Risk factors for morphometric vertebral fractures in subjects aged 60 years and over in the eThekwini Municipality, KwaZulu-Natal, South Africa

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Dedication

To my parents and family for their unconditional support.

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Chapter 1

List of Abbreviations

BMD	Bone Mineral Density.
BMI	Body mass index
CaMos	Canadian Multicentre Osteoporosis Study
CRF	Clinical risk factor
CTSCAN	Computed tomography scan.
DeVOS	Delhi Vertebral Osteoporosis Study.
DRC	Democratic Republic of Congo.
DXA	Dual energy x-ray absorptiometry.
EVOS	European Vertebral Osteoporosis Study.
FRAX	Fracture Risk Assessment Tool.
HAL	Hip axis length.
HRT	Hormonal replacement therapy.
IQR	Interquartile range
KZN	Kwa-Zulu Natal
LAVOS	Latin American Vertebral Osteoporosis Study
LVA	Lateral vertebral assessment
MRI	Magnetic resonance imaging
NHANES	National Health and Nutritional Examination.
PBM	Peak bone mass
RA	Rheumatoid arthritis.
SD	Standard deviation
SA	South Africa

US	United States
VF	Vertebral fracture
VFA	Vertebral fracture assessment.
WHO	World Health Organization

Abstract

With advancing age, the prevalence of osteoporosis increases. Vertebral fractures (VFs) are the most common type of osteoporotic fragility fractures and associated with increased morbidity and mortality. In contrast to hip fractures, VFs are usually silent, with only one third being diagnosed clinically. The majority of VFs are asymptomatic, because they usually occur during normal activities, and only 40% occur after a fall. Furthermore, VFs often develop insidiously over time, and patients may present with multiple fractures which lead to progressive loss of stature and disability. Due to their silent nature, most patients are undiagnosed and not commenced on appropriate treatment. Several risk factors for VFs have been reported in developed countries. Whilst initially thought to be rare in Africans, recent studies suggest a similar incidence in African and White women in South Africa (SA), but no data is available in men.

Objectives

To compare the demographic profile, clinical risk factors and bone mineral density (BMD) measurements in subjects aged 60 years and over with and without morphometric VFs.

Methodology

This is a descriptive study using historical data collected in a primary longitudinal study on hip fractures. A structured questionnaire was used to record demographic data and clinical risk factors for osteoporosis. BMD measurements were made using a Hologic Discovery A densitometer. Morphometric VFs were identified on antero-posterior and lateral spine radiographs using the semi-quantitative Genant method. Descriptive analysis was undertaken using the Student's t test, Mann Whitney U test and the Chi-Square test.

Results

Two hundred subjects were enrolled in the primary study of which 197 subjects had lateral spine radiographs. The median age of subjects was 72.0 years (IQR 67.0 - 78.5 years) and morphometric VFs were identified in 41 (20.8%). Subjects with a VF were significantly older than subjects without a VF [76.0 years (IQR 69.0 - 82.0 years) vs. 72.0 years (IQR 66.0 - 77.0 years), $p = 0.009$]. The prevalence of VFs increased significantly with age, and while a greater proportion of women had a VF (23.8%) compared to men (13.0%), this did not reach statistical significance ($p = 0.095$). Similarly, the prevalence of VFs was higher, but not statistically

significant, in Africans compared to Indians (23.4% vs. 17.4%; p = 0.240). There was no significant difference in clinical risk factors between subjects with and without VFs, except that counterintuitively subjects with a VF were older at the time of menopause than those without a VF (49.6 ± 5.7 years vs. 46.6 ± 7.0 years; p = 0.037). Subjects with a VF had a significantly lower BMD at spine [0.745 g/cm^2 (IQR 0.639-0.958 g/cm^2) vs. 0.870 g/cm^2 (IQR 0.722-0.988 g/cm^2); p = 0.020], but not at the neck of femur and total hip.

Conclusion

Morphometric VFs are common in African and Indian subjects in SA and this study highlights the need for an increased awareness of osteoporosis, screening and management protocols in all ethnic groups in SA.

Key words: Osteoporosis, morphometric vertebral fractures, prevalence, South Africa, bone mineral density.

Chapter 1: Background and Literature Review

Introduction

Osteoporosis is a progressive metabolic skeletal disease characterized by severe bone loss, disruption of skeletal micro architecture, decreased bone strength, and bone quality which predisposes to minimal trauma or atraumatic fractures of the vertebral column, upper femur, distal radius, proximal humours, pubic ramie and ribs [1,2].

Vertebral fractures (VFs) are one of the commonest complications of osteoporosis and contribute significantly to the osteoporotic fracture burden [1], accounting for approximately 700000 of the 1.5 million fractures seen in the United States (US) annually [2]. In contrast to hip fractures, VFs are usually silent with only one third being diagnosed clinically [3]. In a multi-national study in post-menopausal women newly diagnosed with osteoporosis, 68% of the subjects had undiagnosed VFs [4].

The majority of VFs usually occur during normal activities, are therefore asymptomatic, and only 40% occur after a fall in contrast to hip fractures, which are usually, associated with a fall [5]. VFs often develop insidiously over time, and multiple fractures may lead to progressive loss of stature and disability [5]. Due to their inherent silent nature, most patients are undiagnosed, and not commenced on appropriate treatment [6].

VFs can lead to loss of vertebral body height and progressive kyphosis [7]. These can result in a deterioration of the health-related quality of life, loss of independence, disability and increase mortality [7,8].

Treatment of VFs includes pain control medications to facilitate mobility and avoid prolonged bed rest, therapeutic exercises that can reduce pain and strengthen muscles, as well as preserving everyday functioning and quality of life, and finally vertebral augmentation procedure should be considered when patients have unremitting pain, or where the spinal deformity is extremely severe [3,5].

Although the epidemiology and risk factors for VFs are well established in developed countries, there are limited studies on VFs from Africa or South Africa (SA).

Epidemiology of osteoporosis and vertebral fractures

Worldwide, it is estimated that osteoporosis affects 200 million women, about one-tenth of women aged 60 years and over, one-fifth of women aged 70 years and over, two-fifths of women aged 80 aged and over and two-thirds of women aged 90 years and over [10]. It causes more than 8.9 million fractures annually worldwide, resulting in a fragility fracture every 3 seconds [9]. By 2050, the incidence of hip fractures is expected to increase in men and women by 310% and 240% respectively, compared to the 1990s [11]. After the age of 50 years, almost one in three women and one in five men will sustain a fragility fracture during their remaining lifetime [12]. The majority of fractures of the forearm (80%), humerus (75%), hip (70%) and spine (58%) occur in women [10].

The estimated lifetime risk for hip, forearm and vertebral fractures requiring medical attention is approximately 30 to 40%, equivalent to that for cardiovascular disease [13]. Additionally, it is estimated that the residual lifetime risk of experiencing an osteoporotic fracture in men aged 50 years and over is up to 27%, which is higher than the lifetime risk of developing prostate cancer of 11.3% [14,15].

VFs due to osteoporosis are common with one VF occurring every 22 seconds worldwide in men and women aged 50 years and over [10]. A 50 year old Caucasian woman's estimated lifetime risk of sustaining an osteoporotic VF is 16%. In comparison, the estimated lifetime fracture risk for 50 year old Caucasian man is 5% [16]. A woman 65 year of age with one VF has a one in four chance of having a second fracture in the next five years, which can be decreased to one in eight with appropriate treatment [17]. Over 55% of patients with hip fractures have evidence of a prior VF [18].

The incidence of VFs increases with age in both genders. Studies indicate that the prevalence of VFs in men is similar to, or even greater than that seen in women between the ages of 50 to 60 years [19 - 21]. Whilst the prevalence in men was higher at an earlier age in the Canadian Multicentre Osteoporosis Study (CaMos) and in the European Vertebral Osteoporosis Study (EVOS) studies, the prevalence did not increase with age in men, as it did in women [19,21]. Possible explanations are that men may suffer trauma earlier in their working life more than women, and that they have a more stable bone mass compared to women who experience more rapid peri-menopausal bone loss [19,21].

The proportion of VFs that are unrecognized or not diagnosed, during routine assessment of a thoracolumbar lateral x-ray, is as high as 46% in Latin America, 45% in North America, and 29% in Europe and Australia [22].

In the Latin American Vertebral Osteoporosis Study (LAVOS), which included five Latin American countries (Argentina, Brazil, Colombia, Mexico and Puerto Rico), the prevalence of morphometric VFs in women aged 50 years and older was approximately 15%, with 7% occurring within the 50 - 60 years old age group and increasing to 28% for those greater than 80 years old [23].

A study from India found that the prevalence of radiographic VFs in older population was similar to Western population at about 17.9 % [24]. A similar prevalence was reported in Chinese subjects aged 50 years and over at 15%, which rose to 36 - 59% in subjects 80 years and over [25].

There are few studies on prevalence of osteoporosis and VFs from Africa, and Middle East. In a Tunisian study, Sellami et al reported a 16.2% prevalence of osteoporotic fractures in 1,311 menopausal women, based on the thoracolumbar spine lateral radiographs VFs accounted for 59.83% of all these fractures [26]. El Maghraoui et al in 2009, a study in Moroccan women with a mean age of 65 years, reported VFs in 25.6% of subjects, using the vertebral fracture assessment (VFA) software on dual-energy X-ray absorptiometry (DXA) [27]. In Lebanon, the prevalence of VFs in a population-based sample of participants aged 65 - 84 years was reported at 19.9% in women and 12% in men [28]. A recent multi-centre study from Central Africa found an 11.1% prevalence of morphometric VFs in postmenopausal Black women [29].

Bone mineral density (BMD) has been well studied in the South African population. Several studies have reported a lower BMD at the lumbar spine in African women in comparison with White South African women [30,31]. George et al in a more recent study has also reported a lower BMD in Indian woman compared to African women in SA [32].

There are few studies on prevalence VFs from SA, and an early multi-ethnic study in 1968 by Dent et al showed an increase prevalence of morphometric VFs in White South African women compared to urbanized and rural Black women [33]. Nevertheless, this study was mainly based on the visual assessment of lumbar spine lateral X-rays, and the participants were not age matched, had been admitted for unknown indications and therefore participants

with secondary causes of osteoporosis were not necessarily excluded from the study. Finally, the diet differed markedly according to their ethnic groups.

Recent studies however question the belief that VFs are rare in Black women. Micklesfield et al in a multi-ethnic study reported that 38% of Black South African women aged 60 years and over had sustained new vertebral deformities over a five-year period [34]. Additionally, Conradie et al in a recent study reported a similar prevalence of morphometric VFs in White and Black South African women (8.3% and 11.5% respectively) [35]. There is no information, however, on vertebral fractures in Indians in SA.

Definition of osteoporosis

The World Health Organization (WHO) in 1994 defined osteoporosis as "a systemic bone disease characterized by a decreased bone mass and a deterioration of bone microarchitecture resulting in an increased fracture risk" [36]. The National Institute of Health in 2001 defined osteoporosis as "a disease of compromised bone strength, resulting in an increased risk of fracture" [37]. Both definitions emphasize that osteoporosis is not merely a disease but also risk factor for fractures [2].

Whilst it is known that both bone mass and bone quality contribute to bone strength, there are comparatively few methods to assess bone quality [6]. Bone quality refers to bone microstructure, mineralization, turnover, and accumulation of damage, due to microfractures [37,38]. Recent studies have used densitometry and high-resolution images such as radiography, computed tomography (CT scan) and magnetic resonance imaging (MRI) to measure the geometry and microarchitecture of bone [39]. Additionally, microradiography, Fourier-transform infrared spectroscopy or Raman micro-spectroscopy has been used in studies to assess tissue mineralization and bone composition [39]. In contrast, bone mass, which contributes to 70% of bone strength, can easily be measured [40]. The gold standard test to measure bone mass is BMD testing at the hip or lumbar DXA [1]. In 1994, the WHO using the National Health and Nutritional Examination (NHANES III) classified osteoporosis according to DXA findings as shown in Table 1 [36].

Table 1: World Health Organisation definition of osteoporosis according to bone mineral density

Bone Density Category	T-Score
Normal	≥ -1.0
Low bone density (osteopenia)	-1.0 to -2.4
Osteoporosis	≤ -2.5
Severe or established osteoporosis	≤ -2.5 and /or >1 or more fragility fractures.

Adapted from Kanis, Melton, Christiansen, and Khaltaver. [1994] [36].

Osteoporosis is defined using a T score of greater than 2.5 standard deviations (SD) below the young normal adult reference population [36]. In pre-menopausal woman and in men younger than the age 50 years old, the Z score is preferred, which reflects the value compared with that of age and gender matched person. A Z score of -2.0 SD or lower are defined as below the expected range for age, and those above -2.0 SD as within the expected range for age [11].

The WHO criteria however, have some limitations, as they are applicable primarily to White post-menopausal women, since the research data was limited to this group [6]. More importantly, BMD alone does not predict fracture risk in the majority of people at risk for fracture [5]. In addition, bone quality and extra skeletal risk factors are not addressed, causes of a low BMD other than osteoporosis are not considered and therefore the WHO diagnostic categories cannot be employed as the only therapeutic intervention thresholds [1].

In view of these limitations, several tools have been developed to assess fracture risk [6]. The description of osteopenia and assessment of osteoporosis was revised in 2008 and the revised assessment includes BMD with selected clinical risk factors (CRF) for fracture including height and weight [41].

The WHO Fracture Risk Assessment Tool (FRAX®) is a new algorithm that uses clinical risk factors with or without BMD to improve fracture risk prediction in postmenopausal women and men aged 40 years or over [42]. The risk factors used in FRAX® include age, weight, height, previous fragility fracture, parental hip fracture, current smoking, regular intake of

three or more units of alcohol daily, rheumatoid arthritis, oral glucocorticoids (current therapy or former exposure to glucocorticoids) as well as causes of secondary osteoporosis or femoral BMD. It calculates the 10-year probability of hip or major osteoporotic fracture and helps to make individualized therapeutic decisions based on country specific intervention thresholds [42]. The model allows for risk stratification in both genders and different race groups [2].

Pathophysiology of osteoporosis and osteoporotic fractures

There are two main types of bone; cortical bone that makes up 80% of adult bone mass and trabecular bone that accounts for 20% of bone mass [43].

Bone is metabolically active tissue and undergoes remodelling which is a continuous process of resorption and renewal of bone because of the coupled action of bone resorbing cells (osteoclasts) and bone forming cells (osteoblasts) [44]. Any process, which increases the rates of remodelling, can lead to a net loss of bone over time and increase risk of fragility fractures [45].

Peak bone mass (PBM) is achieved by the ages of 25 to 30 years and bone mass slowly decreases thereafter [46]. Failure to achieve PBM contributes to the risk of developing osteoporosis later in life [46,47].

Ageing and loss of gonadal function are two of the most important mechanisms that predispose to significant bone loss [48]. Ageing or senile osteoporosis is secondary to decreased physical activity and change in nutritional intake and requirements [47] and usually affects cortical bone of men and women, thereby increasing the risk of hip fractures in both genders [46]. In contrast, postmenopausal osteoporosis is due to oestrogen deprivation, and affects mostly trabecular bone. It therefore results in increased risk of vertebral and wrist fractures in women [43,48].

Osteoporotic VFs occur when the combined axial and bending loads on the spine exceed the strength of the vertebral body [49]. 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. These sites possibly have increased mobility and flexibility and a higher propensity to fracture [50]. Multiple fractures are thought to occur on a similar basis when large compressive forces are applied [2].

Risk factors for osteoporotic fractures

Epidemiologic studies have identified several factors that increase an individual's risk of fracture. While a thorough review is beyond the scope of this review, several key risk factors are highlighted.

1. Age, gender and ethnicity

Age is recognized as one of the most well-established risk factors for VFs. In Europe, the prevalence of radiological VFs increases with age and is similar in men as in women at 12% [19]. The risk of sustaining one osteoporotic VF increases with age, from 5 - 10% in Caucasian women aged 50 - 54 years old to 30% - 50% in women aged 80 - 84 years old [51]. Further, with advancing age each, each five-year increment increases the risk of VFs up to two-fold [52].

In Europe, men aged 50 - 64 years and over had an overall higher prevalence of fragility fractures than similarly aged women, with the reverse being observed in those aged 65 years and over [53]. This pattern suggests that the aetiology of fractures in young men may relate to higher rates of trauma, whereas fractures occurring at older ages are more likely to be the result of skeletal fragility [53]. The CaMos study showed similar prevalence of VFs in men and women at 21.5% and 23.5% respectively [21]. The prevalence of VFs in the EVOS study involving 19 countries was 20.2% in women and 12.2% in men [19]. The Delhi Vertebral Osteoporosis Study (DeVOS) showed similar prevalence rates of VFs in Indian women and men of 17.9% [24]. In the US, Hispanic women had the highest risk for fragility fractures, followed by Native American, African and Asian Americans who had the lowest risk of fractures [54].

2. Weight and height

In early adulthood, weight is an important determinant of PBM, and persons who are overweight at a younger age may be at an advantage regarding bone mass at an older age [55]. In the general population, epidemiological data show that increased body weight and body mass index (BMI) are both positively correlated with a higher BMD and lower prevalence of VFs [56]. The beneficial effect of a higher body weight may be associated with an increase in secretion of circulating oestrogen from adipose tissue and mechanical protective effect [57]. Intentional and unintentional weight loss is associated with greater bone loss and increased risk of fracture [58]. Both height and a low BMI are associated with

increasing risk of osteoporotic fractures [59,69]. A BMI of less than or equal to 20 kg/cm^2 is associated with an almost doubling of the risk of fragility fracture and taller persons with a longer hip axis length (HAL) also have a higher fracture risk [60,61].

3. Bone mineral density

Bone mass is one of the most significant determinant of bone strength and mechanical resistance and can be measured as BMD, which is considered as an index of bone mass [37].

Bone mineral density is defined as the amount in grams of bone mineral content divided by the region of interest in centimetres squared and measured by using DXA at three different sites; the spine, hips and forearms [40]. The accuracy of DXA at the hip exceeds 90%; therefore, it is the preferred site of measurement in older persons and is a better predictor for fragility fractures than BMD at the spine [38]. The possible reason is that lumbar spine BMD in older persons may be falsely elevated due to effect of osteoarthritis [40]. Bone mineral density has inverse relationship with the risk of fragility fractures [37]. The risk of VFs increases 1.5 – 3 times for each one SD decrease from the mean BMD [38].

4. A prior fragility fracture

Previous fragility fractures are associated with a significantly increased risk of an osteoporotic fracture after the age of 40 to 50 years with or without adjustment for BMD [62]. An individual with a previous VF has a five-fold increased risk of a fracture, and this risk increases further with the number of prior VF [63]. The risk is highest in the first year following the fragility fracture [17,63]. Patients with a history of previous fracture, therefore, should receive further evaluation for osteoporosis and fracture risk assessment [62].

5. Family history of fracture

A family history of fracture, particularly from maternal side is associated with an increased risk of osteoporotic fractures at all sites [64].

6. Hormonal factors

Oestrogen plays a significant role in bone health and has a protective effect in both women and men. The major consequence of the loss of oestrogen is an increase in bone resorption and osteoporosis due to a decrease in BMD and micro architectural deterioration of bone [65]. A late age of menarche and early menopause are associated with a higher risk of VFs,

which can be explained due to oestrogen deprivation [66]. Hypogonadism is a recognized risk factor for osteoporotic fractures [65].

7. Lifestyle factors

Physical activity and adequate exercise are important for normal bone formation, whilst sedentary lifestyle and immobilisation result in rapid bone loss and increase risk of developing fractures [67, 68]. Falls are a recognized risk factor for fragility fractures and are common in the elderly. The aetiology of falls is multifactorial, includes reduced muscle strength, impaired balance, poor vision, and drugs [67].

Smoking can lead to lower BMD and higher risk of fracture [69,70] and this risk increases with age [71]. The risk of fragility fractures increases greatly with a significant alcohol intake, particularly with long-term intake [72].

8. Secondary causes of osteoporosis

Many diseases also increase the risk of osteoporosis and fragility fractures, for example, hyperthyroidism, Cushing's disease, hypogonadism, chronic obstructive pulmonary disease, and inflammatory bowel disease [5]. Rheumatoid arthritis (RA) is an independent risk factor for osteoporotic fractures [73]. Prolonged use of corticosteroids is the most common cause of secondary osteoporosis and it is estimated that 30 - 50% of patients on long-term corticosteroid therapy will experience fractures [74].

Diagnosis of vertebral fractures

1. Conventional radiology

Due to their silent nature and nonspecific symptoms of VFs, only one third are diagnosed clinically [6]. Spinal radiographs are therefore an important tool for diagnosis [63]. Conventional radiographs are easy, quick access procedures and available in almost all hospitals, however performing conventional radiographs in asymptomatic osteoporotic patients can expose them to unnecessary radiations and increase the cost of diagnosis of VFs with limited accuracy of diagnosis [75].

Several methods have been developed for assessment of VFs based on visual assessment; these include quantitative morphometric methods described by Eastell, McCloskey, and Melton, semi-quantitative Genant method and an algorithm-based qualitative method [6]. Out

of these, the Genant method is considered the technique of choice for VF assessment, as it is readily usable in clinical practice [76]. Several studies have demonstrated intra- and inter-rater reliability, concurrent and predictive validity for the Genant method [63]. This approach is based on semi quantitative evaluation of the extent of a vertebral height reduction and morphological change of vertebral bodies on conventional radiographs [77].

A VF is diagnosed when the reduction of height in the anterior, middle or posterior dimension of vertebral body exceeds 20%. The fracture is considered mild (grade 1) when there is 20 – 25 % decrease in anterior, middle and / or posterior height, moderate fracture (grade 2) when approximately 25 – 40% height reduction and severe (grade 3) if there is 40% or greater reduction in height of the vertebral body [77] (Figure 1).

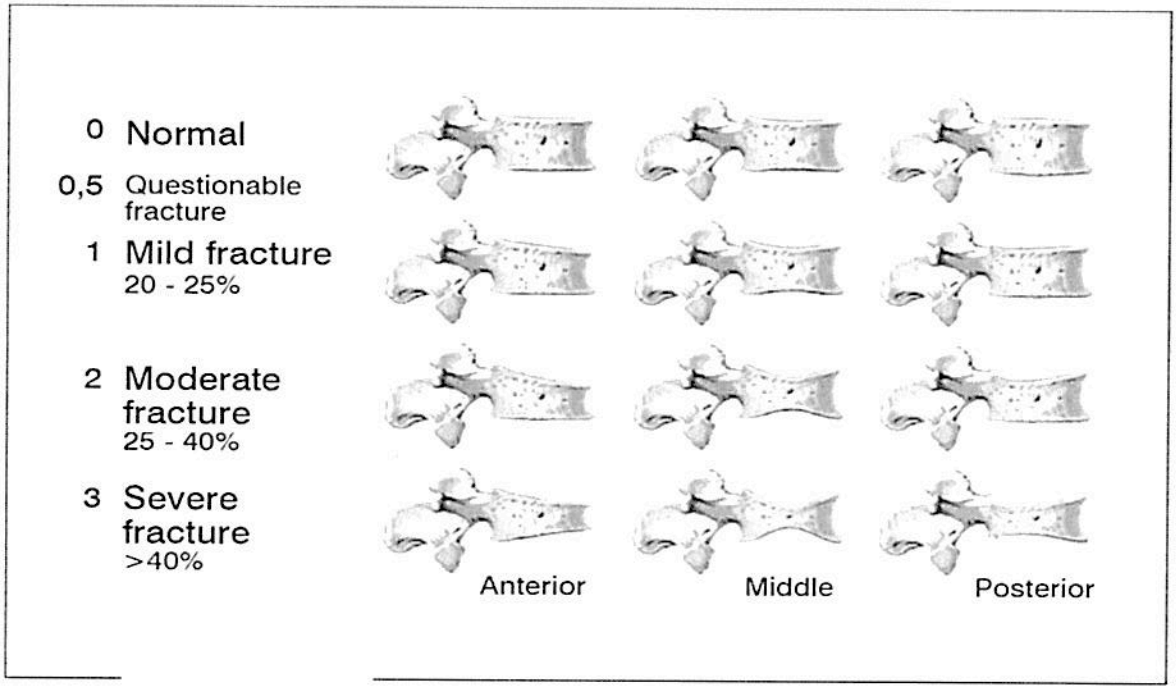

Figure 1: Genant method for assessment of vertebral fractures

Note: Adopted from Genant et al.1993 [77].

2. **Dual energy x-ray absorptiometry**

The introduction of DXA into clinical practice has revolutionized the diagnosis of osteoporotic fractures [40]. It allows accurate measurement of BMD, and visual and morphometric assessment of spine, which increase the sensitivity of diagnosing osteoporosis and VFs [78]. The advantages of using DXA over conventional X ray devices are, it minimizes the radiation exposure, high speed image acquisition and allows combined

evaluation of VF status and BMD, which eventually reduces the cost of diagnosis [79]. Dual - energy lateral vertebral assessment (LVA) imaging is performed in the lateral decubitus position, which increases the accuracy of VF assessment [80].

Morbidity and mortality related to osteoporotic vertebral fractures

Vertebral fractures are one of the commonest complications of osteoporosis and contribute significantly to the osteoporotic fracture burden [1]. Despite the high lifetime risk of osteoporotic VFs, only one-third of cases are clinically diagnosed, and an even a smaller proportion of patients are admitted to hospital [3].

Vertebral fractures can lead to loss of vertebral body height and progressive kyphosis with back pain, loss of height and deformity [7]. The resultant reduction in volume of the thoracic and abdominal cavities leads to reduced pulmonary function, constipation, bowel obstruction, prolonged inactivity, deep venous thrombosis, progressive muscle weakness, increased risk of pneumonia and restrictive lung disease [8].

The impact on quality of life can be profound because of the loss of independence, distorted body image, loss of self-esteem and depression [7]. Vertebral fractures also significantly impact on activities of daily living [81].

Mortality

Patients with VFs have an increased mortality, with age-adjusted mortality rates, increasing with the number of VFs [82,83]. Compared to hip fractures, patients with severe vertebral deformities have an increased risk of death due to pulmonary causes such as chronic obstructive pulmonary disease and pneumonia, even after adjusting for long-term glucocorticoid and tobacco use [8]. Vertebral fractures are associated with an eight-fold increase in age-adjusted mortality [82].

Management

Several clinical trials have demonstrated that if adequate therapy for osteoporosis and its associated fractures could be initiated early, BMD could be increased by 5 – 15%, and the rates of VFs reduced by 40 – 70% [4,84]. This would ultimately lead to improvement in patient mobility, a smaller reduction in health-related quality of life, and lower morbidity and mortality rates [5]. The vast majority of patients are treated non-operatively, either as in- or

outpatients [5]. Surgical therapy is reserved rather for patients with persistent pain symptoms or notable deformities of the affected vertebral bodies [85].

Study Justification

Life expectancy has recently improved in SA, as result of improved quality of life, health services and more importantly due to the introduction of antiretroviral therapy (ART) for Human Immunodeficiency Virus (HIV) infected patients. Therefore, as the population ages, non - communicable diseases including osteoporosis and in particular VFs will have an important impact on the disease spectrum, mortality and morbidity.

VFs have recently been shown to be more common in Africans than previously thought, with a similar prevalence to Whites. This study finding will highlight the need for an increased awareness of osteoporosis, screening and management protocols in all ethnic groups in South Africa.

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Chapter 2: A submission ready manuscript: Risk factors for morphometric vertebral fractures in subjects aged 60 years and over in the eThekwini Municipality, KwaZulu-Natal, South Africa

Abstract

With advancing age, the prevalence of osteoporosis increases. Vertebral fractures (VFs) are the most common type of osteoporotic fragility fractures and associated with increased morbidity and mortality. In contrast to hip fractures, VFs are usually silent, with only one third being diagnosed clinically. The majority of VFs usually occur during normal activities, and are therefore asymptomatic, and only 40% occur after a fall. Furthermore, VFs often develop insidiously over time, and patients may present with multiple fractures, which lead to progressive loss of stature and disability. Due to their silent nature, most patients are undiagnosed and not commenced on appropriate treatment. Several risk factors for VFs have been reported in developed countries. Whilst initially thought to be rare in Africans, recent studies suggest a similar incidence in African and White women in South Africa (SA), but no data is available in men.

Objectives

To compare the demographic profile, clinical risk factors and bone mineral density (BMD) measurements in subjects aged 60 years and over with and without morphometric VFs.

Methodology

This is a descriptive study using historical data collected in a primary longitudinal study on hip fractures. A structured questionnaire was used to record demographic data and clinical risk factors for osteoporosis. Bone mineral density measurements were made using the Hologic Discovery A densitometer. Morphometric VFs were identified on antero-posterior and lateral spine radiographs using the semi-quantitative Genant method. Descriptive analysis was undertaken using the Student's t test, Mann Whitney U test and the Chi-Square test.

Results

Two hundred subjects were enrolled in the primary study of which 197 subjects had lateral spine radiographs. The median age of subjects was 72.0 years (IQR 67.0 - 78.5 years) and morphometric VFs were identified in 41 (20.8%). Subjects with a VF were significantly older than subjects without a VF [76.0 years (IQR 69.0 - 82.0 years) vs. 72.0 years (IQR 66.0 - 77.0

years), p = 0.009]. The prevalence of VFs increased significantly with age, and while a greater proportion of women had a VF (23.8%) compared to men (13.0%), this did not reach statistical significance (p = 0.095). Similarly, the prevalence of VFs was higher, but not statistically significant, in Africans compared to Indians (23.4% vs. 17.4%; p = 0.240). There was no significant difference in clinical risk factors between subjects with and without VFs, except that counterintuitively subjects with a VF were older at the time of menopause than those without a VF (49.6 ± 5.7 years vs. 46.6 ± 7.0 years; p = 0.037). Subjects with a VF had a significantly lower BMD at spine [0.745 g/cm^2 (IQR 0.639 - 0.958 g/cm^2) vs. 0.870 g/cm^2 (IQR 0.722 - 0.988 g/cm^2); p = 0.020], but not at the neck of femur and total hip.

Conclusion

Morphometric VFs are common in African and Indian subjects in SA and this study highlights the need for an increased awareness of osteoporosis and screening and management protocols in all ethnic groups in South Africa.

Key words: Osteoporosis, morphometric vertebral fractures, prevalence, South Africa, bone mineral density.

Introduction

Vertebral fractures (VFs) are the most common complication of osteoporosis and are associated with increased morbidity and mortality [1], accounting for approximately 700 000 of the 1.5 million fractures seen in the United States (US) annually [2]. In contrast to hip fractures, VFs are usually silent, with only one third being diagnosed clinically [3]. In a multi-national study in post-menopausal women newly diagnosed with osteoporosis, 68% of the subjects had an undiagnosed VF [4].

The majority of VFs usually occur during normal activities, and are therefore asymptomatic, and only 40% occur after a fall [5]. Furthermore, VFs often develop insidiously over time, and patients may present with multiple fractures, which lead to progressive loss of stature and disability [6]. Due to their silent nature, most patients are undiagnosed and not commenced on appropriate treatment [7].

Whilst incidence and clinical risk factors for VF are well studied in developed countries, there are limited studies from developing countries.

In a study of five Latin American countries (Argentina, Brazil, Colombia, Mexico and Puerto Rico), the prevalence of VFs in women aged 50 years and over was about 15%, with 7% occurring within the 50 - 60 years old age group and increasing to 28% for those greater than 80 years old [8].

A study from India found that the prevalence of radiographic VFs in older population was similar to the Western population, at about 17.9 % [9]. A similar prevalence was reported in Chinese subjects aged 50 years and over, 15%, which rose to 36 - 59% in subjects aged 80 years and over [10].

There are few studies on prevalence of osteoporosis and VFs from Africa and the Middle East. In a Tunisian study, Sellami et al reported a 16.2% prevalence of osteoporotic fractures in 1,311 postmenopausal women, based on lateral radiographs of the thoracolumbar (TL) spine, with VFs accounting for 59.83% of all these fractures [11]. El Maghraoui et al in 2009, in a study of Moroccan women with a mean age of 65 years, reported VFs in 25.6% of subjects, using the VF assessment software [12]. In Lebanon, the prevalence of VFs in a population-based sample of subjects aged 65 - 84 years was estimated at 19.9% in women and 12% in men [13]. A recent multi-centre study from Central Africa in 2018 found an 11.2% prevalence of morphometric VFs in postmenopausal Black women [14].

Bone mineral density (BMD) has been well studied in the South African population. Several studies have reported a lower BMD at the lumbar spine in African women compared to White women [15,16]. George et al in a recent study has also reported a lower BMD in Indian South African women compared to Black women [17].

There are few studies on prevalence VFs from SA, and an early multi-ethnic study by Dent et al in 1968 showed a higher prevalence of morphometric VFs in White South Africans compared to urbanized and rural Black women [18]. Nevertheless, this study was mainly based on the visual assessment of lumbar spine on lateral X-rays, and the participants were not age matched, had been admitted for unknown indications and therefore participants with secondary causes of osteoporosis were not necessarily excluded from the study. Finally, the diet differed markedly according to their ethnic groups.

There are recent studies, however that question the belief that VFs are rare in Black women. Micklesfield et al in a multi-ethnic study reported that 38% of Black South African women aged 60 years and over had sustained new vertebral deformities over a five-year period [19].

Additionally, Conradie et al in a recent study reported a similar prevalence of morphometric VFs in White and Black South African women (8.3% and 11.5% respectively) [20]. There is no information, however, on Indians in SA nor is there any data on men.

Although the epidemiology and risk factors for VFs are well established in developed countries, there are limited studies on VFs in Africa or SA. The purpose of this study is to define the prevalence and risk factors for VFs in SA.

Methods

Ethical approval for the study was granted by the University of KwaZulu Natal's Biomedical Research Ethics Committee (BE 612/16) (Appendix C).

A descriptive study using historical data collected of control group in a primary longitudinal study on osteoporotic hip fracture was undertaken. The initial study was conducted in five public sector regional hospitals in the eThekwini area, Kwa-Zulu Natal, which provide an orthopaedic service, namely King Edward VIII, Addington, RK Khan, Mahatma Gandhi Memorial and Prince Mshiyeni Memorial Hospital. Participants were recruited between August 2010 and July 2013. Volunteer subjects aged 60 years and older, who were able to give informed consent, were enrolled from the outpatient departments of these hospitals, old age community groups and by word of mouth. Exclusion criteria included prior history of osteoporosis or hip fractures.

A structured questionnaire was used to collect demographic details, weight and height, clinical risk factors for osteoporosis, intake, family history of osteoporosis and gynecological history. The Danish Health and Morbidity Survey was used to assess alcohol use [21] and the World Health Organization (WHO) Monitoring Trends and Determinants in Cardiovascular disease scale (MONICA scale) was used to assess smoking exposure [22]. The International Osteoporosis Foundation (IOF) calcium intake diary was used to assess calcium intake [23] (Appendix D).

Radiological assessment

Antero-posterior (AP) and lateral radiographic views of the thoracic and lumbar spine were acquired using a standardized protocol in 197 control subjects on the day of enrolment. All radiographs were reported by a single blinded experienced specialist radiologist. Thoracic and lumbar vertebrae were deemed abnormal (morphometric fracture) by an experienced

radiologist using the semi-quantitative Genant method i.e. a reduction in height of ≥ 20% in its anterior, middle or posterior section compared to its own or nearest intact posterior vertebra [24,25]. The percentage loss was calculated using the differences in height. Fractures were graded as mild (20 - 25%), moderate (25.1 - 39.9%) or severe (> 40%) according to the degree of deformity [24]. The Genant method has been validated in many studies including the Study of Osteoporotic Fractures (SOF) and correlates well with clinical measurements of height loss, age, back pain, and baseline BMD [26]. The measurements are easy to apply and require no reference range and are accurate even for small sample numbers [27].

Bone mineral density measurements at the hip and spine were obtained using the Hologic Discovery A densitometer. A spine phantom was scanned weekly to determine the coefficient of variation, which was <1.5%.

The data were analysed using IBM® SPSS®25. The significance for all tests was set at $p < 0.05$. For descriptive data, means and standard deviations or median and interquartile range, depending on the distribution of the data, were used. Demographic characteristics were expressed as frequencies and percentages. To compare variables inferential statistics were applied including the Student's t test or the Mann Whitney U test for numerical variables, Chi square test for categorical variables and the Fisher's exact test, where frequencies were small.

Results

Two hundred subjects were enrolled in the primary study from which the 197 subjects, who had had vertebral radiographs, were enrolled in this study. Their median age was 72.0 years (IQR 67.0 - 78.5 years), and the majority of subjects were women 72.6% (Table 1).

Morphometric VFs were identified in 41 (20.8%) patients, and subjects with VFs were significantly older than subjects without VFs (76.0 years [IQR 69.0-82.0 years] vs. 72.0 years [IQR 66.0-77.0 years]; $p = 0.009$). There was a significant increase in the prevalence of fractures with age, with 14.7% in the 60 - 69 years age group increasing to 35.7% in subjects aged 80 years and above, $p = 0.023$ (Table 1).

Although a higher proportion of women had a VF 34 (23.8%) compared to men 7 (13%), this did not reach statistical significance ($p = 0.095$). Similarly, although the prevalence of VFs was higher in African subjects compared to Indians (23.4% vs 17.4%), this was not statistically significant.

Table 1: Comparison of the baseline demographic features in 197 subjects with and without vertebral fractures

		VF subjects	No VF	Total subjects	
		n (%)	n (%)	n (%)	p value
Number of subjects		41 (20.8)	156 (79.1)	197 (100)	
***Age (years)**		76.0 (69.0-82.0)	72.0 (66.0-77.0)	72.0 (67.0-78.5)	**0.009
Age categories	**60 – 69**	11 (14.7)	64 (85.3)	75 (100)	
	70 – 79	15 (18.7)	65 (81.3)	80 (100)	***0.023
	≥ 80	15 (35.7)	27 (64.3)	42 (100)	
Gender	**Male**	7 (13.0)	47 (87)	54 (100)	
	Female	34 (23.8)	109 (76.2)	143 (100)	0.095
Ethnicity	**African**	15 (23.4)	49 (76.6)	64 (100)	
	Indian	19 (17.4)	90 (82.6)	109 (100)	***0.240

*Age represented as median and interquartile range. Statistical analysis **Mann-Whitney U test; ***Pearsons Chi square test. VF: vertebral fracture.

Clinical risk factures of vertebral fractures

No differences in mean height, weight, or BMI were observed between subjects who had a VF compared to those that did not (Table 2).

Although a greater proportion of subjects with a VF smoked and consumed alcohol compared to the subjects who did not have a VF, this was not statistically significant. Similarly, no difference was observed in caffeine and calcium intake, sunlight exposure, family history of osteoporosis or maternal history of osteoporotic fracture (Table 2).

Furthermore, no significant differences were observed in age of menarche, parity and use of hormonal replacement therapy in women with or without VF. Counterintuitively, a later age at menopause was noted in women with VF than those without (49.6 ± 5.7 years vs 46.6 ± 7.0 years; p = 0.037) (Table 3).

Table 2: Comparison of the clinical risk factors in in 197 subjects with and without vertebral fractures aged 60 years and over

	Subjects with VF	**Subjects without VF**	
	n = 41	**n = 156**	p value
	n (%)	**n (%)**	
Height (cm)	156.9 ± 8.6	157.2 ± 9.3	0.856
Weight (kg)	70.2 ± 15.8	73.4 ± 16.5	0.267
BMI (kg/m^2)	28.7 ± 6.6	29.6 ± 6.1	0.403
Smoking history	6 (14.6)	14 (8.9)	0.286
Alcohol intake	2 (4.9)	6 (3.8)	0.766
Caffeine (cups/day)	2.0 ± 2.3	1.9 ± 1.3	0.689
Sun exposure (minutes per day)	19.2 ± 33.0	31.7 ± 59.9	0.528
Dietary calcium intake (grams/day)	501.5 ± 302.4	466.8 ± 261.8	0.504
Maternal history of hip fracture	4 (9.7)	19 (12.1)	0.667
Family history of osteoporosis	3 (7.32)	13 (8.3)	0.824

Results expressed as mean ± standard deviation. Statistical analysis with Students T test. BMI: body mass index; VF: vertebral fracture.

Table 3. Comparison of gynaecological history in women with or without vertebral fractures.

Women	Subjects with VF n= 34	Subjects without VF n = 109	p value
Age of menarche (years)	14.3 ± 1.9	14.0 ± 1.8	*0.446
Age of menopause (years)	49.6 ± 5.7	46.6 ± 7.0	*0.037
Parity	3.2 ± 2.1	3.9 ± 2.4	*0.185
History of HRT use n (%)	1 (2.9)	12 (11.0)	**0.179

Results presented as mean ± SD. Statistical analysis with *Student's t test and **Chi-square test with Fisher's exact

HRT: hormone replacement therapy, VF: vertebral fracture

Comparison of bone mineral density

Subjects with a VF had a significantly lower median BMD at spine compared to subjects without a VF (0.745 g/cm^2 [IQR 0.639 - 0.958 g/cm^2] vs 0.870 g/cm^2 [0.722 - 0.988 g/cm^2], p = 0.020). There was no statistically significant difference in BMD at the neck of femur or total hip (Table 4).

Table 4. Comparison of bone mineral density in subjects with or without vertebral fractures.

	Subjects with VF n = 41	Subjects without VF n = 156	p = value
*BMD spine (g/cm^2)	0.745 (0.639-0.958)	0.870 (0.722-0.988)	***0.020
**BMD neck of femur (g/cm^2)	0.693 ± 0.135	0.716 ± 0.126	0.433
**BMD total hip (g/cm^2)	0.877 ± 0.168	0.878 ± 0.163	0.977

Results expressed as *median and interquartile range or **mean ± standard deviation. ***Statistical analysis with Mann Whitney U test.

BMD: bone mineral density; VF: vertebral fracture.

Discussion

This is a first study to assess the prevalence of morphometric VFs in a predominantly Indian and African cohort and in both men and women in SA.

South Africa has a unique multi-ethnic population, in whom risk factors and disease profile may vary significantly. Earlier studies suggested that African subjects had a ten-fold lower incidence of hip fractures [28] and a lower prevalence of morphometric abnormalities of the lumbar spine than Whites [18], but no data is available for Indians.

In this study, morphometric VF were present in 20.8% of subjects aged 60 years and over, which is consistent with the international published literature which showed prevalence rates of between 20 -23% [8,9,29,30]. None of the subjects had previously been investigated or treated for osteoporosis.

The higher, albeit non-significant, prevalence of VF in women compared to men (23% vs 13%) is similar to that found in a multicentre European Vertebral Osteoporosis Study (EVOS) involving 19 countries, in which the prevalence of VFs in women was 20.2% and 12.2% in men [29]. Similarly, a prevalence of 25.6% has been reported in post-menopausal Moroccan [12] and Lebanese women (19.9%) [13]. In contrast however, a lower prevalence of VFs has been reported in African (9.1%) and White (5.0%) premenopausal and postmenopausal women

in Cape Town [18] and post-menopausal women from the Democratic Republic of Congo (DRC) (11.2%) [14]. The inclusion of younger premenopausal women and the exclusion of women on hormone replacement therapy in the Cape Town study could explain the lower prevalence. Whilst the DRC study enrolled only postmenopausal women, and their average age was 57 years [14], our study median age was 72 years, but we only included subjects 60 years and over in the primary study. In all these studies, the prevalence of VFs increases with age; similarly in our study the highest prevalence was seen in those over the age of 80 years old.

The lower prevalence in men is consistent with international studies [8,9,29,30] and can be explained by the higher bone mass in men and the absence of an abrupt and accelerated bone loss that occurs in women at the menopause. However, a slightly higher prevalence of morphometric VFs has been reported in men (18.8%) compared to women (17.1%) in India [9], and a recent study reported a prevalence of 29.5% in men [31]. In the latter study, the use of lateral vertebral assessment on DXA rather than lateral radiographs may have overestimated VF. Alternatively, Indian men may be particularly at risk for VFs.

Interestingly, in our study the prevalence of VFs was higher, although not statistically different, in African subjects compared to Indian subjects (23.4% and 17.4% respectively), which is contrary to the general belief that Africans have lower rates of VFs. There is no national study comparing the prevalence of VFs in the different ethnic groups in SA, however, ethnic differences have been noted in the US where Hispanic women had the highest risk for fractures, followed by Native American, Black and Asian American who had lowest risk of fractures [32].

Of the several clinical risk factors for osteoporotic fractures, subjects with VFs were older and had a lower BMD at spine than subjects without VFs. Both advancing age and low BMD are established risk factors for fragility fractures [33,34]. Bone mass is one of the most significant determinants of bone strength and has an inverse relationship with the risk of fragility fractures [35]. The risk of VFs increases 1.5 – 3 times for each one standard deviation decrease in BMD [34].

There was however, no association with between low calcium intake, smoking and alcohol use with VFs. Earlier menopause is an established risk factor for osteoporosis and fractures, and it is surprising, that in this study subjects who had a morphometric VF were older at age of menopause than those that did not have a VF. This is difficult to explain, but age of menopause was obtained from recall and may have been erroneous in older women.

Limitations

This study was limited to public sector and therefore did not adequately represent the different ethnic groups due to differences in socio-economic status and utilization of health service providers. The sample size was small with the majority of subjects being either Indians or Africans. The subjects were volunteers and age groups were not equally represented in this study.

Conclusion

Morphometric VFs are common in African and Indian subjects in SA and highlight the need for increasing the awareness and screening for osteoporosis in all South Africans, regardless of ethnicity. Although we did not find any significant risk factor, other than a low BMD at the spine, this may be due to the small sample size and further studies are required to determine a population-based prevalence of VFs in SA to guide screening and management protocols.

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Appendix A: Research Protocol

Title of Study

Risk factors for morphometric vertebral fractures in subjects aged 60 years and over in the eThekwini municipality, KwaZulu - Natal, South Africa.

Aims of the Study

To describe the frequency, and risk factors of morphometric vertebral fractures in subjects aged $\geq$ 60 years.

Specific Objectives

1 To compare demographic profile and clinical risk factors for osteoporosis in subjects with and without morphometric vertebral fractures.

2 To compare bone mineral density measurements in subjects with and without morphometric vertebral fractures.

Abstract

With advancing age, the prevalence of osteoporosis increases. Vertebral fractures (VFs) are the most common osteoporotic or fragility fractures and associated with increased morbidity and mortality. Several risk factors for VFs have been reported in developed countries.

The majority of VFs are silent, and diagnosis is made radiologically. While initially thought to be rare in Africans, limited data suggest a similar incidence in African and White women.

No data is available for Indian men and women. This study is aims to determine the prevalence and risk factors for VF in a multi-ethnic cohort.

Background and Literature Review

Introduction

Osteoporosis is a progressive metabolic skeletal disease characterized by severe bone loss, disruption of skeletal micro architecture, decreased bone strength, and bone quality sufficient to predispose to minimal trauma or atraumatic fractures of the vertebral column, upper femur, distal radius, proximal humours, pubic ramie and ribs [1,2].

Vertebral fractures (VFs) are a common complication of osteoporosis and contribute significantly to the osteoporotic fracture burden [1] accounting for approximately 700 000 of the 1.5 million fractures seen in the United States (US) annually [2]. In contrast to hip fractures, VFs are usually silent with only one third diagnosed clinically [3]. In a multi-national study in post-menopausal women newly diagnosed with osteoporosis, 68% of the subjects had undiagnosed VFs [4].

The majority of VFs usually occur during normal activities, and are therefore asymptomatic, and only 40% occur after a fall [5]. VFs often develop insidiously over time, and multiple fractures may lead to progressive loss of stature and disability [5]. Due to their silent nature, most patients are undiagnosed and not commenced on appropriate treatment [6].

Vertebral fractures can lead to loss of vertebral body height and progressive kyphosis [7]. The resultant reduction in volume of the thoracic and abdominal cavities leads to reduced pulmonary function, constipation, bowel obstruction, prolonged inactivity, deep venous thrombosis, progressive muscle weakness, increased risk of pneumonia and restrictive lung disease [8]. Overall function declines, and patients may lose their ability to live in independently. The impact on quality of life can be profound as a result of loss of self-esteem, distorted body image and depression [7].

Treatment of VF includes pain control medications to facilitate mobility and avoid prolonged bed rest, therapeutic exercises that can reduce pain and strengthen muscles, as well as preserving everyday functioning and quality of life, and finally vertebral augmentation procedure should be considered when patients have unremitting pain, or where the spinal deformity is extremely severe [3,5].

Although the epidemiology and risk factors for VFs are well established in developed countries there are limited studies on VFs from Africa or SA.

Definition of Osteoporosis

The World Health Organization (WHO) in 1994 defined osteoporosis as "a systemic bone disease characterized by a decreased bone mass and a deterioration of bone microarchitecture resulting in an increased fracture risk" [9]. The National Institute of Health in 2001 defined osteoporosis as "a disease of compromised bone strength, resulting in an increased risk of fracture" [10]. Both definitions emphasize that osteoporosis is not merely a disease but also risk factor for fractures [2].

Both bone mass and quality contribute to bone strength, however there are no direct means to assess bone quality [6]. Bone mass which contributes to 70% of bone strength is measured as bone mineral density (BMD) at the hip or lumbar spine [1,11]. The WHO defines osteoporosis as a BMD of greater than 2,5 standard deviations below the young normal adult reference population, also known as T score [9].

TABLE 1

DEFINITION OF OSTEOPOROSIS BASED ON BONE MINERAL DENSITY T-SCORES AND FRAGILITY FRACTURES

Bone Density Category	T-Score
Normal	>1.0
Low bone density (osteopenia)	-1.0 to -2.5
Osteoporosis	>2.5
Severe or established osteoporosis	>2.5 and 1 or more fragility fractures

Note. Adapted from Kanis, Melton, Christiansen, Johnston, & Khaltaev (1994).

Epidemiology

Worldwide, osteoporosis causes about 8.9 million fractures annually, resulting in one osteoporotic fracture every 3 seconds [12]. Most fractures in the elderly are related to osteoporosis and it is estimated that more than 40% of postmenopausal women, and approximately 25% to 33% of men will eventually experience osteoporotic fractures during their lifetime [13].

Vertebral fractures due to osteoporosis are common with one VF occurring every 22 seconds worldwide in men and women over age 50 years [14]. A 50-year-old Caucasian woman's estimated lifetime risk of sustaining an osteoporotic vertebral fracture is 16%. In comparison, the estimated lifetime fracture risk for 50-year-old Caucasian men is 5% [15].

While the prevalence of VF in men was higher at an earlier age in the Canadian Multicentre Osteoporosis Study (CaMoS) and European Vertebral Osteoporosis Study (EVOS) studies, the prevalence did not increase with age in men, as it did in women [16,17]. Possible explanations are that men may suffer trauma earlier in working life more than women, and that they have a more stable bone mass compared to women who experience the more rapid peri-menopausal bone loss [16,17].

In Delhi, the prevalence of radiographic VF in older population is similar to Western population, at about 17.9% [18]. A similar prevalence was reported in Chinese subjects aged 50 years and over, 15%, which rose to 36 - 59% in subjects older than 80 years [19].

There are few studies on prevalence of osteoporosis and vertebral fractures from Africa. Sellami et al reported osteoporotic fractures in 1311 Tunisian postmenopausal women, 16% of whom presented with a fracture. Vertebral fractures accounted for 59,8% of all these fractures [20]. In a study cohort of 328 Moroccan women with a mean age of 65 years, VFs were reported in 25,6% of subjects, using VF assessment [21].

There are few studies on prevalence VFs from SA, and an early multi-ethnic study in 1968 by Dent et al showed an increase prevalence of morphometric VFs in White South African compared to urbanized and rural Black women [22]. Nevertheless, this study was mainly based on the visual assessment of lumbar spine on lateral X-rays, there were scanty information on the reason of the admissions and therefore subjects with secondary causes of osteoporosis were not necessarily excluded from the study.

Pathophysiology of osteoporosis and osteoporotic fractures

There are two main types of bone; cortical bone which makes up 80% of adult bone mass and trabecular bone which accounts for 20% of bone mass [23].

Bone is metabolically active tissue and undergoes remodelling which is a continuous process of resorption and renewal of bone because of the coupled action of bone resorbing cells (osteoclasts) and bone forming cells (osteoblasts) [24]. Any process which increases the rates of remodelling can lead to a net loss of bone over time and increase risk of fragility fractures [25].

Peak bone mass (PBM) is achieved by the age 25 to 30 years and bone mass slowly decreases thereafter [26]. Failure to achieve PBM contributes to the risk of developing osteoporosis later in life [26,27]. Aging and loss of gonadal function are two of the most important mechanisms that predispose to significant bone loss [28].

Risk factors

1. Gender and age

the prevalence of radiological VFs increases with age and is similar in men as in women at 12% [16]. The risk of sustaining one osteoporotic VF increases with age, from 5 - 10% in White women aged 50 - 54 years old to 30% - 50% in women aged 80 - 84 years old [29]. The prevalence of VFs in EVOS study involving 19 countries, was higher in women compared to men 20.2% and 12.2% respectively [16]. Delhi Vertebral Osteoporosis Study (DeVOS) showed similar prevalence rates of VFs in Indian women and men at 17.9% [18].

2. Weight and height

In early adulthood, weight is an important determination of PBM, and persons who are overweight in young age may be at an advantage regarding bone mass in older age [30]. In the general population, epidemiological data show that increased body weight and body mass index (BMI) are positively correlated with high BMD and lower prevalence of VF [31]. There is positive correlation between height and vertebral fractures [26].

3.-Bone mineral density

Bone mineral density is the most significant determinant of bone strength and mechanical resistance [32] The risk of VFs increases 1.5 – 3 times for each one SD decrease from the mean BMD [33].

4. Previous fractures

Previous fractures are associated with a significantly increased risk of an osteoporotic fracture at all ages with or without adjustment for BMD [34]. An individual with a prevalent vertebral fracture has a fivefold increased risk of a future fracture [35].

5. Genetic and hormonal factors

In addition, genetic predisposition and hormonal factors (age of menarche and menopause onset) play a significant role [36].

Diagnosis of Vertebral Fractures

Vertebral fracture can be diagnosed clinically or radiologically based on visual assessment of X-ray. There are several methods of radiographic assessment. However, the most commonly

used is Harry Genant's classification [37]. This approach is based on semi quantitative evaluation of the extent of a vertebral height reduction and morphological change of vertebral bodies on conventional radiographs [38]. A VF is diagnosed when the reduction of height in the anterior, middle or posterior dimension of vertebral body exceeds 20%. The fracture is considered mild (grade 1) when there is 20 – 25 % decrease in anterior, middle and / or posterior height), moderate fracture (grade 2) when approximately 25 – 40% height reduction and severe (grade 3) if there is 40% or greater reduction in height of the vertebral body (Figure 1) [38].

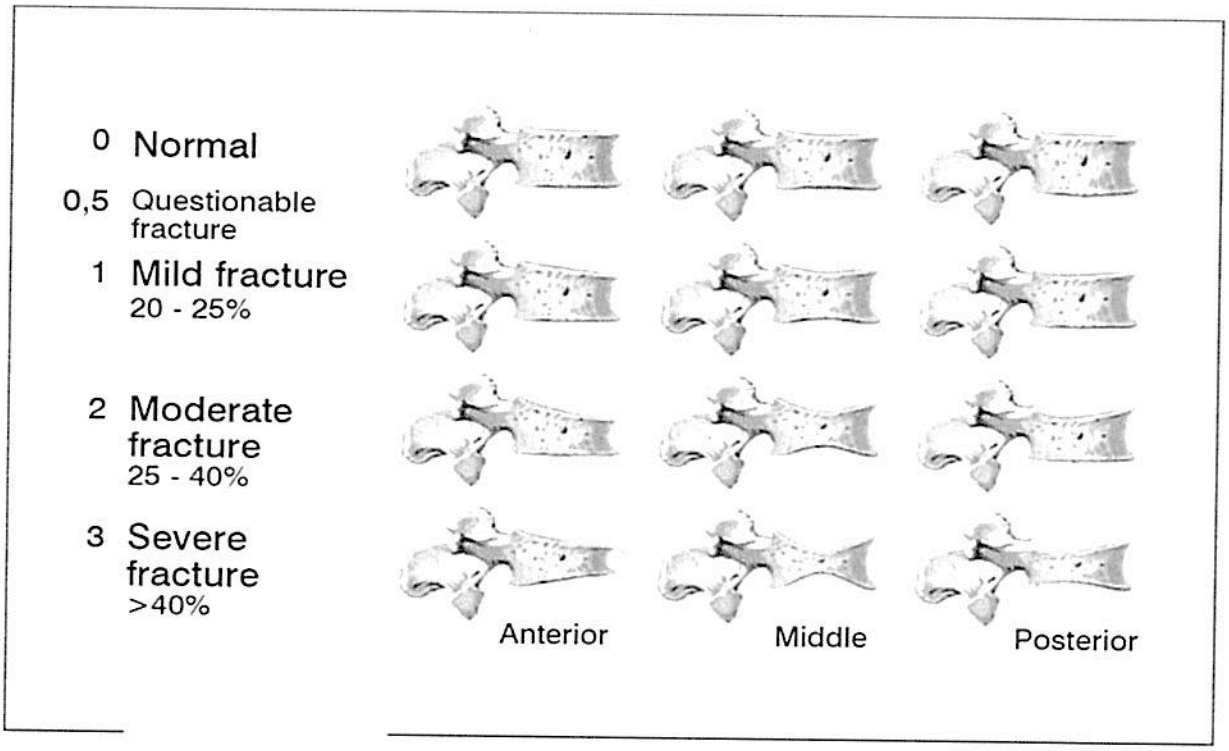

Figure 1: Genant method of Vertical Fracture assessment.

Note: Adopted from Genant et al.1993 [38].

Performing of conventional radiographs in asymptomatic osteoporotic patients can expose them to radiation and increase the cost of diagnosis of VF [39]. On the other hand, the introduction of DXA (dual - energy X-ray absorptiometry) into clinical practice has revolutionized the diagnosis of osteoporotic fracture [11]. It allows accurate measurement of bone density, and visual and morphometric assessment of spine, which increase the sensitivity of diagnosis of VF [40]. The advantages of using DXA system over conventional X ray devices are, it minimizes the radiation exposure, high speed image acquisition and allows combined evaluation of vertebral fracture status and bone mass density, which eventually reduce the cost of diagnosis [41].

Methodology

Study Justification

As a result of improved public health and health care services including the introduction of antiretroviral therapy for patients for Human Immunodeficiency Virus infection, life expectancy in SA has improved. Therefore, as the population ages, non - communicable diseases including osteoporosis and in particular VFs will have an important impact on the disease spectrum, mortality and morbidity.

VFs have recently been shown to be more common in Africans than previously thought, with a similar prevalence to Whites. This study finding will highlight the need for an increased awareness of osteoporosis, screening and management protocols in all ethnic groups in South Africa.

Study design

This is a descriptive study using historical data collected of control group in a primary longitudinal study.

The primary study is 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. It was conducted in the public health sector of eThekwini area, Kwa-Zulu Natal (KZN), South Africa. The original study was approved by UKZN, BREC approval number: **BF043/09,** and currently still certified. it was conducted during the period to August 2010 to May 2013.

Study location

The primary study was conducted in the eThekwini city which is the largest city in KZN and has a mixed ethnic group of 3 468 087 individuals. Of these 236 035 persons (6.9%) are 60 years and over, 144 587 aged between 60 to 69 years and 91 448 above the age of 70 years [42].

Study Population

This study is using historical data of the control subjects on two hundred volunteer subjects aged 60 years and older from the primary study (control group), with no previous history of osteoporosis or hip fractures will be analysed. These subjects were recruited from the hospital's

outpatient departments, by word of mouth and through local community centres for the aged in the defined geographic area during the period August 2010 to May 2013. The control subjects had signed informed consent in the primary study.

No additional patients will be recruited for this study nor any further contact made with enrolled subjects. No further laboratory tests will be done and although blood tests were conducted in the primary study, those results will not be analysed in this study.

Sample size

The original sample size was calculated to determine hip fracture incidence in the defined area. This was based on the prevalence of osteoporotic risk factors; age, gender, ethnicity, a known diagnosis of osteoporosis, previous osteoporotic fractures and family history of fractures.

Inclusion and exclusion criteria

The ability to give informed consent.

No previous history of osteoporosis or hip fractures.

Materials and methods

This study is using historical data of the control subjects on two hundred volunteer subjects aged 60 years and older from the primary study (control group), with no previous history of osteoporosis or hip fractures will be analysed. In the primary study questionnaires were available in both English and IsiZulu and data was collected after informed consent was obtained. The questionnaire included demographic details and clinical risk factors for osteoporosis. All subjects had vertebral radiographs and a bone mineral density test using DXA scanner.

Clinical risk factors for osteoporosis

The osteoporosis risk factor assessment in this study was based on traditional risk factors for osteoporosis including those determined by the FRAX®, which has been validated in many studies.

In the primary study risk factors for hip fracture were analysed. The VFs in the primary study were only documented. However, risk factors for those with VFs were not studied. In this study,

we are now going to analyse this data to see what the risk factors for VFs in subjects who are aged 60 or over.

Therefore, the factors used in predicting fracture risk included:

• Gynaecological history:

Age of menarche and age of menopause.

Use of HRT: Age at which commenced use, duration and side effects of HRT.

Parity.

• Family history:

Family history of osteoporosis, and maternal history of fractures were recorded.

• Smoking history:

The WHO Monitoring Trends and Determinants in Cardiovascular disease scale (MONICA scale), an internationally validated questionnaire was used in the primary study [43].

• Alcohol use:

A self-report scale validated in The Danish Health and Morbidity Survey was used [44].

• Calcium intake: The IOF Calcium Intake Diary was used to record and calculate the dietary calcium intake [45].

Lifestyle factors:

• Illicit drug use, caffeine intake and sunlight exposure were reported.

• Activity level (self-reported) based on their daily activities.

Radiological assessment

The plain radiographs and bone mineral density had been already done in the primary study in the volunteers (the control group). These results will be assessed in this study with regard VFs.

1. Plain radiographs

Antero-posterior (AP) and lateral radiographic views of the thoracic and lumbar spine were acquired using a standardized protocol in 197 control participants on the day of enrolment. All x-rays were reported by a single blinded experienced radiologist. Thoracic and lumbar vertebrae were deemed abnormal (morphometric fracture) using the semi-quantitative Genant method i.e. a reduce in height of the vertebra >20% in its anterior, middle or posterior section compared to its own or nearest intact posterior vertebra [38]. 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 [38]. The Genant method has been validated in many studies including Study of Osteoporotic Fractures (SOF) and correlates with clinical measurements of height loss, age, back pain, and baseline BMD [46].

2.Bone mineral density

Bone mineral density measurements at the hip and spine were obtained using the Hologic Discovery A densitometer. A spine phantom was scanned weekly to determine the coefficient of variation, which was <1.5%.

Statistical Analysis

The data were analysed using IBM® SPSS®25. The significance for all tests was set at $p < 0.05$. For descriptive data, means and standard deviations or median and interquartile range, depending on the distribution of the data, were used. Demographic characteristics were expressed as frequencies and percentages. To compare variables inferential statistics were applied including the Student's t test or the Mann Whitney U test for numerical variables, Chi square test for categorical variables and the Fisher's exact test, where frequencies were small.

Limitations

This study was limited to public sector and therefore did not adequately represent the different ethnic groups due to differences in socio-economic status and utilization of health service providers. The sample size was small with the majority of subjects being either Indians or Africans. The subjects were volunteers and age groups were not equally represented in this study.

Ethical Considerations

As mentioned before this study is using historical data of the control subjects from primary study and there will be no new recruits. All subjects who participated in the original study have signed informed consent in their preferred language (Zulu or English.) The original study has been approved by the KwaZulu Natal Department of Health and BREC (**BF043/09**). Permission has been obtained from Dr Paruk to make use of the data. This study has also received approval from the KwaZulu Natal Department of Health and BREC **(BE612/16).**

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Appendix B: Author guidelines for Osteoporosis International Journal

Manuscript submission

Manuscript Submission

Submission of a manuscript implies: that the work described has not been published before; that it is not under consideration for publication anywhere else; that its publication has been approved by all co-authors, if any, as well as by the responsible authorities – tacitly or explicitly – at the institute where the work has been carried out. The publisher will not be held legally responsible should there be any claims for compensation.

Title page

The title page should include:

- The name(s) of the author(s)
- A concise and informative title
- The affiliation(s) and address(es) of the author(s)
- The e-mail address, and telephone number(s) of the corresponding author
- If available, the 16-digit ORCID of the author(s)

Abstract

Please provide a structured abstract of 150 to 250 words which should be divided into the following sections:

- Purpose (stating the main purposes and research question)
- Methods
- Results
- Conclusions

Keywords

Please provide 4 to 6 keywords which can be used for indexing purposes.

Text

Text Formatting

Manuscripts should be submitted in Word.

• Use a normal, plain font (e.g., 10-point Times Roman) for text.

• Use italics for emphasis.

• Use the automatic page numbering function to number the pages.

• Do not use field functions.

• Use tab stops or other commands for indents, not the space bar.

• Use the table function, not spreadsheets, to make tables.

• Use the equation editor or MathType for equations.

• Save your file in docx format (Word 2007 or higher) or doc format (older Word versions).

Headings

Please use no more than three levels of displayed headings.

Abbreviations

Abbreviations should be defined at first mention and used consistently thereafter.

Footnotes

Footnotes can be used to give additional information, which may include the citation of a reference included in the reference list. They should not consist solely of a reference citation, and they should never include the bibliographic details of a reference. They should also not contain any figures or tables.

Footnotes to the text are numbered consecutively; those to tables should be indicated by superscript lower-case letters (or asterisks for significance values and other statistical data).

Footnotes to the title or the authors of the article are not given reference symbols.

Always use footnotes instead of endnotes.

Acknowledgments

Acknowledgments of people, grants, funds, etc. should be placed in a separate section on the title page. The names of funding organizations should be written in full.

Text formatting

• Introduction: Develop the study rationale and avoid a literature review. Literature should be cited only to the extent that it helps the reader understand why the question is asked. End the introduction with a stated aim or question, preferably expressed as a testable hypothesis. For example, if the study is aimed at identifying the colour of apples, or asks what colour are apples, state "we hypothesized that apples will be green rather than red". The reason for this hypothesis should be contained in the rationale.

• Methods: The methods section should describe the procedures used and provide sufficient information (subjects, measurements, statistical analyses) so that a reader can evaluate the credibility of results and interpretation in the light of possible methodological limitations. Findings should be quantified when possible, and presented with appropriate indicators of measurement error or uncertainty, e.g. confidence intervals.

The source or manufacturer name of all products used should be stated.

Authors should always consider clarity for other workers about how and why a study was in a particular way.

• Results: Results concerning the primary testable hypothesis should be presented first. Do not save the" best" for last. For example, if the main aim is to assess anti-fracture efficacy present these data first and surrogates (BMD or biochemical markers) later. Data should be presented as concisely as possible, if appropriate, in the form of tables and/or graphs, although very large tables should be avoided.

If authors wish to present the full data of the study and any technical details, these can be included as Electronic Supplementary Material.

• Discussion: The following paragraph structure is recommended:

• A summary of the main findings from most to least important including a statement whether the results are consistent with the stated hypothesis.

• Discuss how these results confirm or contrast with the published literature.

• If the results differ, discuss the possible reasons for this. Details of methodology and results of published literature may be appropriate here. Avoid reviewing the literature outside the scope of the study.

• Discuss the significance and implications of this new data. Having developed the rationale to define the limits of current knowledge, how does this new information advance understanding?

• Write a paragraph concerning the limitations of the study. This is critical. The inferences made throughout the Discussion must be written bearing in mind the constraints of the methodological limitations of the work. Papers written without this section will not be considered for publication.

• Summarize and Conclude: The conclusion is an inference. Within the constraints of the limitations of the study, the authors may boldly speculate regarding the

significance of the findings and future research.

References

Citation

Reference citations in the text should be identified by numbers in square brackets. Some examples:

1. Negotiation research spans many disciplines [3].

2. This result was later contradicted by Becker and Seligman [5].

3. This effect has been widely studied [1-3, 7].

Reference list

The list of references should only include works that are cited in the text and that have been published or accepted for publication. Personal communications and unpublished works should only be mentioned in the text. Do not use footnotes or endnotes as a substitute for a reference list.

The entries in the list should be numbered consecutively.

Disclosure of potential conflict of interests

Authors must disclose all relationships or interests that could influence or bias the work. Although an author may not feel there are conflicts, disclosure of relationships and interests affords a more transparent process, leading to an accurate and objective assessment of the work.

Appendix C: Ethical approval

Biomedical Research Ethics Committee (BREC):

UNIVERSITY OF
KWAZULU-NATAL
INYUVESI
YAKWAZULU-NATALI
RESEARCH OFFICE
Biomedical Research Ethics Administration
Westville Campus, Govan Mbeki Building
Private Bag X54001
Durban
4000
KwaZulu-Natal, SOUTH AFRICA
Tel: 27 31 2604769 - Fax: 27 31 2604609
Email: BREC@ukzn.ac.za
Website http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx

17 May 2019

Dr MA Esaadi (214585526)
Discipline of Internal Medicine
School of Clinical Medicine
mohlesaadi@gmail.com

Dear Dr Esaadi

Protocol: Risk factors for morphometric vertebral fractures in subjects aged 60 years and over in the eThekwini municipality, KwaZulu-Natal, South Africa.
Degree: MMed
BREC reference number: BE612/16

RECERTIFICATION APPLICATION APPROVAL NOTICE

Approved:	20 January 2019
Expiration of Ethical Approval:	19 January 2020

I wish to advise you that your application for Recertification received on 18 April 2019 for the above protocol has been noted and approved by a sub-committee of the Biomedical Research Ethics Committee (BREC) for another approval period. The start and end dates of this period are indicated above.

If any modifications or adverse events occur in the project before your next scheduled review, you must submit them to BREC for review. Except in emergency situations, no change to the protocol may be implemented until you have received written BREC approval for the change.

The committee will be notified of the above approval at its next meeting to be held on 11 June 2019.

Yours sincerely

Prof V Rambiritch
Chair: Biomedical Research Ethics Committee

cc Supervisor: essdma@ukzn.ac.za postgraduate administrator: janitjes@ukzn.ac.za

Appendix. D: Study 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)_____

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

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					
Desserts						
Cheesecake, fruit	average slice, 120 g / 94 mg					
Custard made with milk	average portion,					

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
	120 g / 166 mg					

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 E: Turnitin Report

Risk factors for morphometric vertebral fractures in subjects aged 60 years and over in the eThekwini Municipality, KwaZulu-Natal, South Africa

ORIGINALITY REPORT

56%	45%	38%	43%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	Submitted to University of KwaZulu-Natal Student Paper	7%
2	link.springer.com Internet Source	3%
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