand, increases the conversion of androstenedione to oestrogen and indirectly increases bone mass [33, 147, 278].

A significantly higher alcohol use was observed in hip fracture subjects compared to control subjects and in men with hip fractures compared to women. Indian subjects with hip fractures consumed a higher amount of alcohol than did African hip fracture subjects. Therefore alcohol is an important risk factor in men especially of Indian

descent. The higher alcohol intake is also reflected in the higher GGT levels in hip fracture subjects and particularly in men.

The increased fracture risk with alcohol has been shown in several studies in Asians [81], however there are very few studies looking at the use of conventional alcohol in Africans from Africa. Rather, the use of traditional beer home brewed in iron pots has been associated with a higher risk of femoral neck fracture and has been found to be an independent risk factor in African men including in a small study from SA [53, 282, 283]. Despite this several small studies have failed to show a high incidence of femoral neck fractures in sub-Saharan Africa [53]. None of the subjects in this study reported drinking traditional home brewed beer.

5.5 Bone mineral density

BMD is the only measurable marker of bone mass and epidemiological studies have shown an inverse relationship between BMD and fracture risk, with a 1.5 - 3 times increase fracture risk for every one SD decrease in BMD [58]. In this study, only 116 hip fracture subjects were able to have a DXA scan due to logistic reasons. As a 35 patients demised before having a BMD or were too frail or unable to attend it is possible that the BMD represented here may be an under-estimation of true difference between fracture and control subjects.

The BMD in this study, was significantly lower in hip fracture subjects than in controls at the lumbar spine (0.701 ± 0.173 g/cm^2 vs. 0.848 ± 0.183 g/cm^2, $p < 0.0001$), femoral neck (0.518 ± 0.106 g/cm^2 vs. 0.713 ± 0.127 g/cm^2, $p < 0.0001$) and total hip (0.650 ± 0.136 g/cm^2 vs. 0.879 ± 0.163 g/cm^2, $p < 0.0001$). The measured BMD was lower in men, women, Indian and African hip fracture subjects compared to their age matched controls at all three measured sites. The markedly lower BMD values at all sites and for all measurements namely areal and volumetric suggest that there are no significant major skeletal differences between the African and Indian fracture subjects.

When BMD is expressed as a T-score, fracture risk increases 2 - 3 fold with a T - score of less than -2.5 [87]. In this study the mean T - scores were significantly lower in hip fracture subjects compared to controls at the spine (-2.99 ± 1.29 vs. -1.23 ± 1.44; $p<0.0001$) and total hip (-2.91 ± 0.85 vs. -1.26 ± 1.25; $p<0.0001$) and only 2.6% of fracture subjects had a normal BMD implying that hip fractures are extremely unlikely in the presence of a normal T- score. The vast majority of hip

fracture subjects had a T-score in the osteoporotic category, and this study, confirms the usefulness of BMD in predicting hip fractures [272].

Despite this positive association, it has been noted in several other studies that BMD is not the only marker for increased fracture risk and fractures can occur in the setting of normal BMD [152]. In this study, 2.6% and 12.1% of the hip fracture subjects would have been classified as having a normal or low bone mass, respectively based on their T - scores and an overwhelming 85.3% would have been osteoporotic and would have qualified for treatment had they presented prior to the hip fracture; clearly an opportunity missed. The reason for the normal BMD in the three hip fracture subjects cannot be adequately explained. Control subjects would have been categorized as normal (38.7%), low bone mass (32.2%) and osteoporosis (29.1%).

Although it was expected that the BMD would be higher in men compared to women no difference was noted between men and women hip fracture subjects in BMD. However, BMD was higher at the hip in African hip fracture subjects compared to their Indian counterparts (0.692 ± 0.147 g/cm^2 vs. 0.630 ± 0.129 g/cm^2; p = 0.025). In US studies, a higher BMD has been found in African Americans and Whites compared to Asians [44, 61], and a local study showed lower BMD values at all sites in Indians compared to Africans [71]. However, this last study included younger individuals (from age 18 years and onward).

Ethnic differences in BMD are well recognized and Solomon [52] was the first to find a lower than expected BMD in Africans compared to UK Whites and subsequent studies from Cape Town and Johannesburg have confirmed that BMD differences

exist between Whites, Coloured and Africans [52, 385-387, 564]. More recent studies show BMD is similar or slightly lower at the spine but higher at the hip in Africans than Whites [67-69] and a lower in Indians compared to Africans [71]. Further support for these differences is that in school children (8 - 18 years) after adjustment for body size, BMC and BMC/BW was greater in Coloured girls compared to Indians and Whites but no difference was seen in boys [557]. Interestingly, further studies comparing SA African and White children to US African American and White children found that despite African Americans being heavier, SA Africans had a higher BMC. The BMC was also higher in Whites in SA compared to US Whites once more implicating environmental factors in bone mass [56].

Of note is that the T - scores in this study were calculated using the IOF, ISCD and NOFSA recommendations to use a single reference range (White female from NHANES 111 [88, 179,558] rather than gender and ethnic specific ranges, especially since there are no normative data for SA. It is also recommended that the total hip rather than femoral neck is used as the reference point in predicting fracture risk [559]; as BMD at the hip is a better hip fracture risk predictor than BMD at the spine. Possible reasons for this include that lumbar spine BMD in older women may be falsely elevated due effects of osteoarthritis [192]. The ability of the T-score using NHANES III White reference database to diagnose 85.3% of hip fracture subjects as having osteoporosis confirms the validity of the IOF recommendation [179]. A low BMD in all ethnic groups is associated with an increased fracture risk of 54% for each SD decrease in T - score [65], however the absolute risk differs between different ethnic groups. White and Hispanic women have the highest absolute fracture risk and African and Asian women the lowest.

A major limitation and critique of DXA is that it measures the average thickness of minerals in a given area and is therefore a crude measure of hip geometry only. Differences in hip geometry, such as cortical strength and buckling ratio are known to help predict hip fracture risk [560], and ethnic differences have been reported in bone geometry [196]. Although we did not perform skeletal geometry, hip specific analysis studies in the 10 292 participants in the WHI study, showed a significant correlation between conventional femur neck BMD and structural hip geometry measurements [272]. The highest correlation was for cross sectional area, cortical thickness and buckling ratio at the narrow neck. Fracture subjects had a lower BMD, lower cross sectional area, wider outer diameters and higher buckling ratios which were significant independent risk factors after adjustment for body size, ethnicity, clinical risk factors and BMD [272]. The authors however caution that widening of hip geometry is a natural phenomenon seen with ageing to preserve the section modulus and make buckling unlikely [520]. This results in elderly people having a preserved inferior cortex to support them while standing while the superior lateral cortex is thinned out. In the event of a fall the load is suddenly applied in the opposite direction compared to standing and therefore the thinned superior cortex unaccustomed to load bearing easily fractures even with minimal force. Many experts therefore feel that despite hip geometry measurement not being superior to DXA, a single DXA is not sufficiently reliable and DXA technology needs to improve to increase spatial resolution and to include hip geometry measurement which will add further to the predictive value after accounting for clinical risk factors and conventional DXA [563] especially in patients without fractures.

In view of the potential impact of differences in body size differences affecting BMD measurements, volumetric BMAD was calculated using the Katzman and Carter corrections [494, 495]. The BMAD in hip fracture subjects remained significantly lower than controls subjects at the spine (0.199 ± 0.036 g/cm^3 vs. 0.244 ± 0.041g/cm^3, p<0.0001) and hip (0.118 ± 0.092g/cm^3 vs. 0.143 ± 0.025 g/cm^3,p = 0.003). There was no difference in BMAD in men and women hip fracture subjects; and in African and Indian hip fracture subjects, despite a higher BMD at the hip in Africans compared to Indians, suggesting that after correction for body size there is no real difference in bone mass between African and Indian subjects. In contrast, studies in African Americans and US Whites have found that after correction for body or bone size, differences in BMD and BMAD persisted [220, 221, 332].

Despite the strong association between BMD and fracture risk shown in this study routine population screening in a resource constrained environment with limited DXA machines will not be cost effective or efficient and rather subjects should be identified according to clinical risk factors. Additionally in view of significant percentage of subjects with prior fragility the introduction of a FLS is urgently indicated.

5.6 Morphometric vertebral fractures

The increased risk of a future fragility fracture, although present for all fractures is highest with a VF [10, 20, 57, 147, 155]. A prior vertebral deformity increases the risk of a hip fracture by 2.8 – 4.5 fold. In the CaMos study a VF predicted risk for future VF but not for non-VF. A possible reason for this is VFs are often due to primary bone fragility while the aetiology of hip fractures is multifactorial including fall risk and clinical factors [192]. However a prevalent VF is often missed as the majority are may not present clinically [7].

Although self-reported VFs were low in both cohorts, a significant number of morphometric VFs (24.5% in all subjects) were identified on lateral thoracic and lumbar radiographs (32.7% and 20.3% in fracture and control subjects, respectively), with multiple VFs being more common in hip fracture subjects than controls subjects. These results support the findings that prevalent VFs significantly increase subsequent hip fracture risk up to five-fold [353].

Compared to hip fractures, there are fewer large studies on VFs, which report that the geographic and ethnic variation with VFs is much less marked than that with hip fractures. However, similar to hip fractures there is a higher incidence in Whites compared to African American or Asian women [349]. Major obstacles in obtaining correct epidemiological data on VF are the asymptomatic nature of VF, the different approaches in choosing sample sizes [11], and the lack of consensus in defining VF until the recent acceptance of the semi quantitative visual techniques [152].

Prevalence rates in community studies in post-menopausal White women across Europe vary between 6 - 21% [10, 569], while in Rochester the prevalence rate was

25.3% in women aged 50 years and older [350]. In this study VFs were found in 24.5% of all subjects aged 60 years and older, similar to the USA study despite the lower hip fracture incidence. Although there is limited data from developing countries, several studies have found similar results with a similar VF prevalence but lower hip fracture incidence. In the LAVOS study, across five Latin American countries, the prevalence for radiological VFs was 11.2% in women aged 50 years and older and increased to 27.8% in women over 80 years [360,361]. This is comparable to the studies from USA which found a prevalence of 33.9% in over 80 year old women [26]. Several studies from Asia have also reported similar findings with the a prevalence of 23% in Vietnam [561] and 37% in women aged 80 years and older in Beijing, despite a low incidence of hip fractures in China. In contrast, native Japanese women despite having a lower BMD than USA whites, have a 50% lower risk of hip fracture compared to Whites but a higher VF prevalence than both Japanese residing in the USA or Whites. It has been suggested that the lower hip fracture rate is related to a lower fall risk in native Japanese [11, 154]. The first urban community study from India DeVOS has shown a similar trend with a VF prevalence rate of 17.9% in subjects greater than 50 years old [562] and in Morocco the prevalence was 26% in men older than 50 years [38].

The first study to comment on the prevalence of vertebral osteoporosis and VF in SA was undertaken to determine aortic calcification on lumbar spine radiographs by Dent et al.,(1968) [385], in rural and urban African and urban White women. The authors concluded that osteoporosis was rare in Africans but the study had several limitations as only lumbar radiographs were assessed subjectively and no objective measurement was conducted, the sample were not matched for age, and the African

subjects were in-patients at a regional hospital while the White group included community dwellers. More recent studies however have reported a higher prevalence; in White and African women from Cape Town a prevalence of 11.5% and 8.3% respectively was observed [69] while a recent five year longitudinal study reported that 38% of African women developed a new VF (>20% vertebral deformity) [54].

In the total study cohort, VFs were most common in White (44.8%) followed by African (28.3%) and lowest in Indian subjects (22%). Further White hip fracture and control subjects had the highest percentage of VF compared to Indian and African hip fracture and control subjects. This finding may not be surprising as White women in the study were the oldest and it has been shown that the incidence and prevalence of VFs increases with age, from 0.9% and 5 - 10%, respectively in the 50 - 60 year old age group to 1.6% and 30%, respectively in those aged 80 years and over [180,563]. The higher number of VF in African than Indians once again highlights the concern that several authors have expressed that Africans are at a higher risk of VF than hip fractures [56].

Women not unexpectedly, had a higher total number of VFs compared to men in the combined group and in the hip fracture and control groups, respectively which is similar to studies in White women and men from USA where the prevalence in over 60 year older subjects is two or three fold higher in women compared to men [564]. In contrast, community based studies from Europe, Canada and India have reported a similar gender incidence [56, 562,352].

The most common site for VFs was T11/12 and L1 in hip fracture subjects and T6 and T11 in control subjects. The reason for different sites cannot be explained fully but a bimodal fracture distribution has been previously reported [154,565]. Reasons for the difference include difference in activities which resulted in the fracture and the possibility of some studies missing thoracic fractures. In this study, however a single radiographer blinded to hip and control subjects examined all the films and errors are therefore less likely.

Indian fracture subjects were more likely to have severe vertebral deformities compared to African hip fracture and White subjects. The degree of vertebral deformity correlates with future hip fracture risk [294].

A major limitation of the VF results in this study is that 40% of hip fracture subjects did not have radiographs; these subjects were mostly frail or died soon after the hip fracture and therefore number of VF may possibly be under-estimated. Secondly, LVA on DXA was also not available for confirmation and comparison. Although lateral radiographs of thoracic and lumbar spine remain screening tools, LVA is more useful as it uses a combination of digital radiographs and parallel beam geometry to allow for visual fracture assessment and the digital measurement of vertebral height. In contrast, plain radiographs can visualize the entire thoracic spine while LVA usually starts at T7 and radiographs have a wider field and higher resolution [182].

5.7 Functional status

Despite extensive research in hip fracture subjects few studies have compared functional levels in age and gender matched hip fracture and control subjects.

In this study, subjects with hip fractures were more likely to have a poor functional status prior to their fracture than control subjects. In the multivariate analysis, the IADL and QoL remained as significant risk factors.

The PSMS and Lawton IADL scales in combination are sensitive measures of activities of daily living (ADL) and have been found to be reliable in the elderly in multiple studies [478, 479]. Compared to controls, hip fracture subjects had significantly poorer function in both tests with lower overall scores, and were significantly more likely to have difficulty in all areas except eating compared to control subjects. On comparing women and men with hip fractures, men were significantly more likely than women to be unable to eat independently prior to the fracture. In comparison, women were significantly more likely to be unable to lift heavy objects and walk a distance. While there was no difference in the total scores for both the PSMS and IADL between African and Indian subjects with hip fractures; Indian fracture subjects were significantly more likely to be unable to use a telephone, walk a distance, cook and do handiwork. These differences are difficult to explain and may be due to differences in household structures, support systems and expectations.

Although poorer functioning in subjects with hip fractures is consistent with previous studies, it was somewhat surprising, given that self-reported activity level was higher

and they had fewer comorbid illnesses than controls subjects. It must be noted that self-reported activity level used in this study was a crude assessment and possibly affected by the patient mood. It is possible that hip fracture subjects, experiencing the pain, trauma and altered mood, over-estimated their activity level. The functional assessment tools are a more reliable reflection of pre-fracture functioning. Although cognitive impairment was not formally assessed in this study, all subjects were able to give informed consent and complete the questionnaires, making significant cognitive impairment less likely.

Interestingly, in the QoL assessment, which evaluated 5 domains of mobility, self-care, daily activities, pain and mood, hip fracture subjects had greater difficulty with mobility, self-care and were more likely to have pain and a depressed mood. Control subjects were more likely to have limitation of daily activities which is in keeping with the higher self-report of pain and greater fear of falling limiting their activity. These findings suggest that subjects with hip fractures despite their limitations were possibly still more active and therefore at a higher risk of falling.

A similar trend was seen in the individual domains of the ODI with fracture subjects having greater difficulty in the individual domains, except for personal care and standing, however the final total scores were not significantly different between hip fracture and control subjects. Although there was no significant difference in total scores, differences exist in individual parameters and it's possible that a decline in these parameters may help predict fracture risk in the elderly.

5.8 Biochemical and haematological parameters

Biochemical and haematological investigations have multiple roles in the assessment and management of patients with hip fractures and are useful in excluding a secondary cause, to assess general medical status and predict outcome. Often, subjects with hip fractures are elderly, frail and have multiple comorbidities and may have several laboratory abnormalities.

In this study, no further cases of secondary causes of osteoporosis (hypogonadism, multiple myeloma, hyperparathyroidism) were identified from the laboratory investigations. However, significant differences in haematological and biochemical results were present in the hip fracture and control groups and except for total protein and glucose persisted in gender and ethnic matched groups. The haemoglobin, serum sodium and albumin levels were significantly lower in hip fracture subjects than controls, whereas the inflammatory markers (WCC, CRP and ESR), serum bilirubin, ALT, GGT, and random plasma glucose levels were higher. There was no difference in the urea, creatinine and PTH levels.

Anaemia is common and has been reported in 24 – 44% of hip fracture subjects [566] and may be due to the multiple comorbidities in older individuals, bleeding at the time of the injury or due to frailty [567,568]. While hip fracture subjects in this study had less comorbidities, their lower functional status and body weight suggests that the hip fracture subjects were more likely to have frailty, a syndrome common in older persons and often associated with anaemia [569]. Frailty and a poor nutritional status may also explain the low serum albumin. Several studies have reported an

association between a low serum albumin and cognitive impairment, functional impairment and increased mortality after hip fracture [576-573].

Chronic inflammation has been implicated in the pathogenesis of several diseases and may also play a role in osteoporosis [574,575]. This is supported by the increased prevalence of osteoporosis in inflammatory diseases such as RA. High CRP levels have been associated with an increased fracture risk, even in the absence of inflammation. Studies on the association of CRP and hip fractures have however shown conflicting results. The high WCC, ESR and CRP may also be elevated from an acute stress response to trauma [576].

Similar findings to this study, namely, a low BMI, low caloric intake, low serum albumin and raised CRP have been reported in the USA [522]. However, studies on the association between low albumin levels and functional outcome are conflicting [586]. In addition in a meta-analysis, low haemoglobin, raised total lymphocyte count, low albumin, high creatinine and high PTH have been shown to predict mortality [577]. In this study there was no difference in renal function and PTH levels between hip fractures and controls.

The acute stress of a hip fracture may also account for the elevated glucose levels in the hip fracture subjects.

Although the liver enzymes were significantly elevated in hip fracture subjects compared to control subjects, they were within the normal range. It is possible that the significantly higher use of alcohol contributed to the raised liver enzymes, especially as GGT was raised in men with fractures compared to women. The mean current alcohol intake was low in both hip fracture and control subjects with a wide

variation in the amount used. The effect of alcohol is dose dependent, and heavy drinkers (>2 drinks per day) have an increased risk of osteoporosis [147], while moderate to low drinking (0.5 -1 drink per day) may be protective and confer a lower risk for fractures than abstinence [279].

Despite lower vitamin D levels in the hip fracture subjects, *(refer section 5.4.9. lifestyle factors; vitamin D and calcium)* no differences were seen in calcium, thyroid or PTH levels between the two cohorts.

In the backwards stepwise multivariate logistic regression model, low haemoglobin and albumin and an elevated WBCC and CRP levels were independent predictors for hip fractures in this study.

5.9 Hip fractures in men

This study confirms that osteoporotic fractures are important in men with over 25% of fractures occurring in men. This finding is in keeping with other studies which found that between 20 - 35% of all hip fracture occur in men [312] but is contrary to previous studies from developing countries and SA which reported a similar ratio in men and women. However these studies, due methodological issues discussed previously, are not comparable to the current study.

In the limited studies in Africa, there is conflicting data on age and gender; in Cameroon and Morocco [47,48], male hip fracture subjects were younger than women. However in the Nigerian study, men were older [40]. In Indian men (from

India), the mean age of hip fractures was comparable in men and women [43, 511]. The studies from India and Africa however had a small number of subjects.

Although men were taller, there was no significant difference in weight or BMI between male and female fracture subjects. Male fracture subjects were more active, and were more likely to smoke and consume alcohol compared to women, however the extent this contributed to fracture risk in men is unknown as the amount of alcohol consumed was in the moderate to low category which may be protective. Previous studies have reported that the proportion of heavy drinkers is significantly higher in men compared to women (56).

Despite secondary causes of osteoporosis being more prevalent in men [578,579], except for alcohol use, no association was shown between known secondary causes of osteoporosis and hip fractures in men in this study. There was also no difference in the number of falls but sideways falls were less common. This is contrary to other studies which report a lower prevalence of falls in men [298]. Lastly, no male fracture subject and very few male control subjects recalled a family history of osteoporosis or fractures. The presence of a family history of osteoporosis was also low in women (3.5%); suggesting either a low awareness of osteoporosis in both genders or a true absence because of previously lower life expectancy.

Similar to previous studies, in this study, there was no difference in areal or volumetric BMD between men and women with hip fractures [79,580]. This suggests that the skeletal structure of men and women in this study was comparable, with men more likely to be small-framed similar to women. Several studies have attempted to determine the causes of low BMD in men but most of these studies are

from outside Africa with only one recent study from Africa. In the African study, in healthy Moroccan men with a mean age of 49.1 years, 8.7% had osteoporosis and 52.8% had osteopenia [38]. A lower BMD was associated with lower BMI and increasing age, however no relationship was found with smoking with only 15% of the cohort were smokers and none of the subjects consumed alcohol (possible due to religious restrictions). A similar low prevalence of osteoporosis (8.5%) was reported in Indian men [372].

Despite the small numbers of men, this study highlights the high mortality and morbidity in men. The higher mortality rate in men compared to women (41.1% vs 30.6%) at one year is higher than that reported from developed countries (20.7% and 7.5% in men and women respectively) [581]. The reason for a significantly higher rate in men is not readily apparent as CRF, BMD and function were not markedly different between male and female fracture subjects. Other underlying factors including genetic or SES may play a role.

5.10 Outcomes post fractures

At the end of the one year study period, 36.4% (n=67) of hip fracture subjects had died, 58.5% (n=117) were alive and 8% (n=16) lost to follow up.

The majority of patients were managed surgically (86.5%) and the choice of type of surgery and prosthesis was at the orthopaedic surgeons' discretion. Despite the significant comorbid disease burden and the regional hospital setting, only patients with severe and multiple medical conditions were referred for a physician's consult,

in contradiction to current guidelines which advocate an integrated holistic ortho-geriatric management approach [435]. While there are very limited geriatric services, all the study hospitals have a well-established Internal Medicine service. The probable reasons for lack of joint management are overburdened medical and orthopaedic services, and more importantly the lack of appropriate protocols and a special interest in osteoporosis.

Although current guidelines advocate surgery as early as possible, from within 24 hours to 4 days, in an effort to improve functional outcome, decrease hospital stay, decrease pain and post hip fracture complications and possibly mortality [423, 436], the average number of days to admission in this study was 4.2 ± 12.6 days, time from fracture to surgery was 11.3 ± 9.2 days and mean length of stay was 21.9 ± 14.8 days. The delay may have been due to a lack of awareness and a failure of family or local clinic staff to identify fractures in persons with pain and poor mobility. System problems include an overburdened system with acute trauma taking precedence over hip fracture subjects, and lack of facilities in terms of theatre time and surgeons (personal observations during study period). These deficiencies have been identified in several other centres and a system based solution to prevent delays, including having specialized surgical teams available, can be a cost effective method to prevent surgical delays and long term morbidity [437].

Despite the significant mortality post hip fracture, and the fact that a significant number of fracture subjects had had a prior fracture, none of the subjects were prescribed calcium and vitamin D or referred for a BMD measurement prior to discharge. This included subjects who had been assessed by a physician. These findings are not surprising; several studies have noted that post hip fracture a

diagnosis of osteoporosis is made in less than 30%, BMD measured in 15% and less than 30% are prescribed calcium and Vitamin D [29].

Education and awareness programs such as the Capture the Fracture campaign and FLS are urgently required to improve the management of hip fractures [462].

5.11 Mortality

It is well recognized that hip fractures have a high mortality and that death is not directly related to the hip fracture, but rather is a result of the interaction of underlying comorbid diseases and/or surgical complications, including infections and immobility [581].

At the end of the one year study period, 36.4% (n=67) of hip fracture subjects had died, 58.5% (n=117) were alive and 8% (n=16) lost to follow up. The highest number of deaths (n=52) were reported in the first six months (77.6% of all deaths), MR at six months was 28%. In the next six months a further 15 subjects from the remaining 132 died, 11.3% of hip fracture subjects. The overall high MR at 36.4% at one year is also consistent with previously reported rates of between 18 - 31% [343,581].

In developed countries, the MR post hip fracture has been shown to be double that of age matched controls, with the greatest risk seen in the first six months post fracture [184]. Several studies suggest that after the first six months, the excess mortality, if corrected for age, sex, SES, pre-fracture functional status, BMI, co morbid illnesses and overall health status, does not persist [13, 289], while other

studies suggest MR persists for up to a year [406]. In this study although early MR was higher than subsequent period, it persisted up to one year later.

5.11.1 Non modifiable risk factors: Age, gender and ethnicity

The mean age of fracture subjects who died was significantly higher than survivors (75.3 ± 8.6 years compared to 73.6 ± 8 years, p = 0.048) and this study confirmed that advancing age is independently associated with higher mortality [581]. The mortality in men although higher than women (41.1% vs 30.6%) was not significantly different. Gender bias in mortality rates is well described; in a retrospective review in-hospital mortality for men with hip fractures was double that for women in the USA [408]. In support of the gender bias, a 26% higher mortality has been reported in men with a hip fracture compared to men without a hip fracture, compared to only a 12% higher difference women [411]. The increased MR post hip fracture may also persist longer in men than women with some studies suggesting up to two and half years and even more in elderly men [3, 14, 161,582].

Ethnic differences in MR have also been reported. In the USA, a higher mortality has been reported in African Americans compared to Whites [416,583]. In this study, the MR was significantly higher in African subjects compared to Indians. Except for the fact the African subjects were older than Indians; there were no clinical or laboratory explanations for this difference.

5.11.2 Modifiable risk factors: Phenotype, education and lifestyle

The association between a lower body weight and lower BMI with a significantly higher mortality has been consistently reported [14,58]. Postulates for this association include that these parameters are surrogate markers for poor nutrition, the presence of chronic illnesses and possible a lower SES. In this study, in both the univariate and multivariate analysis, weight and BMI were predictors of mortality.

In this study the hip fracture subjects had a lower education level compared to controls, which was contrary to most international studies which report that a higher educational level is associated with better SES and higher fracture risk [47]. Counter-intuitively however, fracture subjects who died had a higher educational level than survivors. It is possible that people with higher educational level had a better SES and were older and therefore had a higher mortality, but the exact association in this study remains uncertain.

There was no difference in calcium intake, smoking or alcohol between subjects who died and survivors, but vitamin D levels were significantly lower in hip fracture subjects who died. Several studies have reported a decrease total mortality, cardiovascular risk and incidence of cancer in subjects receiving vitamin D [585,586] but no significant effects of vitamin D have been shown on mortality post fracture [585,586]]. The lower vitamin D levels may reflect decreased activity and mobility prior to the fracture in subjects who died.

Activity and functioning levels are important in predicting outcomes. In this study fracture subjects who died also self-reported lower levels of physical activity, and pre-fracture were more likely to have difficulty with PSMS, as well as IADLS with a

significantly lower mean IADL score. Similar findings have been reported with subjects who died having greater difficulty with eating and mobility [411,586].

5.11.3 Contributing illness, clinical risk factors and BMD

The study failed to show any significant difference in comorbid disease profile, which is in contrast to other studies which have found dementia, chronic lung disease, myocardial infarction and heart failure increase the risk of death [581]. It should be noted that subjects with dementia were excluded from the study, so the association between cognitive impairment and death could not be investigated. There was also no correlation found between fall risk, prior fracture or BMD. In addition, this study due to the small number of patients, may have failed to prove possible associations.

The significantly lower serum albumin and higher CRP and ESR levels in hip fracture subjects who died, are consistent with previous reports [577] and suggest the presence of frailty, poor nutritional state, liver impairment or complications of chronic diseases. A meta-analysis [576] found that impaired renal function was a risk factor for death, in this study the urea and creatinine were only mildly impaired, possibly secondary to dehydration. But in contrast there was no association between death and with a high WCC or PTH in this study. The relationship between significantly lower sodium level, albeit within the normal range and death may reflect a poorer underlying general medical status [587].

5.11.4 Fracture management

A delay in time to surgery was a significant risk factor for death. In contrast, early surgery has been shown to decrease mortality risk and surgical complications [423]. It is possible the delay in surgery was due to the presence of comorbid diseases which required medical stabilization before surgery (author's observation). More likely though, is that trauma gets precedence for theatre time and in a busy service, older persons are of lower priority.

Although a significant number of subjects were discharged to step down facility, the length of stay at these institutions was not available. However, at the three month follow up visit, there was no significant difference in follow up in the subjects irrespective of place of discharge. In contrast, a higher mortality has been reported in subjects discharged to institutions compared to their home [427].

The study found mortality was higher in patients managed conservatively and this is not unexpected as the main reason for not performing surgery was a poor surgical candidate and high anaesthetic risk and not lack of resources.

5.11.5 Summary of mortality

Although this study comprised a small number of subjects and a smaller number of deaths, an attempt was made to identify risk factors for mortality. In univariate analysis, subjects who died were more likely to be older, and have a lower body weight and BMI, lower physical activity levels, VF, lower serum albumin, sodium and vitamin D levels, and increased levels serum urea, GGT, CRP and ESR levels. The

clinical and laboratory findings in general indicate a poorer general medical status, with possible under-nutrition, renal and liver impairment, higher inflammatory response and increased risk of complications, all of which are known to be associated with a higher mortality.

In a backward conditional logistic regression model ethnicity (Africans), lower body weight or BMI, higher education status, difficulty with cooking, taking medications or managing finances, decreased mobility, decreased albumin or elevated C-reactive protein and longer mean hospital stay remained significant risk factors for death.

5.12 Morbidity

The morbidity post hip fracture is higher than with any other osteoporotic fracture and is increased by the potential for surgical complications. Recovery post fracture has been found in the literature to be dependent on several factors including age, pre-fracture functioning, comorbid disease burden and the place of discharge. Poorer outcomes are seen in older individuals who often are unable to return home and need admission to a nursing home with the rate of admission to a nursing home increasing from 14% in 50 - 55 year age group to 55% in 90 year age group [588].

Following a hip fracture, up to 25% of independent subjects become partially dependent, while 50% of partially dependent become totally dependent [76, 238]. Up to 40% are unable to walk, 60% are restricted in their ability to perform ADL and 80% are unable to perform at least one IADL [201]. Even in developed countries, despite extensive and lengthy rehabilitation post hip fracture, 50% of hip fracture

subjects have long term mobility restriction and further 50% who lived independently require long term nursing care and help with daily activities and a third may need institutional care [26].

Functional status in this study was assessed with five inter-related tools which are additive in determining function and complement each other. To maximise recall, they were administered within a week of the fracture to assess pre-fracture functional status. As discussed earlier, subjects with hip fractures were more likely to have difficulty in performing ADLs and IADLs and had a poorer QoL pre-fracture than did matched controls, and the inability to perform individual IADLs were risk factors for death. In survivors, functional status was assessed at three, six and twelve months. Post hip fracture a significant number of subjects needed to be discharged to a step down care facility and the majority of survivors had a significant decrease in functional activity in all areas except mood. The decline was most marked at three months but persisted over the one year follow up period as observed in other studies [152].

Immediately post hip fracture there was a significant and rapid decline in functional ability, which was consistently documented, irrespective of the functional assessment tool utilized. A nadir in all functional assessment parameters was noted at three months. Varying improvement in most functions assessed were noted thereafter, some far more dramatic than others. Significant functional impairment, however, remained present in most fracture cases at one year post hip fracture. At the end of one year 33.3% still required assistance or were unable to walk independently.

Similarly, the mean VAS for pain increased from 1.4 ± 1.3 to 5 ± 1.9 at three months and remained elevated at almost four-fold from baseline at 4 ± 3.2 at one year. There was also a marked decline in travel and social interaction in the ODI and almost 60% of individuals at one year had failed to return to their pre-fracture social activities. Restriction in social activities and dependency adversely influence mental health status and lead to anxiety and depression [398] and although there was a two fold increase in depression or anxiety compared to baseline, there was no significant difference in mood from baseline to one year.

This study confirms the devastating impact on functioning in the elderly post hip fracture subjects and compares with other studies which report that post hip fracture only 33% of survivors can perform their ADL, 20% their IADL and 26% their social functioning as well as they did pre-fracture [19,589].

The recovery post fracture appears to follow a temporal sequence with an initial improvement in mood, cognition and upper extremity strength at around 4 months followed by improvement in gait, balance and social interaction. Recovery of ADL and IADL of lower extremity starts by one year only, however the majority of subjects may never show full recovery in all areas [590]. The survivors in this study appear to have followed a similar recovery pattern. This study did not analyse outcomes in men and women and different ethnic groups separately due to the small sample size, however despite a higher mortality, several studies report better outcomes in men than women [507,591].

The morbidity from sustaining four VF equates to one hip fracture [156]. There is limited data on ethnic differences post fracture, but it is suggested that non-Hispanic

Africans have poorer outcome than non-Hispanic whites [167,507,594]. The readmission rate in this study was relatively low, at 7%, for surgical complications, but the public health service is overburdened and only extremely ill patients are admitted. Furthermore, it is possible some subjects may have been admitted at their local hospitals and not referred to regional centre for minor complications. Family members also reported that a number of subjects had sought care at local clinic or hospital before death; however they were not admitted (personal correspondence with family members). There is no local data on outcomes post fracture and readmission rates but other studies have found much higher readmission rates of up to 40% however the cause is usually nonsurgical or related to comorbid illnesses [592].

5.13 Health care costs

There is a paucity of data on health care costs, and especially for NCDs, in SA [464] with only one study on hip fracture costs in a public sector hospital [463]. This was however in trauma subjects and the cost per hip fracture was calculated to be R12 637.00 (approximately $1150). In this study, the bottom up approach was used to calculate the cost of acute management of atraumatic hip fractures. This method is more accurate and was modified to calculate the average cost for 169 subjects. The direct cost was calculated to be R62 891.65 per subject. A limitation is the Department of Health does not use specific costs, such as bed costs and cost per [593]therefore used to calculate costs based on procedures performed and number of days in hospitals.

The actual calculated cost at R62 891.65 (approximately USD 5717) per subject was 36.6% higher than the normative costing model based on standard care endorsed by NOFSA [87]. As in most other studies [23,450,593] the largest cost was for the ward admission (87.9% of the total expenses), while surgical costs accounted for 5.1%, investigations, excluding BMD, 4.5%, and the prosthesis only 2.5%. With the delay in surgery, the average duration of admission in this study was longer than expected, and could account for an excess of R4.7 million (USD 427 300) for the 173 patients in whom surgery was performed. If calculated over a 12 month period (for an average of 230 subjects), and assuming an equivalent percentage of subjects having surgery then approximately R5 million (approximately USD 454 500) would have been spent on days awaiting surgery. These costs relate to public sector and are significantly lower than that for the private sector, which are estimated to be more than double (R150 000, approximately USD 13 650) [28, 51].

These costs however, underestimate the true cost of hip fractures as indirect costs from loss of productivity, special transport needs, special diets, home alterations and caregiver costs [24, 450] were not included. The indirect costs in SA may be more significant as rehabilitation services and chronic care are largely not available.

With the predicted increase in the incidence of fractures in SA, the costs of hip fractures will increase commensurately. This is especially so in developed countries where the burden of osteoporosis is higher. Although several efforts have been made to reduce the burden of health care costs associated with hip fractures including early discharge to nursing homes, this has not proven effective as early discharge shifts the costs to nursing homes which equal that of hospital care [594,595,597]. The most effective way to prevent costs of a hip fracture is to prevent fractures and if this is not possible, then efficiency of hospitalisation and rehabilitation need to be improved [596,24].

Effective treatment for osteoporosis is available in SA and medical treatment of established osteoporosis is more cost effective than treating fractures irrespective of age and is recommended for moderate to high risk subjects [598]. The 40% reduction of hip fractures with annual administration of an intravenous bisphosphonate for example at a cost R1534 (approximately USD 140) for 3 years will considerably reduce not only the cost, but also the morbidity and mortality, associated with hip fractures [596].

5.14 Summary and recommendations based on discussion

This is the first study in SA to report the demographic characteristics, incidence, risk factors, outcome and health care costs of osteoporotic hip fractures, in a peri-urban population in SA. The study highlights that osteoporosis hip fractures occur in all ethnic groups in SA, albeit at different rates. Similar to developed countries, hip fractures are more common in women than men and increase with age. However surprisingly, hip fractures occur at an earlier age in men, especially those of Indian descent.

As expected from studies in other multi-ethnic populations, the incidence rate (at least in the public sector) appears to be highest in Indians and lower in Africans. However, the incidence in Africans has risen by more than tenfold compared to the landmark study by Solomon in 1968 [39].

The risk factors for hip fractures are similar to those in developed countries and are similar in Africans and Indians. Specifically weight and BMD were significantly lower in all fracture cohorts compared to controls including men and women; suggesting that men with hip fractures were of smaller frame.

Despite a low calcium intake in Africans subjects, there is no difference in Vitamin D levels in Africans and Indians. In men, smoking and alcohol use are important risk factors. Surprisingly however, no secondary cause for osteoporosis was identified in all fracture cohorts, possibly due to the small sample size.

Morphometric vertebral fractures occur in all ethnic groups with the highest prevalence in Whites, followed by Africans and Indians. Despite a significant

number of subjects having a prior fracture, very few subjects received appropriate treatment resulting in a second fracture. Hip fractures in this study were associated with a significant mortality and morbidity. In addition to other factors, a delay in surgery contributed to the increased mortality. The actual cost of the acute treatment of osteoporosis exceeded the normative costs based on current treatment guidelines.

In summary, hip and morphometric vertebral fractures are common in SA. There appears to be under-recognition of osteoporosis and the risk of fractures in this multi-ethnic population. Despite the presence of strong risk factors for hip fractures, especially a family history of osteoporosis and history of previous fragility fractures, osteoporosis is under-diagnosed and under-treated. Even in the presence of a hip fracture, management is suboptimal.

Limitations

This study was undertaken in the public sector and may have led to an under-representation of the at risk populations especially White and Indian men and women. Further Coloured men and women are under-represented in this geographic area. Known associations may not have been confirmed due to the small numbers.

Furthermore, there is a possible selection bias in the recruitment of controls who may have agreed to participate in the study because they perceived themselves to be at high risk of osteoporosis. This may have under or over-estimated the association of risk factors in the case control study.

Recommendations

Larger national studies with adequate representation of all ethnic groups are needed to confirm age, gender and ethnicity incidence rates of hip fractures. Urgent interventions are required to improve management of hip fractures in the public sector.

Chapter 6 Conclusions

6.1 Introduction

The number of hip fractures in Africa is projected to increase exponentially with increasing longevity [4, 344]. Based on data from the USA [36, 61] and a single South African [39], osteoporotic hip fractures are considered to be rare in Africans. Recent studies have however, suggest that osteoporotic fractures (albeit vertebral fractures) occur with equal frequency in Africans and Whites in SA [54, 68]. This is the first study undertaken in over 40 years to study the demographic profile of subjects with hip fractures, the ethnicity and gender based incidence of hip fractures, risk factors, outcomes and health care costs of hip fractures in SA.

6.2 Main Findings and Contributions to the Field

6.2.1 Demographic profile of hip fractures

Hip fractures were observed in all ethnic groups and in both men and women. There was a significant shift in the female to male ratio from the previous study [39] which had shown a male predominance. The current female to male ratio of 2.8:1 is similar to that in developed countries [26,442]. Another significant finding was that hip fractures occurred at an earlier age in men, (especially those of Indian descent), compared to women, with the majority of fractures occurring before the age of 75 years in men.

This has important public health implications. The current NOFSA guidelines which recommend that BMD density be measured at age 70 years in men [88], will need to be re-considered given the earlier age of fracture in this study.

6.2.2 Incidence rates

The crude incidence rate of hip fractures at 94.7 per 100 000 in subjects aged 60 years and over, while still in the low risk category [518], is the highest reported from Africa. This composite incidence rate reflects the much higher incidence rate in Indians as well as the lower incidence in Africans, which is however significantly higher than previously reported. These rates, together with the increasing LE in SA, support the projection that the burden of osteoporosis will increase substantially. Furthermore there appears to be a difference in the incidence rate in the different ethnic groups and further studies are required to confirm this finding. This will be particularly relevant for computing FRAX® algorithms for SA.

6.2.3 Risk factors

The study confirmed that risk factors for hip fractures are similar to those in developed countries and include increasing age, female gender, sideways falls, alcohol, smoking, a prior fracture, low vitamin D levels and poor pre fracture functional status. Risk factors may be particularly important in identifying persons at risk, especially in the setting of limited resources and unavailability of densitometers.

In addition, a number of these risk factors are modifiable and can be controlled with health education and awareness programs. South Africa already has anti-smoking regulations and these can be strengthened. In addition, an improved functional status can be achieved with exercise and healthy eating programs, and the early identification and appropriate management of risk factors for frailty.

A particular concern is that despite a history of any prior fragility fracture in 27.5% and 8.5% and the presence of morphometric vertebral fractures in 32.7% and 20.3% of subjects with hip fractures and controls, respectively, only one subject had had a prior assessment for osteoporosis. This highlights the lack of awareness of osteoporosis in both health care personnel and the community. Focussed awareness programs, such as the Fracture Liaison Services and Capture the Fracture Campaign [462], are needed to treat individuals at highest risk of osteoporosis

Risk factors such as low education, low body weight, low BMI and low serum albumin suggest that poor socio-economic and nutritional status is a risk factor for osteoporosis [66, 82, 140], contrary to the belief that osteoporosis, like other NCDs, is a disease of affluence [75]. With the high rates of poverty and unemployment in SA, the poor besides being at higher risk for communicable diseases may also have an increased risk of osteoporosis, despite the apparent genetic protection.

It is also possible that as the control sample was a volunteer based sample certain risks may be disproportionately higher in control subjects compared to the general population most notably prior falls, prior fractures and family history of osteoporotic fractures. There are no studies on the general awareness of osteoporosis in the SA

population but screening is seldom undertaken except in tertiary centres and therefore it is possible that controls who were familiar with osteoporosis or had a family history of hip fracture were more likely to volunteer. Further as certain ethnic groups notably Whites have a higher use of the private sector the association with SES may not be truly be represented.

Bone density was significantly lower in hip fracture subjects compared to controls and the majority of subjects with hip fractures were classified as having osteoporosis when T-scores were calculated using the recommended NHANES III reference values for White women [559]. This provides support for using this reference database in the absence of local data. In addition, a BMD assessment would have correctly identified the majority of subjects requiring anti-osteoporosis treatment. The apparent protective effect of any treatment with HRT on hip fracture risk argues for the use of this relatively inexpensive treatment option in appropriately selected individuals.

6.2.4 Mortality and Morbidity

The mortality rate is similar to developing countries and was significantly higher in Africans subjects. Other risk factors included lower body weight or BMI, higher education status, poor pre-fracture function (difficulty with cooking, taking medications or managing finances), decreased mobility, decreased albumin, increased CRP and a longer mean hospital stay. The time to surgery from fracture was longer than other studies and exceeded national and international recommendations. Even though the study was conducted in regional hospitals

which are part of the specialist and subspecialist training platform, screening and treatment was not offered to subjects by the attending clinical team. Survivors of hip fractures had a significant deterioration in function and quality of life post fracture which did not return to baseline at one year.

6.2.5 Health care costs

Health care costs were significantly higher than normative costing and these needs to be addressed in limited resource setting and considerable savings can be achieved by following published hip fracture protocols and screening and treatment of high risk individuals [87, 88, 599].

6.3 Study Limitations

The study was the first to be conducted in the eThekwini area in KZN. The ethnic mix of the SA population varies significantly in the different provinces. In KZN, the majority of the population is African (81.7%) followed by Indians (9.6%); and just 1.4% are Coloureds.

The study only examined public sector patients and therefore is not reliable for the White population group and possibly even Indians due to the high usage of private health care facilities by these two groups. The virtual absence of White men may have resulted in a younger mean age in the male fracture subjects.

An attempt was made to obtain data retrospectively from the private sector, but had to be abandoned due to problems with incorrect coding. The incidence rate is probably accurate for the public sector and for Africans in eThekwini, but may be underestimated for Indians and probably for White women and could not be calculated for White men and Coloured men and women.

Incidence rates need to be investigated periodically to determine trends. The lack of previous incidence rates precludes the determination secular changes in hip fracture incidence in SA.

A substantial proportion of hip fracture subjects gave a history of memory problems and this may have introduced recall bias

The control population in this study was not a population based sample, but volunteer subjects recruited by invitation and word of mouth from outpatient departments and from community centres. This may have introduced a selection

bias as the more educated and those with chronic medical conditions, previous history of falls, concerns about preventing fall complications and prior fragility fractures or family history of falls may have been more willing to participate due to heightened awareness of osteoporosis and need to exclude the disease or seek treatment for it. This may have confounded the risk factor analysis and underestimated the true value of these risk factors in the general elderly community.

6.4 Recommendations from the study

- Awareness and educational programs on osteoporosis and hip fractures need to be strengthened and extended to populations not traditionally thought to be at risk for osteoporosis in SA.

- A prospective national hip fracture registry (private and public sector), is required to provide critical information on incidence, outcomes and costs.

- A national study should be undertaken to determine the incidence of hip fractures in all population and gender groups. This is required to develop a FRAX® tool for SA.

- Multidisciplinary teams must be implemented for management of hip fractures to improve efficiency of care and to decrease mortality and morbidity, and should include fragility fracture prevention, acute management of hip fractures, rehabilitation, step down and long term care with proper resource allocation.

- Simple preventative measures such as lifestyle, exercise and diet programs, supplementation of vitamin D and the appropriate use of HRT should be considered in this resourced constrained study.

Appendix: 2.A

Osteoporosis epidemiological studies used in determining fracture risks for the FRAX® model

List of osteoporosis studies

Cohort	Number	% female	Person-years	Hip fracture	Other osteoporotic fracture	Age (mean)	Age Range
(a) Primary cohorts							
EVOS/EPOS	13,490	52	40,681	50	719	64	40-95
CaMos	9,101	69	25,834	40	307	62	25-103
Rochester	1,001	65	6,227	42	244	57	21-94
Rotterdam	6,851	59	39,593	220	646	69	55-106
DOES	2,089	61	15,994	103	407	71	57-96
Gothenburg II	1,970	59	15,201	271	350	78	20-89
Hiroshima	2,603	70	9,825	32	90	65	47-95
Sheffield	2,170	100	6,894	63	243	80	74-96
Gothenburg I	7,065	100	29,603	29	312	59	69-86
Totals	4,6340	68	189,852	850	3,318	65	
(b) Validation cohorts							
SOF	5,251	100	57,388	523	1,313	71	65-99
EPIDOS	7,435	100	26,665	302	642	81	70-100
WHI	61,014	100	439,296	915	6,250	66	50-79

Appendix 3.A

University of KwaZulu Natal ethics approval letter.

UNIVERSITY OF
KWAZULU-NATAL

RESEARCH OFFICE
Biomedical Research Ethics Administration
Westville Campus Govan
Mbeki Building Private Bag X54001
KwaZulu-Natal,Durban,4000,SOUTH AFRICA Tel:27 31 2604769 -
Fax: 27 31 2604609
Email:BREC@ukzn.ac.za Website:http:/
/research. ukzn.ac.za/ResearchEthi cs/ BiomedicalResearchEthics.aspx

12 April 2010
Professor Bilkish Cassim (Supervisor) Department of Geriatrics
Nelson R. Mandela School of Medicine University of KwaZulu-Natal

Dear Prof Cassim

PROTOCOL: A comparison of the demographic profile, risk factors, outcomes and health care costs in geriatric patients with and without osteoporotic hip fractures in the public health sector in the eThekwini area. Department of Geriatrics UKZN, Dr Farhanah Paruk.
REF: BF043/09.

The Biomedical Research Ethics Committee (BREC) has considered the abovementioned application.
The study was approved by a quorate meeting of BREC on 14 April 2009 pending appropriate responses to queries raised. Your responses dated 23 March 2010 to queries raised on 07 December 2009 have been noted by a sub-committee of the Biomedical Research Ethics Committee. The conditions have now been met and the study is given full ethics approval and may begin as from today; 12 April 2010.
The study protocol and related study documents have been reviewed and approved.
This approval is valid for one year from 12 April 2010. To ensure uninterrupted approval of this study beyond the approval expiry date, an application for recertification must be submitted to BREC on the appropriate BREC form 2-3 months before the expiry date.
Any amendments to this study, unless urgently required to ensure safety of participants, must be approved by BREC prior to implementation.
Your acceptance of this approval denotes your compliance with South African National Research Ethics Guidelines (2004), South African National Good Clinical Practice Guidelines (2006) (if applicable) and with UKZN BREC ethics requirements as contained in the UKZN BREC Terms of Reference and Standard Operating Procedures, all available at http://research.ukzn.ac.za/ResearchEthics/11415.aspx.

BREC is registered with the South African National Health Research Ethics Council (REC-290408- 009). BREC has US Office for Human Research Protections (OHRP) Federal-wide Assurance (FWA 678).

The following Committee members were present at the meeting that took place on 14 April 2009:

Professor D Wassenaar
Professor S Collings
Ms T Esterhuizen
Dr U Govind
Dr Z Khumalo
Professor T E Madiba
Dr Hardcastle
Dr S Paruk
Professor L Puckree
Professor D Pudifin
Professor V Ramdittch
Dr MA Sathar
Prof R Bhimma
Mrs T Makhanya
Professor R E Mhlanga
Dr J Singh
Dr J M Titus

We wish you well with this study. We would appreciate receiving copies of all publications arising out of this study.

Yours sincerely

PROFESSOR D R WASSENAAR
Chair: Biomedical Research Ethics Committee

Appendix 3.B Study Consent: Department of Health

HEALTH
KwaZulu-Natal

Health Research & Knowledge Management sub-component
10 – 103 Natalia Building, 330 Langalibalele Street
Private Bag x9051
Pietermaritzburg
3200
Tel.: 033 – 3953189
Fax.: 033 – 394 3782
Email.: hrkm@kznhealth.gov.za
www.kznhealth.gov.za

Reference : HRKM15/10
Enquiries : Mrs G Khumalo
Telephone : 033 – 3953189

04 February 2010

Dear Dr F Paruk

Subject: Approval of a Research Proposal

1. The research proposal titled **'A comparison of the demographic profile, risk factors, outcomes and health care costs in geriatric patients with and without osteoporotic hip fractures in the public health sector in the eThekwini area'** was reviewed by the KwaZulu-Natal Department of Health.

   The proposal is hereby **approved** for research to be undertaken at **King Edward VIII, Addington, RK Khan, Prince Mshiyeni and Inkosi Albert Luthuli Central Hospitals**

2. You are requested to take note of the following:
   a. Make the necessary arrangement with the identified facility before commencing with your research project.
   b. Provide an interim progress report and final report (electronic and hard copies) when your research is complete.

3. Your final report must be posted to **HEALTH RESEARCH AND KNOWLEDGE MANAGEMENT, 10-102, PRIVATE BAG X9051, PIETERMARITZBURG, 3200** and e-mail an electronic copy to hrkm@kznhealth.gov.za

For any additional information please contact Mrs G Khumalo on 033-3953189.

Yours Sincerely

Dr S.S.S. Buthelezi
Date: 15/02/2010
Chairperson, Health Research Committee
KwaZulu-Natal Department of Health

HEALTH
KwaZulu-Natal

Health Research & Knowledge Management sub-component
10 – 103 Natalia Building, 330 Langalibalele Street
Private Bag x9051
Pietermaritzburg
3200
Tel.: 033 – 3953189
Fax.: 033 – 394 3782
Email.: hrkm@kznhealth.gov.za
www.kznhealth.gov.za

Reference : HRKM15/10
Enquiries : Mrs G Khumalo
Telephone : 033 – 3953189

01 July 2010

Dear Dr F Paruk

Subject: Approval of a Research Proposal

1. The research proposal titled **'A comparison of the demographic profile, risk factors, outcomes and health care costs in geriatric patients with and without osteoporotic hip fractures in the public health sector in the eThekwini area'** was reviewed by the KwaZulu-Natal Department of Health.

   The proposal is hereby **approved** for research to be undertaken at **Mahatma Gandhi Memorial Hospital.**

2. You are requested to take note of the following:
   a. Make the necessary arrangement with the identified facility before commencing with your research project.
   b. Provide an interim progress report and final report (electronic and hard copies) when your research is complete.

3. Your final report must be posted to **HEALTH RESEARCH AND KNOWLEDGE MANAGEMENT, 10-102, PRIVATE BAG X9051, PIETERMARITZBURG, 3200** and e-mail an electronic copy to hrkm@kznhealth.gov.za

For any additional information please contact Mrs G Khumalo on 033-3953189.

Yours Sincerely

Dr S.S.S. Buthelezi
Date: 08/07/2010
Chairperson, Health Research Committee
KwaZulu-Natal Department of Health

Appendix 3.C Information and consent documents: English version

INFORMATION DOCUMENT

Study title: Hip Fracture and Osteoporosis

A comparison of the demographic profile, risk factors, outcomes and health care costs in geriatric patients with and without osteoporotic hip fractures in the public health sector in the eThekwini area.

Good morning/Good afternoon

We, doctors from the Department of Medicine at Nelson R Mandela Medical School, are doing research on the hip fractures and osteoporosis. Research is the process to learn the answer to a question. The answers from this study will assist the doctor in charge of the project to obtain a doctoral degree. In this study we want to learn about how often do people aged 60 years and over, break their hip bones, this is the bone which helps you walk. We also want to know what caused your bones to break, and not someone else's and this is called risk factors. We know that in some people as they get older their bones become less strong. This is called osteoporosis, weak bones. This is mainly due to a decrease in the reproductive hormones; the menopause in women and low levels of testosterone in men, and an effect of ageing. There are also a number of other reasons a person's bone may be weaker for example, a lack of calcium in the diet, low vitamin D, no exercise or being bedridden, some medication you may have been prescribed, smoking, alcohol intake, vitamin D and some medical conditions or due to as yet unknown genetic tendency or because weak bones occur in your family. When a person with weak bones has a minor fall he/she may sustain a broken bone which is called a fracture.

You have had a hip fracture and we would like to find out why. We will be asking you a number of questions to look for risk factors for osteoporosis and we will need to take blood from a vein in your arm. We will take approximately 5 teaspoons of blood and this will not cause you any harm. There may be a little pain after we take blood, but this will be for a short time only. In the meantime you will receive the usual treatment from the doctors looking after you who are specialist in broken bones called orthopaedic surgeons. Once you are able to move, we will measure your bone mineral density. This is special test that we do that tells us your bone mass that is how strong your bones are. This is done by a machine called a densitometer. You may need to go to another hospital for this test. The test will take less than 10 minutes and uses a very small dose of radiation, about 1/10th of the dose used for a chest radiograph. Thereafter you will be started on tablets for osteoporosis if the result shows us your bones are weak. We will use medication that is available at the hospital to treat you. All these medications have been previously tested and are safe to use. Once you have been treated and sent home, we would like you to come to our clinic where we will see how you have improved after your fracture, and how long it takes you to get better and return to your normal self (how much of your daily activities you are able to perform).

During the next year we also want to calculate how much money you spend because of the fracture and how much money you could not make because of the fracture. This will also help us to see how much it cost you and the government every time someone has fracture. We will compare this with how much it would have cost if we had you on medication to prevent a fracture. This information will help us make better treatment plans for old people.
We are inviting you to participate in this research study so we can have more information about how common hip fractures and osteoporosis is in our community and what the outcome is after people have a hip fracture so we can then design protocols to decrease the risk of hip fractures.

What is involved in the study?
If you agree to participate in this study as a subject i.e. someone who has already had a hip fracture then you will be interviewed regarding your medical history and risk factors for fall and osteoporosis. You will have a full examination and blood tests done to look for a cause for your fracture. A sample of blood if you are agreeable will be stored away for future genetic testing should a test in the future become available to detect osteoporosis. There are no tests available currently. See attached genetic tests information sheet for full explanation.

You will be required to perform a special radiograph called a bone mineral density test six weeks after your fracture and commenced on treatment as required for osteoporosis. You will be reviewed six months and a year later to see how you are doing. There will be no further blood test required during this period for the study unless you have other medical conditions which need to be treated and routine tests for these will be performed.

In total 200 hundred patients with hip fractures presenting to hospitals in eThekwini area will be assessed and followed up for one year. After the study period you will be given a referral letter to continue appropriate treatment at your local hospital.

If you wish to stop at any stage you will be free to do so and this will not affect your treatment in any way. You will be sent back to your hospital with a letter to continue treatment for your hip fracture.

If you are a control subject in the study i.e. someone who is above the age of 60 years and has not had a hip fracture then you will be screened for osteoporosis. This is a silent condition. You will need to do some blood and radiology tests to see if you have had any fractures and to assess your risk for fractures. The test will tell us how strong your bones are and what is your fracture risk. You will be commenced on treatment if your bones are found to be weak if you are agreeable and referred to your doctor again. You will have no additional costs to participate in this study.

Risks – There are no associated risks from enrolling in the study apart from mild pain to do the blood tests.

Potential Benefits
Hip fracture subjects- You will be fully tested for an underlying cause for your broken hip bone and if a cause is found which we can treat then you will be started on treatment. You will receive regular follow up visits for one year post hip fracture.
Controls – You will be tested for osteoporosis, which is a silent disease that occurs without causing any problems until you may present with bone pain or a fracture. Osteoporosis is becoming much more common worldwide and by participating in the study you will be
Screened and provided the chance of commencing treatment if your bones are weak and therefore decreasing your chance of getting fractures in the future.

Your participation in this study is voluntary i.e. you can decide whether you want to or not.
If you refuse to take part it will not change the way you are treated and you can continue to come to hospital for treatment. If you agree to participate in the study you are free to stop at any time and this will not affect your treatment in any way in the future
Confidentiality: While every effort will be made to keep personal information confidential, absolute confidentiality cannot be guaranteed as personal information may be disclosed if required by law. Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as the Research Ethics Committee, Data Safety Monitoring Committee and the Medicines Control Council (where appropriate).
If results are published, this will be done anonymously. You will be allocated a code number on entering data in file and the code number and name will only be known to principal investigator.

Contact details of researcher/s – for further information / reporting of study related adverse events.
Dr F Paruk- 031 2604238 (w) or 0828756786 (cell)
Dr S Rauf -031 2604283 (w)

Contact details of BREC Administrator or Chair – for reporting of complaints/ problems:
Biomedical Research Ethics, Research Office, UKZN, Private Bag X54001, Durban 4000
Telephone: +27 (0) 31 260 4769 / 260 1074
Fax: +27 (0) 31 260 2384
Administrator: Ms P Ngwenya Email: ngwenyap@ukzn.ac.za
Chair: email: Prof D R Wassenaar c/o ngwenyap@ukzn.ac.za

Information Document: Hip Fracture and Osteoporosis (Blood Storage)

A comparison of the demographic profile, risk factors, outcomes and health care costs in geriatric patients with and without osteoporotic hip fractures in the public health sector in the eThekwini area.

Good morning/Good afternoon

The study being conducted into hip fractures and osteoporosis is the first in our country. We have no data on any genetic risk factors. Studies from different part of the world show there are different genes that increase or decrease a population's group risk for both fractures and osteoporosis. These tests are not available currently in South Africa.

We would like to take a sample of your blood about one teaspoon and extract from it DNA (genetic code) and store the DNA and left over blood for the next five years. The blood will be stored anonymously and only the study investigators will know which blood matches which patient.

The blood will be stored in the department of Medicine laboratories in Nelson R Mandela School of Medicine, University of Kwa Zulu Natal.

Should genetic test become available for osteoporosis or hip fracture, only then will the blood be analysed. No blood specimens will leave South Africa. If no test becomes available in the next five years then all stored specimens will be disposed according to standard protocols.

Your blood will not be used for any other purpose apart from as outlined above. You are free to partake in the study even if you do not wish to have your blood specimen stored, and this will not impact on your management or follow up in any way.

If you agree and any genetic markers are found and your test comes back positive you will be accordingly informed.

Approval from BREC our advisory and ethics department will be obtained prior to any studies being carried out on stored samples

Consent document: Consent to Participate in Research

Good day

You have been asked to participate in a research study on Hip Fracture and Osteoporosis

as a subject or control (delete which is not applicable)

Dr F Paruk, Specialist in General Medicine at Nelson R Mandela School of Medicine will be conducting the study. The results of this study will help her complete her doctoral studies at the University of Kwa Zulu Natal.

You have been informed about the study by …… .

You may contact Dr F Paruk at 0828756786 or 031 2604801 at any time if you have questions about the research or if you are injured as a result of the research.

You may contact the Biomedical Research Ethics Office on 031-260 4769 or 260 1074 if you have questions about your rights as a research participant.

Your participation in this research is voluntary, and you will not be penalized or lose benefits if you refuse to participate or decide to stop at any time.

If you agree to participate, you will be given a signed copy of this document and the participant information sheet which is a written summary of the research.

The research study, including the above information, has been described to me orally. I understand what my involvement in the study means and I voluntarily agree to participate. I have been given an opportunity to ask any questions that I might have about participation in the study.

_____ _____

Signature of Participant Date

_____ _____

Signature of Witness Date

(Where applicable)

_____ _____

Signature of Translator Date

(Where applicable)

Consent to Store Blood for research purposes

Good day

You have been asked to participate in a research study on Hip Fracture and Osteoporosis

As a subject or control (delete which is not applicable)

Dr F Paruk, Specialist in General Medicine at Nelson R Mandela School of Medicine will be conducting the study.

As part of the study on the causes of hip fracture we would like to store a sample of your blood away at the Department of Medicine laboratory in the Nelson R Mandela School of Medicine in Umbilo Road, Durban,. University of Kwa-Zulu Natal for the next five years. The blood will be kept anonymously and only the investigators will have the code identification.

Should a genetic test applicable to hip fractures or osteoporosis only become available during this period then the blood will be further analysed. Blood will not be sent out of South Africa for any tests. If no appropriate test become available then all specimens will be discarded following standard disposal procedures for medical waste. Your blood will not be used for any other purposes other than outlined above.

If a significant genetic test is found and you are positive, you will be informed of the result.

I hereby agree/do not agree (delete which is not applicable) to having my blood stored for the above purpose only.

If you agree to store your blood, you will be given a signed copy of this document and the participant information sheet which is a written summary of the research.

The research study, including the above information, has been described to me orally. I understand what my involvement in the study means and I voluntarily agree to participate. I have been given an opportunity to ask any questions that I might have about participation in the study.

_____ _____

Signature of Participant Date

_____ _____

Signature of Witness Date

(Where applicable)

_____ _____

Signature of Translator Date (Where applicable

Appendix 3.D: Hip fracture and osteoporosis questionnaire

A comparison of the demographic profile, risk factors, outcomes and health care costs in geriatric patients with and without osteoporotic hip fractures in the public health sector in the eThekwini area.

Date of Interview [dd/mm/yy]		Study Number	
Name of Investigator		Date corrections checked [dd/mm/yy]	
		Date checked [dd/mm/yy]	

A1	I have read the individual information sheet, statement of confidentiality and informed consent form	1=Yes 2=No	
A2	If the participant agreed to participate, did he/she sign the consent form?	1=Yes 2=No	
A3	Has the participant retained a copy of the information sheet?	1=Yes 2=No	

Section A: DEMOGRAPHIC INFORMATION

1. DEMOGRAPHICS		
1.1	Name	
1.2	Date of Birth	dd/ mm/yyyy
1.3	Age (in years)	
1.4	Gender	1 = Male 2 = Female
1.5	Ethnic group	1 = African 2 = Coloured 3 = Indian 4 = White
1.6	Hospital	1 = RKK 2 = MGH 3 = PMMH 4 = ADD 5 = KEH 6 = IALCH
1.7	Hospital Number	Inpatient No: Outpatient No:
1.8	Physical Address	
1.9	Contact number Best number to contact you on even if not your personal phone	
1.10	Contact person	
1.11	Contact number	
1.12	Housing type	1 = Formal housing 2 = Mostly formal housing 3 = Mostly informal housing 4 = Squatter housing/impoverished area 5 = Traditional housing 6 = Hostels 7 = Other (specify)_____
1.13	Employment	= Pensioner = Unemployed, not looking for work = Unemployed, actively looking for work = Self employed full time = Self-employed part time = Employed part-time in formal sector = Employed full-time in formal sector = Employed part-time in the informal sector = Employed full-time in the informal sector
1.14	Education level	= No schooling = Standard 3 or lower = Standard 4 – 5 = Standard 6 – 7 = Standard 8 – 9 = Standard 9 – 10 = Standard 10 and a post schooling qualification

2.Fracture History		
2.1.1	Date of fracture	dd/mm/yyyy
2.1.2	Fracture Site and description and fall type	1= Right 2= Left
2.1.3	Treatment modality	
2.1.4	Date of admission	dd/mm/yyyy
2.1.5	Referred by:	
2.1.6	Weight in Kg	
2.1.7	Height in meters	
NOTE: TO BE COMPLETED AT THE OFFICE		
2.1.8	Body mass index	0 = BMI less than 19 1 = BMI 19 to 24.9 2 = BMI 25 to 29.9 3 = BMI 30 or greater

Comorbid Illnesses			
2.2 Has a doctor or other health professional ever told you in the last 12 months that you have any of the following:			
2.2.1	Hypertension	1 = Yes 2 = No	
2.2.2	Diabetes Mellitus	1 = Yes 2 = No	
2.2.3	Arthritis	1 = Yes 2 = No	
2.2.4	Osteoporosis	1 = Yes 2 = No	
2.2.5	Tuberculosis	1 = Yes 2 = No	
2.2.6	HIV/AIDS	1 = Yes 2 = No	
2.2.7	Chronic Back pain	1 = Yes 2 = No	
2.2.8	Mal-absorption	1 = Yes 2 = No	
2.2.9	Chronic diarrhoea	1 = Yes 2 = No	
2.2.10	Rheumatoid Arthritis	1 = Yes 2 = No	
2.2.11	Hyperthyroidism	1 = Yes 2 = No	
2.2.12	Chronic renal failure	1 = Yes 2 = No	
2.2 .13	Metabolic bone disease	1 = Yes 2 = No	

2.2 .14	Chronic liver disease	1 = Yes 2 = No	
2.2 .15	Hyperparathyroidism	1 = Yes 2 = No	
2.2 .16	Multiple myeloma	1 = Yes 2 = No	
2.2 .17	Prolonged immobilization	1 = Yes 2 = No	
2.2 .18	Malignancy	1 = Yes 2 = No	
2.2.19	Hypogonadism (please specify exact diagnosis)	1 = Yes 2 = No	
2.2 .20	Other - specify		

Specify current treatment:

Illness	Drug	Dose and duration

Drug List

2.3	A. Name of medication	B. Indication	C. Dose	D. Duration	E. Total Dose
2.3.1	Glucocorticoids > 3/12				
2.3.2	Anti-epileptics				
2.3.3	Heparin				
2.3.4	Lithium				
2.3.5	Antidepressants				
2.3.6	Other -specify				
2.3.7					
2.3.8					
2.3.9					
2.3.10					

3. Section C - Osteoporosis Risk Factors			
3.1	Weight < 57kg	1 = Yes ; 2 = No	
3.2	Fragility fractures after age of 40 years	1 = Yes ; 2 = No	
3.2.a	If yes: Date:	dd / mm / yyyy	
3.2.b	Site:		
3.2.c	Treatment received:	1 = Yes ; 2 = No	
3.2.d	Screened for Osteoporosis	1 = Yes ; 2 = No	
3.2.e	Treatment for osteoporosis	1 = Yes ; 2 = No	
3.2.f	Specify treatment		
3.3	Vertebral fractures	1 = Yes ; 2 = No	
3.3.a	If yes, Date:	dd / mm / yyyy	
3.3.b	Site		
3.3.c	Treatment received	1 = Yes ; 2 = No	
3.3.d	Screened for Osteoporosis	1 = Yes ; 2 = No	
3.3.e	Treatment for osteoporosis	1 = Yes ; 2 = No	
3.3.f	Specify treatment		
3.4	Kyphosis	1 = Yes ; 2 = No	
3.5.a	Childhood fractures	1 = Yes ; 2 = No	
3.5.b	Site of Fracture		
3.6	History of falls	1 = Yes ; 2 = No	
3.6.a	If yes, Date:	dd / mm / yyyy	
3.6.b	Type –sideways	1 = Yes ; 2 = N	
3.6.c	Type –forward	1 = Yes ; 2 = No	
3.6.d	Type – other (Specify)		
3.7	Family history of osteoporosis	1 = Yes ; 2 = No	
3.8	Maternal history of falls	1 = Yes ; 2 = No	
3.9	Maternal history of fractures	1 = Yes ; 2 = No	
3.10	Gynaecological History		
3.10.1	Para		
3.10.2	Age of menarche (in years)		
3.10.3	Age of menopause (in years)		
3.10.4	Use of hormone replacement therapy	1 = Yes 2 = No	
3.10.4.a	If yes, Date of onset Duration Side effects		
3.11	Lifestyle factors		
3.11.1	Illicit drugs	1 = Yes 2 = No	
3.11.2	Caffeine (cups per day)	Coffee Tea	
3.11.3	Sunlight exposure -hours/day		
3.11.4	Activity level		
3.11.5	Exercise level	1 = Extremely Active 2 = Moderate 3 = mild 4 = sedentary	

4. SMOKING			
4.1	Do you smoke?	1= yes, regularly Go to 4.2 2= no Go to 4.5 3= occasionally go to 4.3	
4.2	On average, how many cigarettes do you smoke a day?		
4.3	On how many days a week do you smoke cigarettes?	1= usually on one day or less 2= usually on 2 to 4 days 3= almost everyday	
4.4	Did you ever smoke cigarettes regularly in the past?	1= yes, regularly Go to 4.5 2= no Go to 4.8	
4.5	When did you stop smoking cigarettes regularly? If in the last 12 months	1= less than 1 month ago 2= 1 – 6 months ago 3= 6 -12 months ago	
4.6	What is the highest average daily number of cigarettes you have ever smoked for as long as a year?		
4.7	How old were you when you began to smoke cigarettes regularly?		
4.8	Have you ever smoked cigars/cigarillos?	1= yes, regularly Go to 4.9 2= no Go to 4.10 3= occasionally (less than one a day)go to 4.9	
4.9	How many do you smoke a day?		
4.10	Have you ever smoked a pipe?	1= yes, regularly Go to 4.11 2= no 3= occasionally Go to 4.11	
4.11	About how many grams of tobacco do you smoke per week?		
4.12	To be completed by occasional or non-smokers For how many hours, on average each day, are you closely subjected to people's tobacco smoke?		

5. ALCOHOL USE				
5.1	How many alcoholic drinks did you have each day last week?			
5.2	We'll start with yesterday and take one day at a time (one drink= 12g of alcohol)			
1. Sunday		-		
2. Saturday		-		
3. Friday		-		
4. Thursday		-		
5. Wednesday		-		
6. Tuesday		-		
7. Monday		-		
			Score	
1 bottle of beer		= 1 drink	1 bottle of alcohol 75cl	=25 drinks
1 bottle of strong beer		=1,5 drinks	1 glass of red/ white wine	=1 drink
1 bottle of red/ white wine		= 6 drinks	1 glass of port wine	=1 drink
1 bottle of port wine 70cl.		=10 drinks	1 glass of aquavit	= 1 drink

6. Calcium intake calcium calculator

Food	Serving Size (average) /Calcium	How many servings?				
		1 portion a day	2 portions a day	1 portion a week	2 portions a week	3 portions a week
Milk, semi-skimmed	glass, 200 ml / 240 mg					
Milk skimmed	glass, 200 ml / 244 mg					
Milk whole	glass, 200 ml / 236 mg					
Milkshake	takeaway, 300 ml / 387 mg					
Soy drink, calcium enriched	glass, 200 ml / 178 mg					
Yoghurt and cream						
Yoghurt, low-fat, fruit	pot, 150 g / 210 mg					
Yoghurt, low-fat plain	pot, 150 g / 243 mg					
Cream, double, whipped	portion, 45 g / 26 mg					
Cream, single	tablespoon, 15 g / 13 mg					
Cheeses						
Danish blue	portion, 40 g / 195 mg					
Edam	portion, 40 g / 318 mg					
Feta	portion, 40 g / 144 mg					
Camembert	portion, 40 g / 94 mg					
Cheddar	medium chunk, 40 g / 296 mg					
Cheese spread	portion, 30 g / 149 mg					
Cottage	small pot, 112 g / 142 mg					
Mozzarella, fresh	portion, 56 g / 203 mg					
Parmesan, fresh	portion, 30 g / 308 mg					
Vegetables						
Broccoli, boiled	serving, 85 g / 34 mg					
Watercress, raw	small bunch, 20 g / 34 mg					
Curly kale	serving, 95 g / 143 mg					
Okra, stir fried	8 medium, 40 g / 88 mg					
Red kidney beans, canned	3 tablespoons, 105 g / 75 mg					
Chick peas, boiled	3 tablespoons, 90 g / 41 mg					
Green / French beans	serving, 90 g / 50 mg					
Baked beans	serving, 135 g / 72 mg					
Nuts						
Almonds	12 whole, 26 g / 62 mg					
Brazil nuts	6 whole, 20 g / 34 mg					
Hazelnuts	20 whole, 20 g / 28 mg					
Sesame seeds	1 tablespoon, 12 g / 80 mg					
Walnuts	12 halves, 40 g / 38 mg					
Tahini paste	1 heaped teaspoon, 19 g / 129 mg					

Food	Serving Size (average) /Calcium	How many servings?				
		1 portion a day	2 portions a day	1 portion a week	2 portions a week	3 portions a week
Desserts						
Cheesecake, fruit	average slice, 120 g / 94 mg					
Custard made with milk	average portion, 120 g / 166 mg					
Rice pudding, canned	average portion, 200 g / 176 mg					
Ice cream, dairy, vanilla	average serving, 75 g / 75 mg					
Fromage frais, fruit	small pot, 60 g / 52 mg					
Fish						
Sardines in oil, tinned	portion, 100 g / 500 mg					
Whitebait, fried	portion, 80 g / 688 mg					
Salmon, tinned	average portion, 100g / 91 mg					
Fish paste	small jar, 35 g / 98 mg					
Breads and grains						
Pasta, plain, cooked	portion, 230 g / 85 mg					
Rice, white, boiled	portion, 180 g / 32 mg					
White bread	slice, 30 g / 53 mg					
Wholemeal bread	slice, 30 g / 32 mg					
Muesli, Swiss style	portion, 50 g / 55 mg					
Fruits						
Apricots, raw, no stone	4 fruit, 160 g / 117 mg					
Figs, ready to eat	4 fruit, 220 g / 506 mg					
Currants	2 tablespoons, 50 g / 47 mg					
Orange	peeled, 160 g / 75 mg					
Other foods						
Tofu, soy bean, steamed	100 g / 510 mg					
Omelette, cheese	2 eggs, 120 g / 344 mg					
Quiche, cheese & egg	average slice, 140 g / 367 mg					
Macaroni cheese	portion, 220 g / 374 mg					
Pizza, cheese & tomato	9" - 10" pizza, 410 g / 873 mg					
Lasagne	portion, 420 g / 420 mg					
Total Amount:						

7. FALL ASSESSMENT			
	Fall – Risk Screening: Multifactor Questionnaire		
7.1	General:		
7.1.1	Have you ever fallen?	1 = Yes 2 = No	
7.1.1a	If so, how many times?		
7.1.2	Have you experienced a near fall? (E.g. slip, trip, stumble or bumped against a wall?	1 = Yes 2 = No	
7.1.3	Have you previously reported any falls to a health professional?	1 = Yes 2 = No	
7.1.3a	If so, how many falls?		
7.1.4	Have you ever sought medical attention for a fall?	1 = Yes 2 = No	
7.1.5	If you fell, would you need help to get back up from the ground?	1 = Yes 2 = No	
7.1.6	Have you limited any of your activities or decreased how much you leave your home due to a fall, near fall, or fear of falling?	1 = Yes 2 = No	
7.1.7	Have you ever broken a bone?	1 = Yes 2 = No	
7.1.8	Have you been diagnosed with osteoporosis?	1 = Yes 2 = No	
7.1.8a	If so, are you not currently taking calcium, vitamin D supplements and/or medications to stimulate bone growth?	1 = Yes 2 = No	
7.1.9	Do you exercise less than 30 minutes a day most days of the week?	1 = Yes 2 = No	
7.2	Syncope/Drop Attack/ Sudden Unexplained Falls:		
7.2.1	Have you ever fallen because of sudden, unexpected fainting or blackouts?	1 = Yes 2 = No	
7.3	Sensory Problems:		
7.3.1	Do you have vision problems?	1 = Yes 2 = No	
7.3.1a	Blurry, not as sharp	1 = Yes 2 = No	
7.3.1b	Difficulty seeing to the side or different depths or distances	1 = Yes 2 = No	
7.3.2	Sensitive to light or changing light	1 = Yes 2 = No	
7.3.3	Do you have decrease feeling, numbness or tingling in your feet?	1 = Yes 2 = No	
7.3.4	Are you ensure of your footing or have trouble on uneven ground or inclines?	1 = Yes 2 = No	
7.4	Medication Risk:		
7.4.1	Do you take more than 3 prescription medications each day?	1 = Yes 2 = No	
7.4.2	Do you take any medications?		
7.4.2a	To help you sleep?	1 = Yes 2 = No	
7.4.2b	To help control mood (e.g. anxiety, depression)	1 = Yes 2 = No	
7.4.2c	To prevent seizures?	1 = Yes 2 = No	
7.4.2d	To control heart rhythm?	1 = Yes 2 = No	

7.4.3	Have there been any recent changes to your medications (e.g. drugs/ dose that have made you feel dizzy or unsteady?	1 = Yes 2 = No	
7.4.4	Do you have more than one drink of alcohol in a day?	1 = Yes 2 = No	
7.5	Acute or Significant Medical Problems:		
7.5.1	Have you recently had flu-like symptoms or felt unwell at the time of a fall or near fall?	1 = Yes 2 = No	
7.5.2	Do you have health problems that limit your activity?	1 = Yes 2 = No	
7.6	Indication of Cognitive Problems:		
7.6.1	Do you notice that you have problems with your memory? (More than normal, more than other people your age do)	1 = Yes 2 = No	
7.6.2	Do families or friends say that you have problems with your memory?	1 = Yes 2 = No	
7.6.3	Do you have trouble completing familiar tasks (get muddled when doing so)? E.g. writing a cheque, finding your way in a familiar store/ mall)	1 = Yes 2 = No	
7.7	Environmental hazards: Where have you fallen?		
7.7.1	Inside your home	1 = Yes 2 = No	
7.7.2	Outside your home	1 = Yes 2 = No	
7.7.3	In the community at large	1 = Yes 2 = No	
7.7.4	Have you fallen repeatedly in any one place?	1 = Yes 2 = No	
7.7.5	Were there any hazards in the environment where you feel, that you think contributed to your falls?	1 = Yes 2 = No	
7.7.6	Do you think that a safety check of your home, yard and/ or neighbourhood could assist you to avoid future falls?	1 = Yes 2 = No	
7.8	– Gait / Mobility Problems:		
7.8.1	Do you sometimes feel unsteady when you walk?	1 = Yes 2 = No	
7.8.2	Do you think your walking method puts you at risk for falling?	1 = Yes 2 = No	
7.8.3	Do you choose not to use a gait aid even though people tell you it is safer?	1 = Yes 2 = No	
7.8.4	Do you have problems or concerns getting in or out of a bed, chair, tub or toilet?	1 = Yes 2 = No	
7.8	Balance Problems:		
7.8.1	Do you feel you have decreased balance?	1 = Yes 2 = No	
7.8.2	Do you sometimes feel off balance, dizzy or unsteady when you walk?	1 = Yes 2 = No	
7.9	Endurance Problems / Weakness:		
7.9.1	Do you feel you have leg weakness or that tire easily when you walk?	1 = Yes 2 = No	
7.10	Pain / Joint Problems:		
7.10.1	Do you have any sore joint or arthritis?	1 = Yes 2 = No	
7.10.2	Is your activity limited by pain?	1 = Yes 2 = No	

8. PHYSICAL SELF-MAINTENANCE SCALES						
	Are you able to perform the following activities?		Prior to fracture	3/12	6/12	1yr
8.1	Eating	2 = without help 1 = with some help 0 = Unable to do - = not answered				
8.2	Dressing and Undressing (able to pick out clothes, dress and undress yourself)	2 = without help 1 = with some help 0 = Unable to do - = not answered				
8.3	Take care of your appearance (combing your hair, shaving – for men)	2 = without help 1 = with some help 0 = Unable to do - = not answered				
8.4	Walking *Except with a walking stick	2 = without help 1 = with some help 0 = Unable to do - = not answered				
8.4a	*Help from person, walking frame, crutches	2 = without help 1 = with some help 0 = Unable to do - = not answered				
8.5	Getting into and out of bed	2 = without help 1 = with some help 0 = Unable to do - = not answered				
8.5a	*Help from person or aid	2 = without help 1 = with some help 0 = Unable to do - = not answered				
8.6	Bathing (taking a bath, shower, or bath using a basin)	2 = without help 1 = with some help 0 = Unable to do - = not answered				
8.7	Getting to the toilet on time	2 = without help 1 = with some help 0 = Unable to do - = not answered				
8.7a	*have a catheter or colostomy	2 = without help 1 = with some help 0 = Unable to do - = not answered				
8.8	How often do you wet or soil yourself (either day or night)?	1 = once or twice a week 0 = 3 times a week or more - = not answered				
	Score out of 21					

9. INSTRUMENTAL ACTIVITIES OF DAILY LIVING						
Provide an answer that best applies to your situation for the following activities: Can you?			Pre	3/12	6/12	1yr
9.1	Use the telephone	1 = Completely unable to do 2 = with some help 3 = without help				
9.2	Get to places that are out of walking distance	1 = Completely unable to do 2 = with some help (unless special arrangements are made) 3 = without help				
9.3	Go shopping for groceries	1 = Completely unable to do 2 = with some help 3 = without help				
9.4	Prepare your own meals.	1 = Completely unable to do 2 = with some help 3 = without help				
9.5	Do your own housework	1 = Completely unable to do 2 = with some help 3 = without help				
9.6	Do your own handyman work	1 = Completely unable to do 2 = with some help 3 = without help				
9.7	Do your own laundry	1 = Completely unable to do 2 = with some help 3 = without help				
9.8a	Do you take your own medicines *in the right doses at the right time *take medicine if someone prepares it	1 = Completely unable to do 2 = with some help 3 = without help				
9.8b	If you had to take medicine could you do it *in the right doses at the right time *take medicine if someone prepares it	1 = Completely unable to do 2 = with some help 3 = without help				
9.9	Manage your own money	1 = Completely unable to do 2 = with some help 3 = without help				
Score out 27						

10. QUALITY OF LIFE						
What now follows are 5 questions about different topics. Each of the questions has 3 response possibilities. Could you please circle the number before the answer that suits you best?						
			Pre	3/12	6/12	1yr
10.1	Mobility	1=I have no problems walking 2= I have some problems walking 3= I am bed ridden				
10.2	Self-care	1=I have no problems washing or dressing myself 2= I have some problems washing or dressing myself 3= I am not able to wash or dress myself				
10.3	Daily activities (for example work, study, household tasks, family or leisure activities)	1=I have no problems doing my daily activities 2= I have some problems doing my daily activities 3= I am not able to do my daily activities				
10.4	Pain/Complaints	1=I have no pain or other complaints 2= I have some pain or other complaints 3= I have severe pain or other complaints				
10.5	Mood	1=I am not anxious or depressed 2= I am mildly anxious or depressed 3= I am severely anxious or depressed				
Score out of 15						

11. OSWESTRY DISABILITY QUESTIONNAIRE As above						
			Pre	3/12	6/12	1yr
11.1	Section 1 Pain Intensity	1= I have no pain at the moment 2= The pain is very mild at the moment 3= The pain is moderate at the moment 4= The pain is fairly severe at the moment 5= The pain is very severe at the moment 6= The pain is the worst imaginable at the moment				
11.2	Section 2: Personal Care (e.g. washing, dressing)	1=I can look after myself normally without causing extra pain 2= I can look after myself normally but it causes extra pain 3= It is painful to look after myself and I am slow and careful 4= I need some help but can manage most of my personal care 5= I need help every day in most aspects of self-care 6= I do not get dressed, wash with difficulty and stay in bed				
11.3	Section 3: Lifting	1= I can lift heavy weights without extra pain 2= I can lift heavy weights but it gives me extra pain 3= Pain prevents me lifting heavy weights off the floor but I can manage if they are conveniently placed e.g. on a table 4= Pain prevents me lifting heavy weights but I can manage light to medium weights if they are conveniently positioned 5= I can only lift very light weights 6= I cannot lift or carry anything				
11.4	Section 4: Walking*	1= Pain does not prevent me walking any distance 2= Pain prevents me from walking more than 2 kilometres 3= Pain prevents me from walking more than 1 kilometre 4= Pain prevents me from walking more than 500 metres 5= I can only walk using a stick or crutches 6= I am in bed most of the time				
11.5	Section 5: Sitting	1= I can sit in any chair as long as I like 2= I can only sit in my favourite chair as long as I like 3= Pain prevents me sitting more than one hour 4= Pain prevents me from sitting more than 30 minutes 5= Pain prevents me from sitting more than 10 minutes 6= Pain prevents me from sitting at all				
11.6	Section 6: Standing	1= I can stand as long as I want without extra pain 2= I can stand as long as I want but it gives me extra pain				

		3= Pain prevents me from standing for more than 1 hour 4= Pain prevents me from standing for more than 30 minutes 5= Pain prevents me from standing for more than 10 minutes 6= Pain prevents me from standing at all				
11.7	Section 7: Sleeping	1= My sleep is never disturbed by pain 2= My sleep is occasionally disturbed by pain 3= Because of pain I have less than 6 hours sleep 4= Because of pain I have less than 4 hours sleep 5= Because of pain I have less than 2 hours sleep 6= Pain prevents me from sleeping at all				
11.8	Section 8: Sex Life (if applicable)	1= My sex life is normal and causes no extra pain 2= My sex life is normal but causes some extra pain 3= My sex life is nearly normal but is very painful 4= My sex life is severely restricted by pain 5= My sex life is nearly absent because of pain 6= Pain prevents any sex life at all				
11.9	Section 9: Social Life	1= My social life is normal and gives me no extra pain 2= My social life is normal but increases the degree of pain 3= Pain has no significant effect on my social life apart from limiting my more energetic interests e.g. sport 4= Pain has restricted my social life and I do not go out as often 5= Pain has restricted my social life to my home 6= I have no social life because of pain				
11.10	Section 10: Traveling	1= I can travel anywhere without pain 2 =I can travel anywhere but it gives me extra pain 3=Pain is bad but I manage journeys over two hours 4=Pain restricts me to journeys of less than one hour 5=Pain restricts me to short necessary journeys under 30 minutes 6=Pain prevents me from traveling except to receive treatment				
	Score: / x 100 = % measurement) Score calculated out of no of sections answered					

12. Visual Analogue Scale (VAS)		
	Date	Score
Pre fracture		
Post fracture		
3/12		
6/12		
1yr		

13. Section E - Full physical examination		
General examination		
Colour		
Hydration		
Muscle wasting		
Lymphadenopathy		
Clubbing		
Other –general examination		
Cardiovascular system		
Pulse rate		
Blood Pressures		
Heart sounds		
Cardiac failure signs- specify		
Respiratory		
Chest examination		
Deformities		
Lung fields		
Abdomen		
Visceromegaly		
Vision – Counting fingers		
Cranial nerves abnormalities	Right	Left
Tone assessment	Right	Left
Power upper limbs	Right	Left
Lower limbs	Right	Left
Sensation	Light touch	
	Joint Position Sense	
	Vibration	
Musculoskeletal	Synovitis- specify	

4. Section F - Biochemical Investigations		Date	Date	Date	Date
	Results				
Full blood count	Hb WBC Platelets MCV MCH				
Urea and electrolyte	Na K Cl Bicarb Urea Creat				
Liver function test	TP ALB Bil ALT ALP GGT				
Random glucose					
Calcium and phosphate and magnesium	cCa PO4 Mg				
Thyroid function test	TSH T4 T4				
25 Vitamin D					
Parathyroid hormone					
C-reactive protein					
ESR					
LH					
FSH					
Oestrogen					
Total Testosterone					
SPEP					

15. Section G - Radiological Investigation			
	date	XR No.	Report
1. X-Ray Hip			
2. Thoraco-lumbar X-rays			

3. Bone mineral Density			
Date			
Height			
Weight			
Score opposite hip			
Spine			
Splinting			
Surgery- type			
Anesthetist visit			
Physiotherapist			
Other investigation : specify			

Appendix 3.E List of normal reference values for haematological and biochemical investigations

Test	Normal values
Haemoglobin (g/dl)	13 – 17 g/dl
White cell count (×109/L)	4 – 10 x10^9/l
Sodium (mmol/L)	136 – 145 mmol/L
Urea (mmol/L)	2.1 – 7.1 mmol/L
Creatinine (umol/L)	64 – 104 umol/L
Total protein (g/L)	60 – 78 g/L
Albumin (g/L)	35 -52 g/L
Bilirubin (umol/L)	5 – 21 umol/L
Alanine transaminase (IU/L)	10 - 40 U/L
Gamma glutamyl transferase (IU/L)	0 – 60 U/L
Glucose (mmol/L)	3.5 – 6.8 mmol/L
Calcium (mmol/L)	2.15 – 2.55 mmol/L
Thyroid stimulating hormone (ul/L)	0.35 – 5.5 mIU/L
25(OH) Vitamin D (nmol/L)	<12.48 nmol/L Severe vitamin D deficiency 24.96 – 49.92 Mild 49.92 – 174.72 Vitamin D sufficiency 74.88 – 174.72 Desirable for osteoporosis treatment
Parathyroid hormone (pg/ml)	1.2 – 7.1 pg/ml
C-Reactive protein (mg/L)	0-5 mg/L
Erythrocyte sedimentation rate (mm/hr)	0 – 30 Mm/hr
Oestrogen (pmol/L) (women only)	10 – 60 nmol/L
Testosterone (men only) (nmol/L)	8.4 – 28.7 nmol/L

Appendix 3.F Bone Mineral Density Calibration

This calculator is intended for use by advanced bone densitometritsts only.
It may be considered for special clinical practice situations and for clinical research.
Please note that the ISCD recommends expressing precision as RMS SD, and LSC at the 95% confidence level.
The calculator may be used for:
1. Calculate precision error with as many as 50 patients.
2. Express precision error as RMS SD (absolute value in g/cm2), CV, or %CV.
3. Express LSC (Least Significant Change) with a choice of confidence levels

Instructions: Enter BMD measurements to 3 decimal places for at least 15 patients scanned 3 times each, or 30 patients scanned 2 times each.
Precision and LSC must be calculated separately for each skeletal site and ROI (L1-L4, total proximal femur, femoral neck, etc.).
BMD results from as many as 50 patients may be entered. The calculator does the rest.

Phantom results	
Patient	Scan
1	1.005347
2	0.926469
3	0.916721
4	0.910302
5	0.927916
6	0.917881
7	0.919386
8	0.918947
9	0.915709
10	0.919815
11	0.920336
12	0.928739
13	0.91876
14	0.919937
15	0.928707
16	0.921163
17	0.916575
18	0.913022
19	0.918744
20	0.919409
21	0.91285
22	0.923515
23	0.910152

24	0.912427
25	0.923577
26	0.920442
27	0.919139
28	0.920101
29	0.919011
30	0.921343

Number of Patients	n =30
Sum of SD (sq)	Sum = 0.06676
Sum of SD (sq / n)	Sum / n = 0.002225
Square Root of above	SqRT = 0.047
Root Mean Square SD	RMS SD = 0.047 g/cm2
Coefficient of Variation	CV = 0.048
Percentage Coefficient of Variation	%CV = 4.84%

LSC with Different Levels of Confidence					
LSC based on at least 15 patients with triplicate scans					
Precision	95%	90%	85%	80%	Units
RMS SD	0.131	0.110	0.097	0.085	g/cm2
CV	0.134	0.113	0.099	0.088	
%CV	13.42	11.28	9.93	8.77	%
LSC based on at least 30 patients with duplicate scans:					
LSC with Different Levels of Confidence					
Precision	95%	90%	85%	80%	Units
RMS SD	0.131	0.110	0.097	0.085	g/cm2
CV	0.134	0.113	0.099	0.088	
%CV	13.42	11.28	9.93	8.77	%

Developed by E. Michael Lewiecki, M.D., FACP, CCD for ISCD

Appendix 3.G Cost of treating acute hip fractures

Cost at referral clinic/hospital		
Staff – referral clinics	Fixed cost - time	Average cost per patient
Enrolled Nurse		0.00
Registrar		0.00
Anaesthetist		0.00
Paramedic	0.50	1134.48
Specialist surgeon		0.00
Interns		0.00
Pharmacist		0.00
Porter		0.00
Radiologist		0.00
Clerks Level 4	0.17	114.70
Medical officer	0.17	2292.82
Professional Nurse	0.50	2314.04
Grand Total		5856.05

Staff cost per patient		
Staff	Fixed cost - time	Average cost per patient
Enrolled Nurse	0.17	1085.92
Registrar	0.25	11515.70
Anaesthetist	0.25	8479.96
Paramedic	0.25	1391.52
Specialist surgeon	0.25	9950.49
Interns	0.66	1219.70
Pharmacist	0.42	9038.19
Porter	1.17	2075.84
Radiologist	1.92	4826.24
Clerks Level 4	3.08	5102.92
Medical officer	3.17	
Professional Nurse	7.00	79472.89
Grand Total	18.58	

*Excludes theatre - done separately

The following tables were used to calculate cost based on time spent by staff

Clinic				
Procedure	Staff		Time	Hours
Admission	Clerk		10	0.16667
Treatment plan	Medical officer		10	0.16667
Referral	Paramedic		Distance	
Treatment plan	PN		30	0.5
Dr Referral				
Procedure	Staff		Time	Hours
Dr Consult	Medical officer		20	0.33333
X-ray	Radiologist		20	0.33333
Bloods	Lab		Price List	
Referral	Paramedic		Distance	
Hospital				
Location / Procedure	Staff	Event	Time - Min	Hours
Outpatient				
Sorting Stretcher	PN	Once off	5	0.08
Transport	Porter	Once off	10	0.17
Admission	Clerk	Once off	10	0.17
Trauma				
Vitals	EN	Once off	10	0.17
Treatment Plan	Medical officer	Once off	10	0.17
X-ray Dept.				
Radiologist	Radiologist	Once off	15	0.25
Log X-ray	Clerk	Once off	10	0.17
Transport	Porter	Once off	10	0.17
Trauma				
Treatment Plan	Medical officer	Once off	10	0.17
Transport	Porter	Once off	10	0.17
Orthopaedic Outpatients				
Admission	Clerk	Once off	15	0.25
Treatment Plan	Registrar	Once off	15	0.25
Splint Room	PN	Once off	30	0.50
Bloods	Interns	Once off	10	0.17
Transport	Porter	Once off	10	0.17
X-ray Dept.				
Transport	Porter	Once off	10	0.17
CXR	Radiologist	Once off	15	0.25
Surgical Ward				
Admission	PN	Once off	15	0.25
Dr Review	Medical officer	Once off	15	0.25
Admission	Clerk	Once off	15	0.25

Meals	Auxiliary PN	Daily x3	5	0.08
Meal preparation	Catering	Price list		
Linen change	Auxiliary PN	Daily	5	0.08
Review	Registrar	Daily	15	0.25
Review	Interns	Daily	15	0.25
Surgeon Review	Specialist surgeon	Once off	15	0.25
Anaesthetists review	Anaesthetists	Once off	15	0.25
Vitals	PN	Daily X 6	10	0.17
Consumables				
IV Line	PN	Change 72 hours	10	0.17
Foleys	PN	Change 72 hours	10	0.17
Cot Bed	PN	Once off	10	0.17
Traction	PN	Once off	30	0.50
Blood Glucose	PN	Daily	5	0.08
Additional Tests				
ECG	PN	Once off	30	0.50
Bloods	Interns	Once off	10	0.17
Medications				
Administering Medications	PNs	Six hourly - daily	30	0.50
Theatre				
Location / Procedure	Staff	Event	Time - Min	Hours
Transport	Porter	Once off	10	0.17
Pre Surgery prep	PN	Once off	15	0.25
Prosthetic type		Once off	Price list	
Surgeon time	Surgeon	Once off	Theatre time	
Theatre facility time	Rate per hour	Once off	Theatre time	
X-ray	Radiologist	Once off	15	0.25
PN assistance	PN	Once off	Theatre time	
Anaesthetists cost	Anaesthetists	Once off	Theatre time	
Theatre medications	Medications	Once off	Price list	
Theatre consumables	Surgical Consumables	Once off	Price list	
CSSD equipment		Once off	Price list	
Post Op - Surgical Ward				
Location / Procedure	Staff	Event	Time - Min	Hours
Transfer ward	Porter	Once off	10	0.17
PN Monitoring	PN	Daily	30	0.50
Registrar review	Registrar	Daily	10	0.17
Surgeon review	Surgeon	Daily	10	0.17
Meal preparation	Catering	Daily	Price list	

Meals	Auxiliary PNs	Daily	60	1.00
Linen Change	Auxiliary PNs	Daily	5	0.08
Linen Wash	Laundry	Daily	Per kg	
Hospital Gowns	Laundry	Daily	Per kg	
Medications	PN	Daily	30	0.50
Bloods	Intern	Once off	10	0.17
X-ray	Radiologist	Once off	10	0.17
Physiotherapist	Physiotherapist	Daily	30	0.50
OT	Occupational Therapist	Daily	30	0.50
Crutches	Stores	Once off	Price List	
Wheelchair	Stores	Once off	Price List	
Discharge - Transfer Clairwood				
Location / Procedure	Staff	Event	Time - Min	Hours
Discharge Clerk	Clerk	Once off	15	0.25
Transport Ambulance	Paramedic	Once off	15	0.25
Admission	PN	Once off	15	0.25
Dr Review	Medical officer	Once off	15	0.25
Admission	Ward Clerk	Once off	15	0.25
Review	Interns	Daily	15	0.25
Vitals	PN	Daily X 6	30	0.5
Medications	Pharmacist	Once off	15	0.25
Consumables				
IV Line	PN	Change 72 hours	10	0.16667
Foleys	PN	Change 72 hours	10	0.16667
Cot Bed	PN	Once off	10	0.16667
Traction	PN	Once off	30	0.5
Blood Glucose	PN	Daily	5	0.08333
Medications	PN	Daily	30	0.5
Bloods	Intern	Once off	10	0.16667
Physiotherapist	Physiotherapist	Daily	30	0.5
OT	Occupational Therapist	Daily	30	0.5
Discharge - Home				
Location / Procedure	Staff	Event	Time - Min	Hours
Discharge Clerk	Clerk	Once off	15	0.25
Dr Review	Medical officer	Once off	15	0.25
Consumables - removal				
IV Line	PN	Change 72 hours	10	0.16667
Foleys	PN	Change 72 hours	10	0.16667
Cot Bed removal	PN	Once off	10	0.16667
Traction removal	PN	Once off	30	0.5
Discharge meds	PN	Once off	10	0.16667
Med request	Pharmacist	Once off	10	0.16667

Discharge - Death				
Location / Procedure	Staff	Event	Time - Min	Hours
Discharge Clerk	Clerk	Once off	15	0.25
Dr Review	Medical officer	Once off	15	0.25
Consumables - removal				
IV Line	PN	Change 72 hours	10	0.16667
Foleys	PN	Change 72 hours	10	0.16667
Cot Bed removal	PN	Once off	10	0.16667
Traction removal	PN	Once off	30	0.5
Other				
Family Notification	PN	Once off	10	0.16667
Family Notification	Medical officer	Once off	10	0.16667
Follow up treatment 2 weeks				
Location / Procedure	Staff	Event	Time - Min	Hours
Outpatient visit	Clerk	Once off	15	0.25
Remove stitches	PN	Once off	30	0.5
Review	Medical officer	Once off	20	0.33333

Sum of Hours					
Row Labels	Applied on separate spreadsheet	Daily cost	Fixed cost	Theatre time	Grand Total
Anaesthetists			0.25		0.25
Auxiliary PNs		0.17			0.17
Auxiliary PN		0.33			0.33
Catering					
Clerk	0.17		2.83		3.00
EN			0.17		0.17
Intern			0.33		0.33
Interns		0.50	0.33		0.83
Lab					
Laundry					
Medical officer	0.50		3.17		3.67
Medications					
Occupational Therapist		0.50			0.50
Paramedic			0.25		0.25
Pharmacist			0.42		0.42
Physiotherapist		0.50			0.50
PN		3.17	7.00		10.17
PNs		0.50			0.50
Porter			1.17		1.17
Radiologist	0.33		1.92		2.25

Rate per hour					
Registrar		0.25	0.25		0.50
Registrar		0.17			0.17
Specialist surgeon			0.25		0.25
Stores					
Surgeon		0.17			0.17
Surgical Consumables					
Ward Clerk			0.25		0.25
(blank)					
Grand Total	1.00	6.25	18.58		25.83

Normative Costs

Clinic / District Hospital Costs	
Normal time	
Staff	Average cost per patient
Enrolled Nurse	0
Registrar	0
Anaesthetists	0
Paramedic	1134.484615
Specialist surgeon	0
Interns	0
Pharmacist	0
Porter	0
Radiologist	0
Clerks Level 4	114.7029231
Medical officer	2292.824654
Professional Nurse	2314.042308
Grand Total	5856.0545

**Excludes theatre - done separately

Hospital Costs		
Bone mineral density scan		472.00
Chest radiograph		167.00
Radiograph of the hip		167.00
CT head / chest		2 257.00
Ultrasound abdomen		472.00
ECG		167.00
Echo		472.00
Thompsons Prosthesis		2 974.00

Bipolar Prosthesis		2 974.00
General Ward Fees		1592.00 per day
High Care Fees		3430.00 per day
ICU Fees		7130.00 per day
Theatre costs		
Category A free patients)		2 065.00
Category B		3 177.00
Category C		5 408.00
Category D		13 898.00

Hospital de-identified patient data:	Detailed costing	
Average cost per patient :	Hip fracture 2010/2011	
Ward Fees	17 days	21 607.00
Theatre Fees		12 306.00
Medication Fees		1 200.00
Pathology Fees		425.00
Radiology Fees		4 800.00
Length of Stay	17 days	
Consumables		Material number
Epidural pack		16F E302520 / 18F E3025202 / 17F 3025203
Skin Staples		E3056002
Post Op Dressing		E3023428
Vicryl		E3023695
Oxygen (price per minute)		
O2 Mask Set		E30368938
IV line sets		E3049016 / E3049090 / E3049091
Syringes (10cc, 5cc, 20cc)		E3057218 / E3057236 / E3057219
Cotton wools		E3056803
Jelco (different size)		24G E3006210 / 14G E3006212 / 16G E3006213
		18G E3006214 / 20G E3006215 / 22G E3006209 /24G E3006211
Foleys catheter		E3013300
Porto vacuum wound drain		-
Needles (different sizes)		18G E5169899 / 20G E5169899 / 21G E5169909 / 22G 5169904
Bio-scrub hand sanitizer		E400192

Current pricing according to the hospital fees manual - 2012

Hospital	No of patients	Length of stay						Total blood cost	Total Meds cost	Referral (travel)
		Wdays LOS	Sat LOS	Sun LOS	Public LOS	Total LOS	Average LOS			
1. RKK	76	1076	220	199	41	1536	20	79583	60764	793
2. MGMH	26	478	97	94	12	681	26	27767	31286	987
3. PMMH	14	357	70	66	14	507	36	16250	19944	53
4. ADD	55	611	119	103	34	867	16	61274	39537	1944
5. KEH	29	551	111	105	27	794	27	33397	39374	1786
Grand Total	200	3073	617	567	128	4385	22	218270	190905	5563

Hospital	No of patients	Type of Surgery			Theatre time	No of referrals	Paramedics Travel cost	Theatre cost	Staff Costs	X-ray Cost	Ward Costs	Prosthesis cost	Total Cost	Per patient
		General	Spinal	No Surgery										
1. RKK	76		65	11	74	15	793	180757	2790713	151665	141412	533358	3939838	51840
2. MGMH	26		19	7	27	11	987	52837	1199243	47010	60042	189682	1609841	61917
3. PMMH	14	1	11	2	16	2	53	33964	868489	30750	42854	107597	1119953	79997
4. ADD	55	5	45	5	70	26	1944	142012	1663382	102085	83995	503735	2599907	47271
5. KEH	29	6	22	2	34	15	1786	81426	1410476	61545	69552	256994	1956335	67460
Grand Total	200	12	162	27	221	69	5563	490995	7932303	393055	397855	1591366	11225874	56129

Appendix 3.H. Normative Costing Model

Normative cost for surgery					
Hospital	Bipolar	Femoral Nail	Pin & Plate	Thompsons Prosthesis	Total
3				1	1
4	3		2		5
5	3	1	2		6
Total	6	1	4	1	12
Cost Of Surgery	227474	41680.29	161570.9	37912.33	468637.52
Spinal					
Hospital	Bipolar	Femoral Nail	Pin & Plate	Thompsons Prosthesis	
1	14	9	25	16	64
2	9	2	7	1	19
3	3	3	3	2	11
4	19	4	16	3	42
5	9	3	9		21
Total	54	21	60	22	157
Cost of Surgery	2079392	887779.4	2459259	847159.5	6273589.41

Normative Costing												
		Prosthesis							**Theatre**			
	Staff Cost	**Bipolar**	**Femoral Nail**	**Pin & Plate**	**Thompsons**	**Ward costs**	**Meds**	**Bloods**	**Spinal**	**General**	**Facility**	**X_RAY**
Normative Costing Framework per patient	11965	2974	6741.96	5454.4	2974	14244.62	963	208.73	1718.4	3748	4765.5	1668

Appendix 4.A Functional Comparison in men and women fracture subjects compared to matched controls

Table 4.A.1 Subjects unable to perform basic activities of daily living independently in men and women hip fracture subjects pre-fracture and age gender and ethnic matched controls

		Men			Female		
Physical self-maintenance scale		**Fracture subjects (n=56)**	**Control subjects (n=56)**	**p-value**	**Fracture subjects (n=144)**	**Control subjects (n=144)**	**p-value**
Eating	**Unable/need help**	4 (7.1)	0	*0.044	1 (0.7)	1 (0.7)	1.000
Dressing	**Unable/need help**	6 (10.7)	0	*0.013	12 (8.3)	3 (2.1)	*0.020
Grooming	**Unable/need help**	6 (10.7)	1 (1.8)	0.058	14 (9.7)	4 (2.8)	*0.018
Walking	**Unable/need help**	11 (18.7)	3 (5.4)	0.376	18 (12.5)	7 (4.9)	*0.021
Transfer bed	**Unable/need help**	6 (10.7)	1 (1.8)	0.058	11 (7.6)	4 (2.8)	0.071
Bathing	**Unable/need help**	5 (8.9)	1 (1.8)	0.103	15 (10.4)	5 (3.5)	*0.018
Toileting	**Unable/need help**	5 (8.9)	2 (3.6)	0.261	14 (9.7)	4 (2.8)	*0.012
Physical score (mean ± SD)		13.2 ± 2.3	13.9 ± 0.5	*<0.0001	13.4 ± 1.72	13.8 ± 1.1	*<0.0001

- Number of subjects and n (%)

Table 4.A.2 **Subjects unable to perform independent activities of daily living independently in men and women hip fracture subjects pre-fracture and age gender and ethnic matched controls**

Instrumental activity of daily living		**Male Fracture subjects (n = 56)**	**Male Control subjects (n = 56)**	**p-value**	**Female Fracture subjects (n = 144)**	**Female Control subjects (n = 144)**	**p-value**
Telephone	Unable/need help	26 (46.4)	6 (10.7)	*<0.0001	76 (52.8)	35 (24.3)	*<0.0001
Walking distance	Unable/need help	27 (48.2)	5 (8.9)	*<0.0001	81 (56.3)	32 (22.2)	*<0.0001
Shopping	Unable/need help	27 (48.2)	4 (7.1)	*<0.0001	51 (35.4)	15 (10.4)	*<0.0001
Cooking	Unable/need help	26 (46.4)	2 (3.6)	*<0.0001	62 (43.1)	27 (18.8)	*<0.0001
Housework	Unable/need help	28 (50.0)	6 (10.7)	*<0.0001	91 (63.2)	31 (21.5)	*<0.0001
Handiwork	Unable/need help	31 (55.4)	6 (10.7)	*<0.0001	71 (49.3)	29 (20.1)	*<0.0001
Laundry	Unable/need help	11 (19.6)	1 (1.8)	*0.003	26 (18.1)	8 (5.6)	*0.001
Medication	Unable/need help	13 (23.2)	2 (3.6)	*0.004	34 (23.6)	6 (4.2)	*<0.0001
Finances	Unable/need help	11 (19.6)	4 (7.1)	0.070	41 (28.5)	23 (16)	*0.006
IADL scores (mean ± SD)		22.3 ± 4.9	26.3 ± 1.9	*<0.0001	22.1 ± 4.8	25.2 ± 3.7	*<0.0001

Number of subjects and n (%)

Table 4.A.3 Subjects with difficulty in quality of life activities in men and women hip fracture subjects pre-fracture and age gender and ethnic matched controls

		Male			Female		
Quality of life		**Fracture subjects (n=56)**	**Control subjects (n=56)**	**p-value**	**Fracture subjects (n=144)**	**Control subjects (n=144)**	**p-value**
Mobility	**Unable/need help**	6 (10.7)	0	*0.013	15 (10.4)	4 (2.8)	*0.011
Self-care	**Unable/need help**	16 (29.6)	4 (7.1)	*0.003	53 (36.8)	18 (12.5)	*<0.0001
Daily activities	**Unable/need help**	15 (26.8)	21 (37.5)	0.225	49 (34)	74 (51.4)	*0.003
Pain	**Has Pain**	7 ()	2 (3.6)	0.082	22	7	*0.003
Mood	**Depressed**	13	2 (3.6)	*0.002	37	15	0.001
QOL Score (mean ± SD)		6 ± 1.5	5.5 ± 0.7	*<0.0001	6.3 ± 1.7	5.9 ± 1.2	*<0.0001

- Number of subjects and n (%)

Table 4.A.4 Subjects with difficulty in Oswestry Disability Index in 56 men and 144 women hip fracture subjects pre-fracture and age gender and ethnic matched controls

		Male			Female		
Oswestry Disability Index		**Fracture subjects (n=56)**	**Control subjects (n=56)**	**p-value**	**Fracture subjects (n=144)**	**Control subjects (n=144)**	**p-value**
Pain	**Strong pain/some pain**	3 (5.4)	0	0.079	14 (9.7)	5 (3.5)	*0.033
Personal care	**Unable/need help**	21 (37.5)	25 (44.6)	0.442	88 (61.1)	84 (58.3)	0.631
Lifting	**Unable/need help**	7 (12.5)	0	*0.006	39 (27.1)	14 (9.7)	*<0.0001
Walking	**Unable/need help**	2 (3.6)	0	0.154	7 (4.9)	3 (2.1)	0.198
Sitting	**Unable/need help**	3 (5.4)	2 (3.6)	0.647	18 (12.5)	31 (21.5)	*0.041
Standing	**Unable/need help**	1 (1.8)	1 (1.8)	1.000	6 (4.2)	6 (4.2)	1.000
Sleeping	**Unable/need help**	3 (5.4)	2 (3.6)	0.632	25 (17.4)	13 (9)	*0.037
Social life	**Unable/need help**	3 (5.4)	3 (5.4)	1.000	25 (17.4)	11 (7.6)	*0.013
Travelling	**Unable/need help**	3 (5.4)	3 (5.4)	1.000	25 (17.4)	11 (7.6)	*0.013
Oswestry Score (mean ± SD)		26.4 ± 12.7	24.2 ± 7.3	0.249	32.2 ± 15.8	29.6 ± 11.6	0.117
VAS score (mean ± SD)		1.3 ± 1.2	3.7 ± 2.7	*<0.0001	1.4 ± 1.3	3.2 ± 2.5	*<0.0001

- Number of subjects and n (%)

Appendix 4.B Functional comparison in between African and Indians subjects and age and gender matched controls.

Table 4.B.1 **Subjects unable to perform basic activities of daily living independently in African and Indian fracture subjects pre-fracture and matched controls**

Activity		African			Indian		
		Fracture (n = 66)	Control (n = 66)	p-value	Fracture (n = 110)	Control (n = 110)	p-value
Eating	**Unable/need help**	2 (3)	0 (0)	0.159	3 (2.7)	1 (0.9)	0.32
Dressing	**Unable/need help**	6 (9.1)	1 (1.5)	0.058	11 (10)	2 (1.8)	*0.012
Grooming	**Unable/need help**	5 (7.6)	3 (4.5)	0.484	14 (12.7)	2 (1.8)	*0.002
Walking	**Unable/need help**	8 (12.1)	4 (6.1)	0.251	19 (17.3)	4 (3.6)	*0.041
Transfer bed	**Unable/need help**	5 (7.6)	3 (4.5)	0.484	11 (10.0)	2 (1.8)	*0.012
Bathing	**Unable/need help**	5 (7.6)	4 (6.1)	0.742	14 (12.7)	1 (0.9)	*<0.0001
Toileting	**Unable/need help**	7 (10.6)	3 (4.5)	0.208	11 (10)	3 (2.7)	*0.020
Physical score		13.4 ± 2.1	13.7 ± 1.37	*<0.0001	13.2 ± 1.9	13.9 ± 0.7	*<0.0001

- Number of subjects and n (%)

Table 4.B.2 **Subjects unable to perform instrumental activities of daily living independently in African and Indian fracture subjects pre-fracture**

Instrumental activity of daily living		African			Indian		
		Fracture (n = 66)	Control n (%)	p-value	Fracture (n = 110)	Control (n = 110)	p-value
Telephone	**Unable/need help**	28 (42.4)	17 (25.8)	*0.043	65 (59.1)	21 (19.1)	*<0.0001
Walking distance	**Unable/need help**	30 (45.5)	13 (19.7)	*0.001	67 (60.9)	21 (19.1)	*<0.0001
Shopping	**Unable/need help**	21 (31.8)	10 (15.2)	*0.027	49 (44.5)	9 (8.2)	*<0.0001
Cooking	**Unable/need help**	21 (31.8)	14 (21.2)	0.168	56 (50.9)	13 (11.8)	*<0.0001
Housework	**Unable/need help**	34 (51.5)	18 (27.3)	*0.004	72 (65.5)	17 (15.5)	*<0.0001
Handiwork	**Unable/need help**	27 (40.9)	18 (27.3)	0.129	64 (58.2)	15 (13.6)	*<0.0001
Laundry	**Unable/need help**	14 (21.2)	5 (7.6)	*0.028	20 (18.2)	3 (2.7)	*<0.0001
Medication	**Unable/need help**	15 (22.7)	4 (6.1)	*0.004	28 (25.5)	3 (2.7)	*<0.0001
Finances	**Unable/need help**	15 (22.7)	15(27.1)	1	32 (29.1)	11 (10)	*<0.0001
IADL scores (mean ± SD)		13.4 ± 2.1	13.7 ± 1.4	*<0.001	21.6 ± 4.7	25.7 ± 3	*<0.0001

- Number of subjects and n (%)

Table 4.B 3. Subjects with difficulty with Quality of Life activities in African and Indian fracture subjects pre-fracture and matched control subjects

Quality of life		African			Indian		
		Fracture (n = 66)	Control (n = 66)	p-value	Fracture (n = 110)	Control (n =110)	p-value
Mobility	**Unable/need help**	7 (10.6)	3 (4.5)	0.208	12 (10.9)	1 (0.9)	*0.002
Self-care	**Unable/need help**	17 (25.8)	11 (16.7)	0.159	45 (40.9)	8 (7.3)	*0.001
Daily activities	**Unable/need help**	19 (28.8)	40 (60.6)	*<0.0001	39 (35.5)	47 (42.7)	0.26
Pain	**Has Pain**	7 (10.6)	3 (4.5)	0.159	17 (15.5)	4 (3.6)	*0.004
Mood	**Depressed/Anxious**	13 (19.7)	9 (13.6)	0.350	33 (30)	8 (7.2)	*<0.0001
[+]QOL Score **(mean ± SD)9**		6.1 ± 1.6	6.2 ± 1.4	*<0.0001	6.4 ± 1.7	5.7 ± 0.9	*0.0001

- Number of subjects and n (%)

Table 4.B.4 **Oswestry Disability Index and Visual Analogue Score in African and Indian fracture subjects pre-fracture and matched control subjects**

Oswestry Disability Index		**African**			**Indian**		
		Fracture (n = 66)	**Control (n = 66)**	**p-value**	**Fracture (n = 110)**	**Control (n = 110)**	**p-value**
Pain	**Strong pain/some pain**	7 (10.6)	3 (4.5)	0.188	9 (8.2)	2 (1.8)	*0.030
Personal care	**Unable/need help**	28 (42.4)	45 (68.2)	*0.003	65 (59.1)	55 (50)	0.176
Lifting	**Unable/need help**	11 (16.7)	6 (9.1)	0.194	30 (27.3)	7 (6.4)	*<0.0001
Walking	**Unable/need help**	4 (6.1)	1 (1.5)	0.171	5 (4.5)	2 (1.8)	0.249
Sitting	**Unable/need help**	5 (7.6)	12 (18.2)	0.069	14 (12.7)	13 (11.8)	0.837
Standing	**Unable/need help**	2 (3)	2 (3)	1	5 (4.5)	5 (4.5)	1
Sleeping	**Unable/need help**	7 (10.6)	6 (9.1)	0.77	18 (16.4)	8 (7.3)	*0.035
Social life	**Unable/need help**	7 (10.6)	9 (13.6)	0.594	18 (16.4)	4 (3.6)	*0.002
Travelling	**Unable/need help**	7 (10.6)	9 (13.6)	0.594	18 (16.4)	4 (3.6)	*0.002
Oswestry Score (mean ± SD)		29.3 ± 15.9	30.9 ± 12.7	0.524	31.7 ± 15.1	26.9 ± 9.6	*0.006
VAS- (mean ± SD)		1.2 ±1.2	3.4 ± 2.3	*<0.0001	1.5 ± 1.4	3.4 ± 2.7	*<0.0001

- Number of subjects and n (%)

Appendix 4.C Functional comparison in hip fracture survivors over one year period.

Table 4.C.1 Comparison of basic activities of living in surviving hip fracture subjects over a twelve month period (n = 117)

		Baseline	3 months	p- value	6 months	p- value	12 months	p-value
Eating	**Able**	117 (100)	103 (88)	n/a	107 (91.5)		108 (92.3)	
Dressing	**Able**	109 (93.2)	63 (53.8)	*<0.0001	83 (70.9)	*<0.0001	92 (78.6)	n/a
Grooming	**Able**	109 (93.2)	62 (53)	*<0.0001	83 (70.9)	*<0.0001	92 (78.6)	n/a
Walking	**Able**	104 (88.9)	25 (21.4)	*<0.0001	51 (43.6)	*<0.0001	66 (56.5)	*<0.0001
Transfer to bed	**Able**	112 (95.7)	55 (47)	*<0.0001	76 (65)	*<0.0001	89 (76.1)	*<0.0001
Bathing	**Able**	108 (92.3)	50 (42.7)	*<0.0001	77 (65.8)	*<0.0001	83 (70.9)	*<0.0001
Toileting	**Able**	107 (91.5)	64 (54.7)	*<0.0001	83 (70.9)	*<0.0001	68 (58.1)	*<0.0001
Physical self-maintenance score (mean ± SD)		13.5 ± 1.6	9.6 ± 3.9	*<0.0001	11.1 ± 3.8	*<0.0001	11.5 ± 3.6	*<0.0001

- Number of subjects and n (%)

Table 4.C.2 Comparison of Instrumental activities of daily living in hip fracture survivors over a twelve month period (n = 117)

		Baseline	**3 months**	**p- value**	**6 months**	**p- value**	**12 months**	**p-value**
Telephone	**Able**	60 (51.3)	9 (7.7)	*<0.0001	12 (10.3)	*<0.0001	18 (15.4)	*<0.0001
Walking distance	**Able**	60 (51.3)	9 (7.7)	*<0.0001	13 (11.1)	*<0.0001	21 (17.9)	*<0.0001
Shopping	**Able**	77 (65.8)	15 (12.8)	*<0.0001	30 (25.6)	*<0.0001	36 (30.8)	*<0.0001
Cooking	**Able**	71 (60.7)	10 (8.5)	*<0.0001	15 (12.8)	*<0.0001	18 (15.4)	*<0.0001
Housework	**Able**	49 (41.9)	6 (5.1)	*<0.0001	8 (6.8)	*<0.0001	8 (6.8)	*<0.0001
Handiwork	**Able**	60 (51.3)	11 (9.4)	*<0.0001	17 (14.5)	*<0.0001	21 (17.9)	*<0.0001
Laundry	**Able**	97 (82.9)	67 (57.3)	*<0.0001	71 (60.7)	*<0.0001	69 (59)	*<0.0001
Medication	**Able**	95 (81.2)	71 (60.7)	*<0.0001	74 (63.2)	*<0.0001	71 (60.7)	*<0.0001
Finance	**Able**	92 (78.6)	15 (12.8)	*<0.0001	28 (23.9)	*<0.0001	33 (28.2)	*<0.0001
IADL scores (mean ± SD)		22.5 ± 4.6	15.5 ± 4.4	*<0.0001	16.5 ± 4.8	*<0.0001	16.8 ± 5.1	*<0.0001

- Number of subjects and n (%)

Table 4.C.3 Comparison of Quality of life in surviving hip fracture subjects over a twelve month period (n = 117)

		Baseline	3 months	p- value	6 months	p- value	12 months	p-value
Mobility	**Able**	109 (93.2)	38 (32.5)	*<0.0001	66 (56.4)	*<0.0001	78 (66.7)	*<0.0001
Self-care	**Able**	79 (67.5)	10 (8.5)	*<0.0001	18 (15.4)	*<0.0001	23 (19.7)	*<0.0001
Daily activities	**Able**	80 (68.4)	17 (14.5)	*<0.0001	29 (24.8)	*<0.0001	40 (34.2)	*<0.0001
Pain	**No Pain**	100 (85.5)	53 (45.3)	*<0.0001	67 (57.3)	*<0.0001	76 (65)	*<0.0001
Mood	**Normal**	89 (76.1)	37 (31.6)	*<0.0001	62 (53)	*<0.0001	81 (69.2)	0.312
QOL score (mean ± SD)		6.2 ± 1.7	10.3 ± 2.6	*<0.0001	9.1 ± 2.6	*<0.0001	8.7 ± 2.6	*<0.0001

- Number of subjects and n (%)

Table 4.C.4 Comparison of Oswestry Disability Index and Visual Analogue Scale in surviving hip fracture subjects over a twelve month period

(n = 117)

		Baseline	3 months	p- value	6 months	p- value	12 months	p-value
Pain	**No pain**	108 (92.3)	46 (39.3)	*<0.0001	71 (60.7)	*<0.0001	83 (70.9)	*<0.0001
Personal Care	**Able**	56 (47.9)	6 (5.1)	*<0.0001	6 (5.1)	*<0.0001	8 (6.8)	*<0.0001
Lifting	**Able**	94 (80.3)	20 (17.1)	*<0.0001	28 (23.9)	*<0.0001	45 (38.5)	*<0.0001
Walking	**Able**	114 (97.4)	82 (70.1)	*<0.0001	94 (80.3)	*<0.0001	101 (86.3)	*0.001
Sitting	**Able**	105 (89.7)	31 (26.5)	*<0.0001	41 (35.0)	*<0.0001	52 (44.4)	*<0.0001
Standing	**Able**	114 (97.4)	84 (71.8)	*<0.0001	98 (83.8)	*<0.0001	101 (86.3)	*0.002
Sleeping	**Able**	102 (87.2)	26 (22.2)	*<0.0001	31 (26.5)	*<0.0001	33 (28.2)	*<0.0001
Social life	**Able**	101 (86.3)	23 (19.7)	*<0.0001	30 (25.6)	*<0.0001	32 (27.4)	*<0.0001
Travelling	**Able**	101 (86.3)	23 (19.7)	*<0.0001	30 (25.6)	*<0.0001	32 (27.4)	*<0.0001
Oswestry Disability Score (%) (mean ± SD)		29.7 ± 14.4	66 ± 19.3	*<0.0001	58.8 ± 19.5	*<0.0001	55 ± 18.1	*<0.0001
VAS pre fracture (mean ± SD)		1.4 ± 1.3	5.04 ± 1.99)	*<0.0001	4.4 ± 2	*<0.0001	4 ± 2 (0 - 8.2)	*<0.0001

- Number of subjects and n (%)

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