The clinical characteristics, complications and treatment outcomes of patients with osteoporosis at Groote Schuur Hospital

by

Omer Alawad Homaida Abdelfadiel

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Supervisor:

Associate Professor JA Dave

Division of Endocrinology

Groote Schuur Hospital

Department of Medicine

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DECLARATION

I, *Omer Abdelfadiel*, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.
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Date: 01/02/2021

SUPERVISOR

This study was conducted from March 2019 to March 2020 under the supervision of Associate Prof JA Dave, Division of Endocrinology, Medicine, University of Cape Town.

As a candidate Supervisor, I have approved this dissertation for submission.

Name: Joel Dave

Signed: Signature Removed

Date: 03 February 2021

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ABBREVIATIONS

ARCH	Active-contRolled fraCture study in postmenopausal women with osteoporosis at High risk
ART	Antiretroviral therapy
AFF	Atypical femoral fractures
BMD	Bone mineral density
BMI	Body mass index
CAD	Coronary artery disease
Cbfa1	Core-binding factor alpha 1
CI	Confidence interval
CKD	Chronic kidney disease
COPD	Chronic obstructive pulmonary disease
CTX-1	C-telopeptide crosslink of type 1 collagen
CVA	Cerebrovascular accident
DEXA	Dual energy x-ray absorptiometry
EMA	European Medicines Agency
FDA	Food and drug administration
FRAME	FRActure study in postmenopausal woMen with ostEoporosis
FRAX	Fracture Risk Assessment tool
FREEDOM	Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months
GSH	Groote Schuur Hospital
HIV	Human immunodeficiency virus
HORIZON	Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly
IBD	Inflammatory bowel disease
IGF-1	Insulin growth factor 1
IHD	Ischemic heart disease
IL-1	Interleukin 1
IL-6	Interleukin 6
IOF	International osteoporosis foundation
IU	International unit

IV	Intravenous
MI	Myocardial infarction
NOF	National osteoporosis foundation
NOFSA	National osteoporosis of South Africa
NTX-1	N-telopeptide crosslink of type 1 collagen
ONJ	Osteonecrosis of the jaw
OPG	Osteoprotegerin
PEPI	Postmenopausal Estrogen/Progestin Interventions
P1NP	Procollagen type 1 N-terminal propeptide
P1CP	Procollagen type 1 C-terminal propeptide
PPI	Proton pump inhibitor
PROOF	Prevent Recurrence of Osteoporotic Fractures
RA	Rheumatoid arthritis
RANK	Receptor activator of nuclear factor kappa B
RANKL	Receptor activator of nuclear factor kappa B- ligand
RR	Relative risk
Runx2	Runt-related transcription factor 2
SA	South Africa
SD	Standard Deviation
Sp7	Specificity protein transcription factor 7
SSRI	Selective serotonin uptake inhibitor
TB	Tuberculosis
TGF-β	Transforming growth factor beta
UCT	University of Cape Town
UCTHREC	UCT Human Research Ethics Committee
US	United States
USPTEF	United States preventive services task force
VTE	Venous thromboembolism
WHI	Women’s health initiative
WHO	World health organisation
Wnt	Wingless-related integration site
ZA	Zoledronic acid

CHAPTER 1

1. LITERATURE REVIEW

1.1 Introduction

Osteoporosis is a systemic skeletal disease characterised by low bone mass and microarchitectural deterioration of bone tissue, with subsequent increased bone fragility and vulnerability to fracture (1). Fragility or low trauma fractures are fractures that result from minimal trauma, such as a fall from a standing height or less.
Typical sites for fragility fracture are the vertebrae, hip and distal forearm; though other sites, including the upper arm, pelvis, ribs and clavicle may be involved (2).

1.2 Physiology of Bone

The skeleton has locomotive and structural functions, and it serves as a reservoir of calcium and phosphate essential for homeostasis maintenance (3). It consists of 80 percent cortical bone and a minimum of 20 percent trabecular bone (4). Skeletal sites determine cortical to trabecular bone ratios. The vertebra is made of a 25:75 ratio of cortical to trabecular bone. The ratio in the femoral head is 50:50 and in the radial diaphysis is 95:5 (5).
Bone turnover is a lifelong process carried out by osteoclasts and osteoblasts. It incorporates growth, modelling and remodelling to repair microdamage and access to the mineral reservoir (3).
Bone remodelling is coordinated to preserve a balance between the amount of bone formed and the amount resorbed. Basic multicellular units (BMUs) carry out bone remodelling and consist of osteoblasts, osteoclasts, cells in the bone lining and osteocytes (4). The remodelling cycle comprises three sequential phases: resorption, during which osteoclasts digest old bone; reversal, when mononuclear cells emerge on the bone surface; and formation when osteoblasts lay down new bone to replace the resorbed bone completely (5).
Bone resorption: Osteoclast formation, differentiation and activation are regulated by the ratio of RANKL to osteoprotegerin, IL-1 and IL-6, colony-stimulating factor (CSF), PTH, 1,25-dihydroxy vitamin D, and calcitonin (6), (7). The osteoclasts in the resorbing compartment secrete hydrogen ions using cell membrane H^+-ATPase pumps and chloride channels to reduce the pH to as low as 4.5, thus helping to mobilise bone

mineral (8). Resorbing osteoclasts secrete tartrate-resistant phosphatase acid, cathepsin K, matrix metalloproteinase 9, and cytoplasmic lysosomal gelatinase to digest the organic matrix (9).

Osteoblasts express RANKL that binds its receptor, RANK, on the osteoclasts surface and their precursors. RANK activation stimulates differentiation, activation and survival of osteoclasts (10). Osteoprotegerin, a glycoprotein secreted by osteoblasts, inhibits bone resorption by binding to RANKL and preventing it from attaching to its receptor, RANK (11).

Bone formation: Osteoblasts arise from mesenchymal stem cells in the stroma of the bone marrow and are responsible for the synthesis and subsequent mineralisation of bone matrix (12). Bone morphogenetic proteins (BMPs), TGF-β, PTH, and WNTs are amongst the cytokines involved in osteoblast differentiation (13). Runx2 / Cbfa1 (14) and Osterix/ Sp7 (15) are crucial regulators of bone formation involved both in endochondral and intramembrane ossification. Upon recruitment into to the reabsorbed area, osteoblasts produce the new, initially uncalcified (osteoid) bone matrix and then promote (facilitate) its mineralisation, thus (thereby) completing the cycle of bone remodelling (16).

The Wnt/β-catenin signalling pathway plays an important role in the osteoblasts differentiation and proliferation (17). Activation of Wnt/β-catenin signalling occurs by binding of Wnt to the low-density lipoprotein receptor protein 5/6 (LRP5/6) and the Frizzled co-receptor. The receptor complex prevents the phosphorylation and degradation of β-catenin resulting in cytoplasmic accumulation and subsequent nuclear translocation of β-catenin (18). Upon translocation into the nucleus, β-catenin regulates osteoblasts gene transcription (19).

Sclerostin, a glycoprotein produced by osteocytes, inhibits bone formation by exerting antagonistic effect on Wnt/β-catenin signalling pathway. It acts by binding LRP5/6, displacing the Wnt proteins, and leading to dissociation of the LRP5/6 and Frizzled receptor complexes (20).

Peak bone mass, defined as the most substantial amount of bone that an individual can achieve, is an essential determinant of risk for an osteoporotic fracture (21). The age at which PBM is reached varies by sex and skeletal site; Lumbar spine PBM occurs at ages 33 to 40 years in females and 19 to 33 years in males, while total hip PBM occurs at ages 16 to 19 years in females and 19 to 21 years in males (22). Several factors impact the acquisition of peak bone mass during growth. These factors

include genetics, vitamin D, calcium, protein, sex steroids, IGF-1, physical activity and body weight (23).

1.3 Diagnosis of osteoporosis

The WHO describes osteoporosis as a bone mineral density (BMD) measured by Dual Energy X-ray Absorptiometry (DEXA scan) at hip or spine of 2.5 standard deviations (SD) or more below the mean for a young adult woman. Other categories as per WHO classification include (24), (25):

- Normal: T-score at -1.0 SD and above.
- Osteopaenia: T-score between – 1.0 and < 2.5 SD.
- Severe osteoporosis: T-score at or below −2.5 with one or more fractures.

In clinical practice, osteoporosis can also be diagnosed with the presence of a fragility fracture in postmenopausal women or men over the age of 50 with or without BMD measurement (26).

Despite BMD measurement remains the most useful tool for diagnosis of osteoporosis and determining fracture risk, it has some limitations. These limitations include:

- Technical factors can affect BMD measurements made by DEXA scan. Falsely elevated BMD is commonly caused by vertebral disease, such as osteoarthritic spondylosis, osteophytes, scoliosis, or vertebral fracture, as well as extrinsic artefacts from calcifications and surgical metalwork. Incorrect positioning can also affect BMD accuracy (27).
- A single BMD measurement has a high specificity (±85%) for predicting fracture risk, but it lacks sensitivity, with less than half of patients with a known osteoporotic fracture having a BMD value in the osteoporotic range (i.e. T-score ≤ -2.5) (28).
- A low BMD can also be caused by metabolic bone diseases other than osteoporosis (e.g. osteomalacia), which are treated differently than osteoporosis (28).
- DEXA scans produce two-dimensional images of complex three-dimensional structures, and BMD is calculated as the ratio of bone mineral content to bone area. An obvious flaw of this method is that a larger bone may appear to have greater strength, but it may actually have the same BMD as a smaller bone (29).
- BMD alone cannot be used to diagnose osteoporosis in men under the age of 50 (30).

1.4 Epidemiology of Osteoporosis

As the life expectancy is getting longer and society is getting older, the number of new cases of osteoporosis is anticipated to increase significantly worldwide.
Osteoporotic fractures are expected to rise in both men and women by more than three-fold over the next 50 years (31). Annually, osteoporosis causes more than 8.9 million fractures worldwide, and an osteoporotic fracture occurring every three seconds (32).

Osteoporosis in sub-Saharan Africa

Sub-Saharan Africa's population is aging more rapidly than any other region in the world, with projections of 161 million people over 60 by 2050 (33). This aging process with rapid urbanisation are shifting disease burdens across the region, resulting in a higher prevalence of noncommunicable diseases such as osteoporosis (34).
Studies on osteoporosis in sub-Saharan Africa, including South Africa, are scarce and challenged by many factors including paucity of data and limited resources which need to be allocated to more epidemic diseases such as HIV and tuberculosis (TB). The lack of publications of osteoporosis research in sub-Saharan Africa was demonstrated in a recent study published in January 2020 (A call to action for osteoporosis research in sub-Saharan Africa) (35).
In Kenya, Sitati *et al* (2020) reported a prevalence of osteoporosis of 26.4% in a cross-sectional survey of 254 postmenopausal women, with a positive correlation with age, poverty, illiteracy, and underweight (36).
In a 5-year retrospective study conducted in Tanzania in 222 patients who sustained a hip fracture, 75.6% of these fractures were fragility fractures. Over 5 years, the authors observed a 2.34% increase in fragility fractures per year in all included hip fractures (37).
Unlike Afro-Americans, who have significantly higher BMD than their white counterparts, local studies in South Africa have revealed that vertebral BMD in blacks and whites is the same, and vertebral fracture rates appear to be comparable in the black and white populations. Hip BMD values in blacks, on the other hand, are significantly higher (38).
The incidence of hip fractures in black South Africans is the lowest globally, as represented by the study done by Paruk et al. (39). This lower incidence might be explained by the higher femoral BMD in older black South Africans compared with

their white peers, as reported by Conradie et al. (40). Matsela et al. 2017 in a small cohort of 68 black South African women, showed that 11.1% of premenopausal women had osteopenia while 34.4% and 25% of postmenopausal women had osteopenia and osteoporosis, respectively (41).

1.5 Risk factors for osteoporosis and fracture

There are modifiable and non-modifiable risk factors for osteoporosis and fracture (Table I).

Assessment of fracture risk due to osteoporosis was vastly improved in 2008 by the introduction of the FRAX tool by the WHO Collaborating Centre at the University of Sheffield (42). FRAX estimates the 10 year probability of hip fracture and other major osteoporotic fracture (spine, distal forearm, and proximal humerus) by using clinical risk factors, either alone, or in combination with femoral neck BMD (42). These factors include age between 40 and 90 years, female gender, previous osteoporotic fracture, parental history of hip fracture, current smoking, excess alcohol intake (3 or more units/day), glucocorticoids use (7.5 mg or more for 3 months or longer at present or in the past), rheumatoid arthritis, and other secondary causes of osteoporosis (42).

1.6 Screening for Osteoporosis

The US National Osteoporosis Foundation (NOF) recommends BMD testing for women ≥ 65 years old and men ≥ 70 years old. For postmenopausal women and men between the ages of 50 – 69 years, NOF recommends BMD testing based on a risk factor profile (26). The US Preventive Services Task Force (USPTEF) recommends screening with the same NOF criteria for women but doesn't recommend any screening in men (43). The National Osteoporosis Foundation of South Africa (NOSFA) supports a risk factor-based, case-finding strategy, as opposed to population screening (Table II) (28).

Table I: Risk Factors for Osteoporosis

1. Modifiable Risk Factors (44–49)
Smoking
Excess alcohol consumption
Physical inactivity
Low BMI
Reduced intake of calcium,
vitamin D deficiency
Frequent falls
2. Non-modifiable Risk Factors (50–54)
Advanced age
Female sex
White ethnicity
Personal history of fracture
Parental history of fracture
3. Secondary causes (55–66)
Rheumatoid arthritis
Gastrointestinal diseases (e.g. post-gastrectomy state, inflammatory bowel disease (IBD), and celiac disease),
Chronic liver disease
Chronic renal failure
COPD
Endocrine disorders (e.g. Cushing's syndrome, thyrotoxicosis, primary hyperparathyroidism, diabetes, primary or secondary hypogonadism)
Haematological malignancies
HIV
Use of certain drugs (e.g. long term use of glucocorticoids, levothyroxine, anticonvulsants, aromatase inhibitor, heparin, PPI, SSRI).

1.7 Treatment of Osteoporosis

Treatment of osteoporosis is recommended for postmenopausal women and men over the age of 50 years with a hip or vertebral fracture, a T score of ≤ –2.5, or a combination

Table II: Indications for BMD measurement

1. Women ≥ 65 years, and men > 70 years.
2. Known causes of secondary osteoporosis:
• Early menopause (< 45 years of age), prolonged (longer than one year) oligo- or amenorrhoea in premenopausal women, or other causes of hypogonadism in women or men.
• Systemic diseases known to adversely affect bone (Table I).
• Bone-toxic drugs (Table I).
3. Radiographic evidence of vertebral fracture or apparent osteopenia.
4. History of fragility fracture after age 40 years.
5. Presence of strong clinical risk factors:
• Family history of hip fracture or osteoporosis.
• Excessive leanness (BMI < 19 kg/m2).
• Regular alcohol intake (more than two drinks per day).
• Smoking.
• Poor nutrition/calcium intake/Vitamin D exposure.
6. To facilitate decisions regarding drug initiation or discontinuation (e.g. hormone therapy, bisphosphonates).

of osteopenia (T-score between –1 and –2.5) and a FRAX score showing a 10-year probability of a hip fracture of ≥ 3% or a major osteoporotic fracture of ≥ 20% (28), (67).

1.7.1 Lifestyle measures

Increasing the level of physical activity and regular weight-bearing exercise, smoking cessation, decreasing alcohol consumption to ≤2 units per day, reducing the risk of falls and ensuring adequate dietary calcium intake and vitamin D status are the most effective lifestyle measures to improve bone health (68).

Small increases in BMD have been shown by increasing calcium intake, either through the diet or in the form of supplements (69). A calcium intake of 1,000 to 1200 mg per day should be ensured if possible through dietary intake. This dose is shown in a recent meta-analysis to significantly reduce the risk of any fracture by 6% and a hip fracture by 16% (70). If it is not possible, as is the case in South Africa (food

fortification is rare and ample exposure to ultraviolet light is often difficult to achieve), supplementation may be required (28).

Vitamin D when combined with calcium supplementation results in a small reduction in hip and nonvertebral fractures, and possibly also in vertebral fractures (71). A greater effect is noted in individuals with low dietary calcium intake than in those whose dietary intake is high (71). For postmenopausal women and men ≥ 50 years who are at an increased risk of fracture, a daily dosage of 800 IU cholecalciferol is recommended (68). A dose of ≥800 of vitamin D may also reduce the risk of falls (72).

1.7.2 Pharmacological treatment

Prior to commencing pharmacotherapy, patients should be assessed for secondary causes of osteoporosis and have their BMD measured by DEXA, when available, and vertebral imaging studies when appropriate.

Pharmacologic agents used for the treatment and prevention of osteoporosis are classified into two main categories: 1. Antiresorptives (i.e., inhibiting osteoclast-mediated bone resorption) 2. Anabolics (i.e., stimulating osteoblasts to form new bone).

1.7.2.1 Antiresorptive agents

1.7.2.1.1 Bisphosphonates

Bisphosphonates are the most widely used pharmacological agents for the prevention and treatment of osteoporosis (73). They strongly bind to calcium crystals and inhibit osteoclastic bone resorption by causing apoptosis of osteoclasts or interfering with specific intracellular pathways in those cells (74).

Bisphosphonates registered for the treatment of osteoporosis in South Africa include oral alendronate (daily and weekly), oral risedronate (weekly and monthly), ibandronate which is available as a three-monthly IV injection and monthly oral tablets, and zoledronate, which is given as an annual IV infusion (28).

Several randomised placebo-controlled clinical trials have shown that bisphosphonates decrease fracture risk in postmenopausal women and men with osteoporosis (75).

Zoledronic acid is the most potent bisphosphonate available. It is given as 5 mg once-yearly intravenous infusion over a period of at least 15 - 30 minutes (76). It is more convenient and an alternative option for patients who cannot tolerate oral bisphosphonates or who have adherence issue.

The HORIZON Pivotal Fracture Trial showed that once-yearly infusion of zoledronic acid over three year period compared to placebo decreased the risk of hip fracture, nonvertebral fractures, any clinical fractures, and clinical vertebral fractures by 41% (P=0.002), 25% (P<0.001), 33%(P<0.001), and 77% (P<0.001), respectively, over a 3-year period. There was also significant increment in BMD at the total hip (6.02%), lumbar spine (6.71%) and femoral neck (5.06%) with zoledronic acid as compared to placebo (P<0.001 for all comparisons) (77).

A meta-analysis of 8 randomised controlled trials including a total of 13,335 patients showed zoledronic acid, compared with placebo, significantly reduced the incidences of nonvertebral fractures (p=0.00), vertebral fractures (p=0.00), and hip fractures (p=0.02) (78). The same meta-analysis revealed significant increment of BMD from baseline at all measured sites (lumbar spine [p=0.00], total hip [p=0.00], femoral neck [p=0.00], and trochanter [p=0.02]) when zoledronic therapy compared to placebo.

Bisphosphonates generally have a good safety profile, but upper gastrointestinal (GI) adverse effects (reflux, esophagitis, oesophageal ulcers) are relatively common with oral preparations, particularly when the patient reclines within 30- 60 minutes after taking the drug (79). A flu-like syndrome characterised by low-grade fever, myalgias, and arthralgias, may occur 24 to 72 hours after an intravenous (IV) bisphosphonate infusion (80). ONJ and AFF are rare but serious adverse events that may occur with the use of bisphosphonates. ONJ has been more commonly reported in cancer patients on higher cumulative doses of bisphosphonates than osteoporotic patients treated with lower doses and AFF with prolonged use of bisphosphonates (median treatment seven years) (81).

After five years of oral bisphosphonate or three years of intravenous bisphosphonate, NOFSA suggests considering drug holiday in patients who are not at high risk for fracture (28). In patients with high risk (e.g., older women, a low hip T-score or high fracture risk score, previous major osteoporotic fracture, or those who fracture on

therapy), continuation of treatment for up to ten years (oral) or six years (intravenous), with periodic evaluation, should be considered (81).

There remain uncertainties about the optimum treatment regimen, namely the effective lowest dose and/or longest dosing interval (82). In a randomized control trial, 180 postmenopausal women were randomized to receive single baseline doses of placebo, or 1 mg, 2.5 mg, or 5 mg zoledronic acid, to investigate the effects of doses of zoledronic acid lower than 5 mg. Every zoledronic acid dose resulted in similar increases in bone density and decreases in bone turnover markers after a year (83). While the effects of the 1 mg dose had been offset/reversed after two years, the 2.5 mg dose showed effects comparable to the 5 mg dose (84). In study by Bolland *et al* (2012), increases in BMD and decreases in bone turnover markers were maintained for at least 5 years after zoledronic acid administration in 43 HIV-infected men randomized to two annual doses of placebo or 4 mg intravenous zoledronic acid (85).

1.7.2.1.2 Oestrogen

Estrogen alone or combined with progestin (in women with an intact uterus) used to be one of the common treatments for postmenopausal osteoporosis (86). Its main action is to inhibit osteoclastic bone resorption. A network meta-analysis assessing the efficacy of estrogen with or without progestin in postmenopausal women with osteoporosis revealed a reduction in the risk of vertebral, hip and nonvertebral fractures of 34%, 29%, and 21%, respectively (87). Three years of estrogen therapy increases spine BMD by 3.5% to 5% and hip BMD by 1.7%, as shown in the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial (88). Due to significant side effects (increased risk of breast cancer, VTE, and CAD) demonstrated by the WHI study, estrogen therapy is now less favourable (89).

1.7.2.1.3 Selective Oestrogen Receptor Modulators (SERMS)

SERMS act as estrogen agonists in bone, reducing bone loss by suppressing bone resorption. Tamoxifen and raloxifene have antagonistic estrogen action on breast, however only; tamoxifen has an agonistic estrogen effect on the uterus and is associated with an increased risk of endometrial cancer with long-term use (90). The FAD approved raloxifene for the prevention and treatment of osteoporosis

in postmenopausal women. In the study conducted by Delmas et al. 1997, raloxifene had a significant increase in BMD in the lumbar spine (2.5%), femoral neck (2%), and full-body (1.9%) (91).
The Multiple Outcomes of Raloxifene Evaluation (MORE) trial showed that treatment with raloxifene 60 or 120 mg/day for three years decreased the risk of vertebral fracture by 30% and 50% in postmenopausal women with osteoporosis, respectively (92).

1.7.2.1.4 Calcitonin

Calcitonin acts by binding osteoclast receptors inhibiting bone resorption. The Salmon calcitonin, is more potent than human calcitonin and is the most widely used. The FDA has approved both nasal and subcutaneous calcitonin for the treatment of postmenopausal osteoporosis. The PROOF study showed that nasal calcitonin at a dose of 200 IU/day decreased vertebral fractures by 33% (93). Endocrine Society guidelines suggest nasal spray calcitonin in postmenopausal osteoporosis who cannot tolerate other antiresorptive and/or anabolic medications.
Calcitonin nasal spray has also been found to be beneficial in decreasing the pain associated with osteoporosis-related vertebral compression fractures and can be used with standard analgesics (94). NOFSA considers the use of calcitonin in the treatment of symptomatic vertebral fracture syndrome not cost-effective and does not recommend it. Salmon calcitonin is often associated with side effects such as nausea, vomiting, and flushing; these side effects are far less frequent with the nasal route (95). Rhinitis and epistaxis may occur with the use of calcitonin nasal spray (96). Although a causal relation between cancer and calcitonin use has been postulated before, a meta-analysis published in Osteoporosis International found that the relationship is weak and causality is unlikely (97).

1.7.2.1.5 Strontium Ranelate

The precise mechanism of action of strontium ranelate is not well understood. One study revealed dual effects for strontium ranelate; stimulating osteoblastic bone formation and inhibiting osteoclastic bone resorption (98). In a 3-year randomised placebo-controlled trial (RPCT), strontium reduced the risk of vertebral fractures by

41% and increased BMD in lumbar spine and femoral neck by 14.4% and 8.3%, respectively (99). It was approved by European Medicines Agency (EMA) in 2004 for treatment of osteoporosis in postmenopausal women. An increased risk of myocardial infarction, venous thromboembolism, and heart failure has been associated with strontium use. The available trial data indicate that the risk of cardiovascular events and VTE outweigh any benefit of strontium in fracture prevention (100). Due to the reported increased risk of cardiac events, EMA published new recommendations for strontium ranelate use in February 2014 (101). These new recommendations include:
- Strontium Ranelate should only be used in men and postmenopausal women with severe osteoporosis when other medications are contraindicated or not tolerated.
- Strontium Ranelate use must be avoided in patients with a history of IHD, peripheral arterial disease, and/or cerebrovascular disease or in patients with uncontrolled hypertension.
NOFSA recommends strontium ranelate as second-line therapy for patients who cannot be treated with other osteoporosis approved medications. Strontium ranelate is currently not approved by the FDA.

1.7.2.1.6 Denosumab

Denosumab is a human monoclonal antibody that binds RANKL and reduces bone resorption by inhibiting osteoclast formation, function and survival (102). The Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM) trial showed that denosumab increased spine BMD by 9.2% and hip BMD by 4.0% (103). A post hoc analysis of the FREEDOM trial and its extension demonstrated an increased risk of multiple vertebral fractures, especially in those with a prior history of vertebral fractures, on cessation of denosumab (104). Therefore, in patients who stop denosumab for any reason, another antiresorptive agent like a bisphosphonate should be initiated without delay.
It is recommended as a 60 mg dose sc every 6 months for men and postmenopausal women with osteoporosis who are at high risk for fracture failed or are not tolerating bisphosphonates, or have advanced renal impairment (105). ONJ and atypical femur fracture are uncommon (106).

1.7.2.2 Anabolic agents

1.7.2.2.1 Teriparatide and abaloparatide

Teriparatide [PTH (1–34)] and abaloparatide (PTH-related protein analogue) are anabolic peptides that increase bone formation and bone mineral density when given intermittently (107). They are recommended for treating osteoporosis in postmenopausal women at high risk for fracture (women with a history of osteoporotic fractures or have multiple risks for fracture) or those who fail or are intolerant to other agents (108). The FDA has also approved teriparatide for osteoporotic men at high risk of fracture (109).

Based on reported cases of osteosarcoma in rats treated with high doses of PTH (1-34) (110), both teriparatide and abaloparatide are given for only up to 2 years and antiresorptive agents should be commenced thereafter to preserve bone density (108).

A meta-analysis has reported that teriparatide decreases the risk of vertebral fractures by 74 % and the risk of nonvertebral fractures by 39% in postmenopausal women (87). In the same meta-analysis reported, a reduction of 87% in the risk of vertebral fractures and a reduction of 46% in the risk of nonvertebral fractures using abaloparatide.

Side effects of teriparatide include dizziness and leg cramps (111), whereas side-effects of abaloparatide include nausea, postural hypotension, dizziness, headache, and palpitations (112). Botha agents can cause mild hypercalcemia (112).

1.7.2.2.2 Romosozumab

Romosozumab is a monoclonal antibody against sclerostin. Binding of romosozumab to sclerostin inhibits its activity and enhances osteoblastic bone formation and bone mineral density increment. (113) The FDA approved romosozumab in April 2019 for postmenopausal women with a history of a fragility fracture or multiple risk factors for a fracture, or those who do not tolerate or fail other osteoporotic therapies. It has not been approved yet for the treatment of osteoporosis in men.

In the FRAME trial, a monthly injection of romosozumab for 12 months reduced the risk of a vertebral fracture by 73% and continued to show a substantial reduction in vertebral fracture (75%) at 2 years after the transition to denosumab (114). The ARCH

study found that 1 year of romosozumab followed by alendronate compared to 2 years of alendronate resulted in a reduction in the risk of vertebral fractures (by 48%), hip fractures (by 38%), and nonvertebral fractures (by 19%) at 24 months (115). Romosozumab is only recommended for one year, and an antiresorptive agent should be started thereafter to maintain bone density. Side effects of romosozumab include an increased frequency of injection site reactions, and CV events (CAD and CVA) (115). Patients with a prior history or at increased risk of MI or stroke should not receive romosozumab.

1.7.3 Monitoring of therapy

Guidelines recommend using a DEXA scan to monitor BMD in patients who are being treated for osteoporosis. The Endocrine Society suggests monitoring BMD by DEXA at the spine and hip every 1 to 3 years to assess the response to treatment (108). The frequency of BMD measurements may be decreased if the BMD appears to reach a plateau (109). Although the evidence for using BMD to monitor treatment response is weak, it does suggest that it can be used for this purpose (116).

Bone turnover markers are an alternative method suggested for monitoring of therapy. The cost, limited availability of DEXA and the delay in detecting changes in BMD after initiation of treatment support the function of bone turnover markers (BTMs) as short-term therapy monitoring tools (117). They include markers of bone formation and bone resorption.

Markers of bone formation are active osteoblast products expressed at various stages of their development and are considered to represent various aspects of osteoblast function and bone formation. They include by-products of collagen synthesis (propeptides of type 1 collagen [C-terminal: P1CP, N-terminal: P1NP]), osteoblast enzymes (total and bone-specific ALP), and matrix proteins (osteocalcin).

Markers of bone resorption are products formed during the bone resorption phase of bone remodelling. They include collagen degradation products (telopeptides of type 1 collagen [C-terminal: CTX-1, N-terminal: NTX-1], hydroxyproline, and pyridinium crosslinks [pyridinoline, deoxypyridinoline]), noncollagenous proteins (bone sialoprotein), osteoclastic enzymes (Tartrate-resistant acid phosphatase, Cathepsin K), and Osteocyte activity markers (RANKL, OPG, sclerostin) (118).

Serum P1NP (as a reference of bone formation) and serum CTX-1 (as a reference of bone resorption) have been suggested by the International Osteoporosis Foundation (IOF) and International Federation of Clinical Chemistry and Laboratory Medicine to be used for assessment of monitoring of treatment (119).

In-patient variability, biological variability (age, gender, BMI, food intake, circadian and menstrual variation); and poor standardisation of most assays are some of the limitations that need to be considered when using BTMs for monitoring treatment (120).

1.7.4 Treatment failure

By consensus, the IOF established criteria to define treatment failure in patients adherent to therapy (121). These criteria include:

- two or more incident fragility fractures
- one incident fracture with a substantial decrease in bone density
- one incident fragility fracture that occurs with the lack of suppression of bone-remodelling markers
- persistently elevated bone formation (example, PINP) and bone resorption markers (example, βCTX-I) with a significant decrease in bone density.

A substantial decrease in bone density is when it exceeds 5% in the lumbar spine and 4% in the proximal femur. When monitoring bone turnover markers, a 25% change (decrease for anti-resorptive agents and an increase for anabolic agents) in levels from baseline is considered an adequate response (121).

Predictors of treatment failure include higher FRAX score, ≥2 falls in the past year, previous fracture, current use of glucocorticoids, arms more frequently required to help in standing, and unexplained weight loss ≥4.5 kg (122).

There is no evidence available on the efficacy of alternative treatments when one has been considered to have failed treatment. Three general rules are recommended, based on the opinion of IOF working group (121):

(1) A more potent anti-resorptive medication fairly replaces a weaker one of the same class.

(2) An injectable drug reasonably substitutes an oral drug.

(3) An anabolic agent judiciously replaces a strong anti-resorptive agent.

8 References:

1. NIH NI of H. National Institutes of Health (NIH) Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy. JAMA. 2001;285(6):785-95.
2. Chrischilles EA, Butler CD, Davis CS, Wallace RB. A model of lifetime osteoporosis impact [published erratum appears in Arch Intern Med 1922 Mar;152(3):655]. Archives of Internal Medicine. 1991;151(10):2026-32.
3. Walsh JS. Normal bone physiology, remodelling and its hormonal regulation. Surg (United Kingdom) [Internet]. 2015;33(1):1–6. Available from: http://dx.doi.org/10.1016/j.mpsur.2014.10.010
4. Eriksen EF. Cellular mechanisms of bone remodeling. Rev Endocr Metab Disord. 2010;11(4):219–27.
5. Hadjidakis DJ, Androulakis II. Bone remodeling. Ann N Y Acad Sci. 2006;1092:385–96.
6. Blair HC, Athanasou NA. Recent advances in osteoclast biology and pathological bone resorption. 2004;189–99.
7. Takayanagi H. Osteoclast differentiation and activation. Vol. 17, Clinical calcium. 2007. p. 484–92.
8. Silver IA, Murrills RJ, Etherington DJ. Microelectrode studies on the acid microenvironment beneath adherent macrophages and osteoclasts. Exp Cell Res. 1988;175(2):266-76.
9. Delaissé JM, Andersen TL, Engsig MT, Henriksen K, Troen T, Blavier L. Matrix metalloproteinases (MMP) and cathepsin K contribute differently to osteoclastic activities. Microsc Res Tech. 2003;61(6):504-13.
10. Boyce BF, Xing L. The RANKL/RANK/OPG pathway. Curr Osteoporos Rep. 2007;5(3):98–104.
11. Boyce BF, Xing L. Functions of RANKL/RANK/OPG in bone modeling and remodeling. Arch Biochem Biophys. 2008;473(2):139–46.
12. Raisz LG. Physiology and pathophysiology of bone remodeling. In: Clinical Chemistry. 1999;45(8 Pt 2):1353-8.
13. De Gorter DJJ, Sánchez-Duffhues G, Ten Dijke P. Signal transduction cascades controlling osteoblast differentiation. Prim Metab Bone Dis Disord Miner Metab. 2018;54–9.
14. Komori T, Yagi H, Nomura S, Yamaguchi A, Sasaki K, Deguchi K, et al.

Targeted disruption of Cbfa1 results in a complete lack of bone formation owing to maturational arrest of osteoblasts. Cell. 1997;89(5):755-64.

15. Nakashima K, Zhou X, Kunkel G, Zhang Z, Deng JM, Behringer RR, et al. The novel zinc finger-containing transcription factor Osterix is required for osteoblast differentiation and bone formation. Cell. 2002;108(1):17-29.
16. Rucci N. Molecular Biology of Bone Biology. Clin Cases Miner Bone Metab. 2008;5(1):49–56.
17. Khosla S, Westendorf JJ, Oursler MJ. Building bone to reverse osteoporosis and repair fractures. Journal of Clinical Investigation. 2008;118(2):421-8
18. Krishnan V, Bryant HU, MacDougald OA. Regulation of bone mass by Wnt signaling. J Clin Invest. 2006;116(5):1202–9.
19. Rachner TD, Khosla S, Hofbauer LC. Osteoporosis: Now and the future. Lancet. 2011;377(9773):1276–87.
20. Power J, Poole KES, Van Bezooijen R, Doube M, Caballero-Alías AM, Lowik C, et al. Sclerostin and the regulation of bone formation: Effects in hip osteoarthritis and femoral neck fracture. J Bone Miner Res. 2010;25(8):1867–76.
21. Bonjour J-P, Theintz G, Law F, Slosman D, Rizzoli R. Osteoporosis International Peak Bone Mass. Osteoporos Int [Internet]. 1994;1:7–13. Available from: https://link-springer-com.login.ezproxy.library.ualberta.ca/content/pdf/10.1007%2FBF01623429.pdf
22. Berger C, Goltzman D, Langsetmo L, Joseph L, Jackson S, Kreiger N, et al. Peak bone mass from longitudinal data: Implications for the prevalence, pathophysiology, and diagnosis of osteoporosis. J Bone Miner Res. 2010;25(9):1948–57.
23. Bonjour JP, Chevalley T, Ferrari S, Rizzoli R. The importance and relevance of peak bone mass in the prevalence of osteoporosis. Salud Publica Mex. 2009;51 Suppl 1:S5-17.
24. Jeon YK, Kim BH, Kim IJ. The diagnosis of osteoporosis. J Korean Med Assoc. 2016;59(11):842–6.
25. Kanis JA, Glüer CC. An update on the diagnosis and assessment of osteoporosis with densitometry. Osteoporosis International. 2000;11(3):192-202.
26. Cosman F, de Beur SJ, LeBoff MS, Lewiecki EM, Tanner B, Randall S, et al.

Clinician's Guide to Prevention and Treatment of Osteoporosis. Osteoporos Int. 2014;25(10):2359–81.

27. Sheu A, Diamond T. Bone mineral density: Testing for osteoporosis. Aust Prescr. 2016;39(2):35–9.
28. Hough S, Amod A, Ascott-evans BH, Brown SL, Cassim B, Davey M, et al. Revised South African Clinical Guideline for the Diagnosis and Management of Osteoporosis : 2017. 2017;15(3):107–8.
29. Choksi P, Jepsen KJ, Clines GA. The challenges of diagnosing osteoporosis and the limitations of currently available tools. Clin Diabetes Endocrinol. 2018;4(1):1–13.
30. Baim S, Binkley N, Bilezikian JP, Kendler DL, Hans DB, Lewiecki EM, et al. Official Positions of the International Society for Clinical Densitometry and Executive Summary of the 2007 ISCD Position Development Conference. J Clin Densitom. 2008;11(1):75–91.
31. Kanis J a. Assessment of osteoporosis at the primary health care level. World Heal Organ. 2007;1–17
32. Johnell O, Kanis JA. An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. Osteoporos Int. 2006;17(12):1726-33.
33. United Nations Population Division. Sub-Saharan Africa's growing population of older persons. Popul Facts [Internet]. 2016;(2016):2015–6. Available from: http://www.un.org/en/development/desa/population/publications/pdf/popfacts/PopFacts_2016-1.pdf
34. Paruk F, Matthews G, Gregson CL, Cassim B. Hip fractures in South Africa: mortality outcomes over 12 months post-fracture. Arch Osteoporos. 2020; 15(1):76.
35. Atiase Y, Quarde A. A call to action for osteoporosis research in sub-saharan Africa. Ghana Med J. 2020;54(1):58–67.
36. Sitati FC, Gichangi P, Obimbo MM. Prevalence of osteoporosis and its associated factors among postmenopausal women in Kiambu County, Kenya: a household survey. Arch Osteoporos. 2020;15(1):31.
37. Tsabasvi M, Davey S, Temu R. Hip fracture pattern at a major Tanzanian referral hospital: focus on fragility hip fractures. Arch Osteoporos. 2017;12(1):47.
38. Hahn PL. The Middle East. A Companion to Lyndon B Johnson. 2011;439–49.

39. Paruk F, Matthews G, Cassim B. Osteoporotic hip fractures in Black South Africans: a regional study. Arch Osteoporos. 2017;12(1):5–10.
40. Conradie M, Conradie MM, Kidd M, Hough S. Bone density in black and white South African women: contribution of ethnicity, body weight and lifestyle. Arch Osteoporos. 2014;9:193.
41. Matsela L, Towobola O, Mokgokong ET. Osteoporosis in Black South African Women: Myth or Reality. J SAFOMS. 2017;5(2):111–6.
42. Kanis JA, Johnell O, Oden A, Johansson H, McCloskey E. FRAX^{TM} and the assessment of fracture probability in men and women from the UK. Osteoporos Int. 2008;19(4):385–97.
43. Curry SJ, Krist AH, Owens DK, Barry MJ, Caughey AB, Davidson KW, et al. Screening for osteoporosis to prevent fractures us preventive services task force recommendation statement. JAMA - J Am Med Assoc. 2018;319(24):2521–31.
44. Kanis JA, Johnell O, Oden A, Johansson H, De Laet C, Eisman JA, et al. Smoking and fracture risk: A meta-analysis. Osteoporos Int. 2005;16(7):737–42.
45. Kanis JA, Johansson H, Johnell O, Oden A, De Laet C, Eisman JA, et al. Alcohol intake as a risk factor for fracture. Osteoporos Int. 2005;16(7):737–42.
46. Chastin SFM, Mandrichenko O, Helbostadt JL, Skelton DA. Associations between objectively-measured sedentary behaviour and physical activity with bone mineral density in adults and older adults, the NHANES study. Bone [Internet]. 2014;64:254–62. Available from: http://dx.doi.org/10.1016/j.bone.2014.04.009
47. M.R. S, A.H. S, I. A, M. J. Relationship between weight, body mass index, and bone mineral density in men referred for dual-energy X-ray absorptiometry scan in Isfahan, Iran. J Osteoporos [Internet]. 2013;2013. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed11&NEWS=N&AN=2013681174
48. Dawson-Hughes B, Heaney RP, Holick MF, Lips P, Meunier PJ, Vieth R. Estimates of optimal vitamin D status. Osteoporos Int. 2005;16(7):713–6.
49. Woolf AD. Preventing fractures in elderly people. Bmj [Internet]. 2003;327(7406):89–95. Available from: http://www.bmj.com/cgi/doi/10.1136/bmj.327.7406.89

50. Ganguly P, El-Jawhari JJ, Giannoudis P V., Burska AN, Ponchel F, Jones EA. Age-related Changes in Bone Marrow Mesenchymal Stromal Cells: A Potential Impact on Osteoporosis and Osteoarthritis Development. Cell Transplant. 2017;26(9):1520–9.
51. Alswat KA. Gender Disparities in Osteoporosis. J Clin Med Res [Internet]. 2017;9(5):382–7. Available from: http://www.jocmr.org/index.php/JOCMR/article/view/2970
52. Harvey NC, Curtis EM, van der Velde R, Moon RJ, van den Bergh JPW, Geusens P, et al. On epidemiology of fractures and variation with age and ethnicity. Bone. 2016;93:230–1.
53. Kanis JA, Johnell O, Laet C De, Johansson H, Oden A, Delmas P, et al. A meta-analysis of previous fracture and subsequent fracture risk. 2004;35:375–82.
54. Kanis JA, Johansson H, Oden A, Johnell O, De Laet C, Eisman JA, et al. A family history of fracture and fracture risk: A meta-analysis. Bone. 2004;35(5):1029–37.
55. Kroger H, Honkanen R, Saarikoski S, Alhava E. Decreased axial bone mineral density in perimenopausal women with rheumatoid arthritis - a population based study. Ann Rheum Dis. 1994;53(1):18–23.
56. Oh HJ, Ryu KH, Park BJ, Yoon B. Osteoporosis and Osteoporotic Fractures in Gastrointestinal Disease. 2018;25(4):213–7.
57. Güerri-Fernandez R, Vestergaard P, Carbonell C, Knobel H, Avilés FF, Castro AS, et al. HIV infection is strongly associated with hip fracture risk, independently of age, gender, and comorbidities: A population-based cohort study. J Bone Miner Res. 2013;28(6):1259–63.
58. Nguyen KD, Bagheri B, Bagheri H. Drug-induced bone loss: a major safety concern in Europe. Expert Opin Drug Saf [Internet]. 2018;17(10):1005–14. Available from: https://doi.org/10.1080/14740338.2018.1524868
59. Guañabens N, Parés A. Osteoporosis in chronic liver disease. Liver Int. 2018;38(5):776–85.
60. Damasiewicz MJ, Nickolas TL. Rethinking Bone Disease in Kidney Disease. JBMR Plus. 2018;2(6):309–22.
61. Watanabe R, Tai N, Hirano J, Ban Y, Inoue D, Okazaki R. Independent association of bone mineral density and trabecular bone score to vertebral

fracture in male subjects with chronic obstructive pulmonary disease. Osteoporos Int. 2018;29(3):615–23.

62. Hardy RS, Zhou H, Seibel MJ, Cooper MS. Glucocorticoids and bone: Consequences of endogenous and exogenous excess and replacement therapy. Endocr Rev. 2018;39(5):519–48.
63. Ale AO, Ogbera AO, Ebili HO, Adeyemo OL, Afe TO. Prevalence, predictive factors, and characteristics of osteoporosis in hyperthyroid patients. Int J Endocrinol. 2018;2018:3540256.
64. Lewiecki EM, Miller PD. Skeletal Effects of Primary Hyperparathyroidism: Bone Mineral Density and Fracture Risk. J Clin Densitom [Internet]. 2013;16(1):28–32. Available from: http://dx.doi.org/10.1016/j.jocd.2012.11.013
65. Golds G, Houdek D, Arnason T. Male Hypogonadism and Osteoporosis: The Effects, Clinical Consequences, and Treatment of Testosterone Deficiency in Bone Health. Int J Endocrinol. 2017;2017:4602129.
66. Ruchlemer R, Amit-Kohn M, Tvito A, Sindelovsky I, Zimran A, Raveh-Brawer D. Bone loss and hematological malignancies in adults: a pilot study. Support Care Cancer. 2018;26(9):3013–20.
67. Cosman F, Lindsay R, LeBoff MS, Jan de Beur S, Tanner B. Guide to Prevention and Treatment of Osteoporosis. Washington, DC: National Osteoporosis Foundation; 2014. Natl Osteoporos Found. 2014;25(10):2359-81.
68. Compston J, Cooper A, Cooper C, Gittoes N, Gregson C, Harvey N, et al. UK clinical guideline for the prevention and treatment of osteoporosis. Arch Osteoporos. 2017;12(1):43.
69. Tai V, Leung W, Grey A, Reid IR, Bolland MJ. Calcium intake and bone mineral density: Systematic review and meta-analysis. BMJ. 2015;351:1–14.
70. Yao P, Bennett D, Mafham M, Lin X, Chen Z, Armitage J, et al. Vitamin D and Calcium for the Prevention of Fracture: A Systematic Review and Meta-analysis. JAMA Netw open. 2019;2(12):e1917789.
71. Tang BM, Eslick GD, Nowson C, Smith C, Bensoussan A. Use of calcium or calcium in combination with vitamin D supplementation to prevent fractures and bone loss in people aged 50 years and older: a meta-analysis. Lancet. 2007;370(9588):657-66.
72. Bischoff-Ferrari HA, Dawson-Hughes B, Staehelin HB, Orav JE, Stuck AE,

Theiler R, et al. Fall prevention with supplemental and active forms of vitamin D: A meta-analysis of randomised controlled trials. BMJ. 2009;339:b3692.

73. Wysowski DK, Greene P. Trends in osteoporosis treatment with oral and intravenous bisphosphonates in the United States, 2002-2012. Bone. 2013;57(2):423-8.
74. Soares AP, do Espírito Santo RF, Line SRP, Pinto M das GF, Santos P de M, Toralles MBP, et al. Bisphosphonates: Pharmacokinetics, bioavailability, mechanisms of action, clinical applications in children, and effects on tooth development. Environmental Toxicology and Pharmacology. 2016;42:212-7.
75. Lewiecki EM. Bisphosphonates for the treatment of osteoporosis: Insights for clinicians. Therapeutic Advances in Chronic Disease. 2010;1(3):115-28.
76. Miller PD. The kidney and bisphosphonates. Bone [Internet]. 2011;49(1):77–81. Available from: http://dx.doi.org/10.1016/j.bone.2010.12.024
77. Black DM, Delmas PD, Eastell R, Reid IR, Boonen S, Cauley JA, et al. Once-Yearly Zoledronic Acid for Treatment of Postmenopausal Osteoporosis. N Engl J Med. 2007;356(18):1809-22.
78. Wang C. Efficacy and Safety of Zoledronic Acid for Treatment of Postmenopausal Osteoporosis. Am J Ther [Internet]. 2017;24(5):e544–52. Available from: http://insights.ovid.com/crossref?an=00045391-201709000-00006
79. Cryer B, Bauer DC. Oral bisphosphonates and upper gastrointestinal tract problems: What is the evidence? Mayo Clin Proc. 2002;77(10):1031–43.
80. Sieber P, Lardelli P, Kraenzlin CA, Kraenzlin ME, Meier C. Intravenous bisphosphonates for postmenopausal osteoporosis: Safety profiles of zoledronic acid and ibandronate in clinical practice. Clin Drug Investig. 2013;33(2):117–22.
81. Adler RA, El-Hajj Fuleihan G, Bauer DC, Camacho PM, Clarke BL, Clines GA, et al. Managing Osteoporosis in Patients on Long-Term Bisphosphonate Treatment: Report of a Task Force of the American Society for Bone and Mineral Research. Journal of Bone and Mineral Research. 2016;31(1):16-35.
82. Grey A. Intravenous zoledronate for osteoporosis : less might be more. 2016;119–23.
83. Grey A, Bolland M, Wong S, Horne A, Gamble G, Reid IR. Women : A Randomized Controlled Trial. 2012;97(January):286–92.

84. Randomized A, Trial PC, Grey A, Bolland M, Mihov B, Wong S, et al. J BMR Duration of Antiresorptive Effects of Low - Dose Zoledronate in Osteopenic Postmenopausal Women. 2014;29(1):166-72.
85. Bolland MJ, Grey A, Horne AM, Briggs SE, Thomas MG, Ellis-pegler RB, et al. Effects of Intravenous Zoledronate on Bone Turnover and Bone Density Persist for at Least Five Years in HIV-Infected Men. 2012;97(June):1922–8.
86. Prestwood KM, Raisz LG. [27] Prevention and treatment of osteoporosis. Clin Cornerstone. 2002;4(6):34–44.
87. Barrionuevo P, Kapoor E, Asi N, Alahdab F, Mohammed K, Benkhadra K, et al. Efficacy of pharmacological therapies for the prevention of fractures in postmenopausal women: A network meta-analysis. J Clin Endocrinol Metab. 2019;104(5):1623–30.
88. Group W. Effects of hormone therapy on bone mineral density: results from the postmenopausal estrogen/progestin interventions (PEPI) trial. The Writing Group for the PEPI. JAMA. 1996;276(17):1389-96.
89. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, et al. Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women. Jama [Internet]. 2009;288(3):321–33. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12117397
90. Vogel VG, Costantino JP, Wickerham DL, Cronin WM. Re: Tamoxifen for prevention of breast cancer: Report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study [1]. J Natl Cancer Inst. 2002;94(19):1504.
91. England TN. Effects of Raloxifene on Bone Mineral Density , Serum Cholesterol Women. Medicine (Baltimore). 1997;337:1641–7.
92. Ettinger B, Mitlalc BH, Nickelsen T, Genant HK, Christiansen C, Zanchetta JR, et al. Reduction of Vertebral Fracture Risk in Postmenopausal Women With Osteoporosis Treated With Raloxifene. Jama. 1999;282(7):637–45.
93. Chesnut CH, Silverman S, Andriano K, Genant H, Gimona A, Harris S, et al. A randomized trial of nasal spray salmon calcitonin in postmenopausal women with established osteoporosis: The prevent recurrence of osteoporotic fractures study. Am J Med. 2000;109(4):267–76.
94. Dewar C. Diagnosis and treatment of vertebral compression fractures. Radiol Technol. 2015;86(3):301–23.
95. Reginster JY, Franchimont P. Side effects of synthetic salmon calcitonin given

by intranasal spray compared with intramuscular injection. Clin Exp Rheumatol. 1985;3(2):155-7.

96. Downs RW, Bell NH, Ettinger MP, Walsh BW, Favus MJ, Mako B, et al. Comparison of alendronate and intranasal calcitonin for treatment of osteoporosis in postmenopausal women. J Clin Endocrinol Metab. 2000;85(5):1783–8.
97. Wells G, Chernoff J, Gilligan JP, Krause DS. Does salmon calcitonin cause cancer? A review and meta-analysis. Osteoporos Int. 2016;27(1):13–9.
98. Bonnelye E, Chabadel A, Saltel F, Jurdic P. Dual effect of strontium ranelate: Stimulation of osteoblast differentiation and inhibition of osteoclast formation and resorption in vitro. Bone. 2008;42(1):129-38.
99. Meunier PJ, Roux C, Seeman E, Ortolani S, Badurski JE, Spector TD, et al. The Effects of Strontium Ranelate on the Risk of Vertebral Fracture in Women with Postmenopausal Osteoporosis. N Engl J Med. 2004;350(5):459–68.
100. Bolland MJ, Grey A. Ten years too long: Strontium ranelate, cardiac events, and the European Medicines Agency. BMJ [Internet]. 2016;354(September):1–8. Available from: http://dx.doi.org/doi:10.1136/bmj.i5109
101. Ema. European Medicines Agency recommends that Protelos / Osseor remain available but with further restrictions. 2014;44(February):1–3. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Protelos_and_Osseor/Opinion_provided_by_Committee_for_Medicinal_Products_for_Human_Use/WC500161968.pdf
102. Hanley DA, Adachi JD, Bell A, Brown V. Denosumab: Mechanism of action and clinical outcomes. Int J Clin Pract. 2012;66(12):1139–46.
103. Cummings SR, Martin JS, McClung MR, Siris ES, Eastell R, Reid IR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. Obstet Gynecol Surv. 2009;64(12):805–7.
104. Cummings SR, Ferrari S, Eastell R, Gilchrist N, Jensen JEB, McClung M, et al. Vertebral Fractures After Discontinuation of Denosumab: A Post Hoc Analysis of the Randomized Placebo-Controlled FREEDOM Trial and Its Extension. J Bone Miner Res. 2018;33(2):190-198.
105. Zaheer S, LeBoff M, Lewiecki EM. Denosumab for the treatment of osteoporosis. Expert Opin Drug Metab Toxicol. 2015;11(3):461–70.
106. Lewiecki EM. New and emerging concepts in the use of denosumab for the

treatment of osteoporosis. Ther Adv Musculoskelet Dis. 2018;10(11):209–23.
107. Makino A, Takagi H, Takahashi Y, Hase N, Sugiyama H, Yamana K, et al. Abaloparatide Exerts Bone Anabolic Effects with Less Stimulation of Bone Resorption-Related Factors: A Comparison with Teriparatide. Calcif Tissue Int [Internet]. 2018;103(3):289–97. Available from: http://dx.doi.org/10.1007/s00223-018-0422-4
108. Eastell R, Rosen CJ, Black DM, Cheung AM, Murad MH, Shoback D. Pharmacological management of osteoporosis in postmenopausal women: An endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2019;104(5):1595–622.
109. Watts NB, Adler RA, Bilezikian JP, Drake MT, Eastell R, Orwoll ES, et al. Osteoporosis in men: An Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2012;97(6):1802–22.
110. Vahle JL, Sato M, Long GG, Young JK, Francis PC, Engelhardt JA, et al. Skeletal changes in rats given daily subcutaneous injections of recombinant human parathyroid hormone (1-34) for 2 years and relevance to human safety. Toxicol Pathol. 2002;30(3):312–21.
111. Neer RM, Arnaud CD, Zanchetta JR, Prince R, Gaich GA, Reginster JY, et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. N Engl J Med. 2001;344(19):1434–41.
112. Miller PD, Hattersley G, Riis BJ, Williams GC, Lau E, Russo LA, et al. Effect of abaloparatide vs placebo on newvertebral fractures in postmenopausalwomen with osteoporosis a randomized clinical trial. JAMA - J Am Med Assoc. 2016;316(7):722–33.
113. Lim SY, Bolster MB. Profile of romosozumab and its potential in the management of osteoporosis. Drug Des Devel Ther. 2017;11:1221–31.
114. Cosman F, Crittenden DB, Adachi JD, Binkley N, Czerwinski E, Ferrari S, et al. Romosozumab treatment in postmenopausal women with osteoporosis. N Engl J Med. 2016;375(16):1532–43.
115. Saag KG, Petersen J, Brandi ML, Karaplis AC, Lorentzon M, Thomas T, et al. Romosozumab or alendronate for fracture prevention in women with osteoporosis. N Engl J Med. 2017;377(15):1417–27.
116. Watts NB, Lewiecki EM, Bonnick SL, Laster AJ, Binkley N, Blank RD, et al.

Clinical value of monitoring BMD in patients treated with bisphosphonates for osteoporosis. J Bone Miner Res. 2009;24(10):1643–6.

117. Wu CH, Chang YF, Chen CH, Lewiecki EM, Wüster C, Reid I, et al. Consensus Statement on the Use of Bone Turnover Markers for Short-Term Monitoring of Osteoporosis Treatment in the Asia-Pacific Region. J Clin Densitom. 2021;24(1):3-13.
118. Shetty S, Kapoor N, Bondu J, Thomas N, Paul T. Bone turnover markers: Emerging tool in the management of osteoporosis. Indian J Endocrinol Metab. 2016;20(6):846–52.
119. Vasikaran S, Cooper C, Eastell R, Griesmacher A, Morris HA, Trenti T, et al. International Osteoporosis Foundation and International Federation of Clinical Chemistry and Laboratory Medicine Position on bone marker standards in osteoporosis. Clin Chem Lab Med. 2011;49(8):1271-4.
120. Hlaing TT, Compston JE. Biochemical markers of bone turnover - uses and limitations. Ann Clin Biochem. 2014;51(2):189–202.
121. Diez-Perez A, Adachi JD, Agnusdei D, Bilezikian JP, Compston JE, Cummings SR, et al. Treatment failure in osteoporosis. Osteoporos Int. 2012;23(12):2769–74.
122. Díez-Pérez A, Adachi JD, Adami S, Anderson FA, Boonen S, Chapurlat R, et al. Risk factors for treatment failure with antiosteoporosis medication: The global longitudinal study of osteoporosis in women (GLOW). J Bone Miner Res. 2014;29(1):260-7.

CHAPTER 2

2.1 Abstract

Clinical characteristics, complications and treatment outcomes of patients with osteoporosis at Groote Schuur Hospital

Omer Abdelfadiel, Joel A Dave

Division of Endocrinology, Groote Schuur Hospital and University of Cape Town

Background: Osteoporosis has become a major problem worldwide as the population ages. An osteoporotic fracture is associated with a high rate of morbidity and mortality. Data on the prevalence, risk factors and outcome of osteoporotic fractures in South Africa remains sparse.

Method: A retrospective audit was undertaken in all patients attending the Endocrine Clinic at Groote Schuur Hospital between March 2019 and March 2020 for the treatment of osteoporosis. Patients folders were reviewed to obtain the following information: demographic data, risk factors, laboratory investigations, treatment, baseline and follow up DEXA scans.

Results: 264 patients were evaluated, average age 65.7 ± 12.3 years, 92.8% (n=245) were female. Common risk factors included smoking (50.8%, n=134), vitamin D deficiency (29.2%, n=77), steroid use (21.6%, n=57) and primary hyperparathyroidism (15.2%, n=40). A fragility fracture was diagnosed in 68.6% (n=181) - vertebral only (54.7%, n=99), hip only (14.9%, n=27), vertebral and hip (10.5%, n=19), wrist (7.2%, n=13) and other (12.7%, n=23). Bisphosphonates were used by 75% (n=198) of patients at the time of enrolment. Of these, 80.8% (n=160) received intravenous zoledonic acid alone, 6.1% (n=12) received oral alendronate alone and 13.1% (n=26) initially received alendronate followed by intravenous zoledronic acid. Over 5.4 years there was an improvement in bone mineral density (BMD) of 4.4% at the lumbar spine, while there was slight worsening of BMD at the left femoral neck (- 0.5%). A fracture whilst on treatment occurred in 10.6% (n=21) of patients.

Conclusion: The majority of patients with osteoporosis at Groote Schuur Hospital had a fragility fracture at diagnosis with a vertebral fracture being most common. Bisphosphonate treatment showed a measurable improvement in BMD at the lumbar spine. However, there was no improvement at the femoral neck. Despite this, few patients had symptomatic vertebral or hip fracture whilst on treatment.

Keywords: Osteoporosis, South Africa, BMD, fragility, fracture, bisphosphonates, zoledronic acid, alendronate

2.2 Aims and Objectives

The aim of this study was to conduct an audit of all patients with osteoporosis managed at the Endocrine Clinic at Groote Schuur Hospital between March 2019 and March 2020. These findings will contribute to the development of a cost-effective strategy for the management of patients with osteoporosis at Groote Schuur Hospital.

Objective 1: To describe the patient characteristics, risk factors and causes for osteoporosis.

Objective 2: To maintain an active database of patients with osteoporosis seen at the Endocrine Clinic at Groote Schuur Hospital.

Objective 3: To describe the prevalence, phenotype, clinical presentation and risk factors for patients presenting with a fracture.

Objective 4: To determine the effectiveness of the various treatment modalities used to reduce fracture risk.

Objective 5: To determine the outcome of using intravenous zoledronic acid

2.3 Methods

2.3.1 Study design

Retrospective Cross-sectional Study

2.3.2 Setting

Endocrine Clinic at Groote Schuur Hospital (GSH), a tertiary hospital in Cape Town, South Africa.

2.3.3 Study population

All patients attending the Endocrine Clinic at Groote Schuur Hospital between March 2019 and March 2020 who have a diagnosis of osteoporosis. These patients were referred with either a fragility fracture or low BMD.

2.3.4 Procedures

Folder reviews were done to retrieve the following information:

1. Demographic details: age, sex
2. Past history: fractures, co-morbidities, previous medications and supplements.
3. Risk factors: vitamin d deficiency, primary hyperparathyroidism, CKD, diabetes, inflammatory bowel disease, hyperthyroidism, HIV, hypogonadism, smoking, and alcohol.
4. Family history: osteoporosis, fractures
5. Clinical details: weight, height, and BMI.
6. Treatment: type of medication, doses, response to treatment, fractures whilst on treatment. Was patients with current steroid use included?
   How many women received HRT?
7. Laboratory results: vitamin D level, calcium, phosphate, PTH, serum protein electrophoresis, creatinine, ALT, AST, GGT, ALP, sex steroids.
8. DEXA scan result at diagnosis and latest.

2.3.5 Data safety, analysis and monitoring

All patient data were de-identified, and study participants were given a unique study number. Data and analysis records are kept in a password-protected database on a secure computer. The password was unique and known only to the investigators. This was in keeping with the Declaration of Helsinki 2013.
This data was constantly updated as new information was gathered

2.3.6 Statistical analysis

Descriptive statistics were used to summarise demographic characteristics, known risk factors, fracture history, changes in bone mineral density, medical management received, and fracture while on treatment. The primary outcomes of interest were response to treatment, changes in bone mineral density, and fracture while on treatment. Depending on the distribution of the data, mean with standard deviation (SD) or median with interquartile range (IQR) were used to summarise continuous variables. Frequencies with percentages were used to summarise categorical data.
The Wilcoxon rank-sum or the Kruskal-Wallis test were used to compare continuous variables between groups. Where continuous variables were not normally distributed between two groups, they were compared using ANOVA, and binary and categorical variables were compared using Pearson's chi-squared test. Data analysis were performed using Stata/SE version 16.1 (StataCorp®, College Station, Texas).

2.3.7 Ethical aspects

Ethics approval was obtained from the UCT - Faculty of Health Sciences Human Research Ethics Committee (UCTHREC ref 169/2019) (Ethics approval for the study – see Appendix 2). Since it is a retrospective study, no individual patient consent was required.

2.4 Results

A retrospective folder review was done on all patients attending the Endocrine Clinic at GSH from 15 March 2019 to 15 March 2020 for management of osteoporosis. The 12-month period for the study was selected in order to capture most of the patients with osteoporosis attending the Endocrine Clinic as the majority of these patients come for follow up at least every 6 to 12 months. Over the study period, 271 patients were included, 7 were excluded on the basis of incomplete data or wrong diagnosis (4 had no DEXA scan, 1 had osteomalacia, 2 had osteopenia). Therefore, 264 patients were included in the final analysis. The majority of these patients [68.6% (n =181)] were referred with a fragility fracture (Figure 1).

Baseline characteristics and risk factors

The baseline characteristics and pre-existing risk factors are shown in Table 1. Of the 264 patients enrolled in the study, females represented the majority of the cohort (n=245, 92.8%). The mean age at diagnosis was 65.7 ±12.3 years, with males presenting at a younger age (60.1 ± 15.9 years) compared with females (66.2 ± 11.9 years). The average BMI of all the patients was 26.7 ± 5.5 kg/m^2, with males having a slightly higher BMI (27.1 ± 6.9 kg/m^2) than females (26.6 ± 5.4 kg/m^2).

In the females, the mean age of menarche was 13.7 ± 1.9 years whilst 12.8 % (n=26) had premature menopause, 13.1% (n=31) had early menopause and 5.9% (n=14) had late menopause.

Smoking was the most prevalent risk factor (50.8%, n=134), followed by vitamin D deficiency (29.2%, n=77), history of steroid use (21.6%, n=57), and history of hyperparathyroidism (15.2%, n=40). Although alcohol consumption was documented in 22.0% (n=58), there was no precise quantification of the amount of alcohol consumed. HIV infection and celiac disease accounted for the least described risk factors (0.4%, n=1 each). None of the male population had a history of rheumatoid arthritis.

Baseline blood tests (Table 2) documented vitamin D deficiency and insufficiency in 25.8% (n=68) and 26.9% (n=71), respectively, whilst 2.3% (n=6) of patients had hyperthyroidism and 10.6% (n=28) had renal failure.

Fragility fracture at presentation/diagnosis

Table 3 and Figure 2 show the history of fragility fractures at presentation. Sustaining a fragility fracture was the referring reason in 68.6% (n=181) of patients. Of these, 91.7% (n=166) were females and 8.3% (n=15) were males. The vertebrae were the commonest site of a fragility fracture (54.7%, n=99), followed by hip (14.9%, n=27), whilst the wrist represented the least prevalent site (7.2%, n=13). A fracture at both the hip and vertebrae was found in 10.5% (n=19) of the patients, denoting that some of the vertebral fractures were asymptomatic and only radiologically discovered after a hip fracture. Fractures at other sites, like the humerus, ribs, pelvis and ankle accounted for 12.7% (n=23) of all fractures.

Vertebral fracture vs nonvertebral fracture

Comparisons between patients who had a vertebral fracture and those who had a nonvertebral fracture at diagnosis are shown in Table 4 and Table 5. Age, sex and BMI didn't reveal any significant difference between the two groups (p=0.11, 0.66, and 0.25 respectively). Vitamin D deficiency was positively associated with vertebral fracture (p=0.003). Height was significantly lower in those patients who had a vertebral fracture (p=0.009) and is more likely to be a consequence of the fracture than a cause of the fracture as height loss is known to be associated with vertebral fractures. (Table 4)

Baseline blood tests showed that hypercalcemia was more common in patients with a vertebral fracture ($p<0.05$). There were no other significant differences between the two groups (Table 5).

The baseline BMD of patients with a non-vertebral or vertebral fracture is shown in Table 6. In comparison to patients with a non-vertebral fracture, patients with a vertebral fracture had lower baseline BMD at all sites. The difference was greater at the lumbar spine (0.31 g/cm^2), but it was not statistically significant.

Fracture vs no fracture

Patients presenting with a fragility fracture were older (67.3±11.6 years) compared to those who had no fractures (62.3±13.0 years) (Table 7). The BMI in patients with a fragility fracture was 27.3 ± 5 kg/m^2, while it was 25.5 ± 5.7 kg/m^2 in those without a history of fracture. Females accounted for 91.7% (n=166) of patients who had fracture and 95.2% (n=79) of patients with no fracture at diagnosis. A history of primary hyperparathyroidism, hypogonadism, and vitamin D deficiency was noticed more frequently in patients who had no fracture at diagnosis [25.3% (n=21), 21.7% (n=18), and 31.3% (n=26) respectively] compared with those who had fractures [10.5% (n=19), 6.1% (n=11), and 28.2% (n=51) respectively]. (Table 7)

Hypercalcemia was more common in patients with no fracture (21.7%, n=18), compared with those with a fracture (7.7%, n=14) while hypocalcemia and renal failure were more common in patients with a fracture [4.4% (n=8), and 12.7% (n=23),

respectively] than those with no fracture [0.0% (n=0), and 6.0%, (5), respectively] (Table 8).

Medications prescribed

Most of the cohort were on vitamin D (93.2%, n=246) and calcium supplements (86%, n=227) at the time of enrolment (Table 9). Bisphosphonates constituted the only definitive treatment for osteoporosis with 70.4% (n=186) receiving IV ZA, 9.8% (n=26) received alendronate followed by IV ZA, 60.6% (n=160) received IV ZA alone while alendronate alone was received by 4.5% (n=12).

Among those who received IV ZA (n=186), 28.1% (n=45) received 1 dose of IV ZA, 15.9% (n=42) received 3 doses, and 2.5% (n=4) received a total of 7 doses; the mean accumulative dose was 11.6 mg (2.9 doses).

About 25% (n=66) of the cohort were not yet started on treatment at the time of enrolment either because it was their initial visit or their first follow-up visit after completion of workup, including DEXA scan.

Change in BMD on treatment

Table 10 and Figure 2 show the change in BMD after an average follow-up duration of 5.4 ± 0.53 years. The BMD remained stable overall with some improvement in L1-L4. Lumbar spine (L1-L4) BMD increased in 73.5% (n=111) of patients, decreased in 25.8% (n=39) and remained unchanged in 0.7% (n=1); the mean change in lumbar spine BMD was 0.033 g/cm^2 (4.4%). At the Left femoral neck, 47.7% (n=71) of patients had an increase in BMD, 50.3% (n=75) had a decrease in BMD and 2.0% (n=3) showed no change in BMD; the mean change in BMD was – 0.003 g/cm^2 (- 0.5%). The total left hip BMD increased in 54.7% (n=82) of patients, 44.0% (n=66) had a decreased BMD, while 1.3% (n=2) had no change in BMD; the mean change in left total hip BMD was 0.003 g/cm^2 (0.4%). The BMD at the right femoral neck and right total hip remained the same with a mean change of 0.001 g/cm^2 (0.2%, and 0.1%, respectively). Although the DEXA scan was repeated after 3 years of bisphosphonates treatment in most patients during follow up, which is the routine practice in the Endocrine Clinic at Groote Schuur Hospital, we used the latest DEXA result to see the change in BMD on treatment.

Fracture vs no fracture on treatment

Tables 11, 12, 13 and 14 compare patients who had a fracture and patients who had no fracture whilst on treatment with bisphosphonates. A new fracture was diagnosed in 10.6% (n=21) of patients treated with bisphosphonates based on VFA for most of the vertebral fractures and clinical presentation with conventional radiography for hip and other fractures. Of these, 95.2% (n=20) were females. Of these fractures whilst on treatment 61.9% (n=13) were vertebral, 23.8% (n=5) were hip and 14.3% (n=3) were other. Of note, fracture at diagnosis was reported in 85.7% (n=18) patients with fracture on treatment compared to 68.4% (n=121) of patients with no fracture on treatment. A history of a vertebral fracture at diagnosis was reported in 71.4% (n=15) of patients with a fracture on treatment but in only 48.0% (n=85) of patients with no fracture on treatment.

Of the 139 patients on treatment and who had a fracture at diagnosis, 12.9% (n=18) had a refracture during follow up.

While primary hyperparathyroidism was noted in 16.4% (n=29) of patients who had no fracture on treatment, none of the patients who had a fracture on treatment had a history of primary hyperparathyroidism. Vitamin D deficiency was present in 24.3% (n=43) of patients with no fracture on treatment whilst in 14.3% (n=3) of patients with a fracture on treatment. Premature menopause was present in 42.1% (n=8) of women who had a fracture on treatment and 8.3% (n=14) of women with no fracture on treatment. A history of smoking was reported in more patients who had a fracture on treatment (61.9%, n=13), than who had no fracture (49.2%, n=87). Steroid use was described in more patients who had fracture on treatment (33.3%, n=7) than patients who had no fracture on treatment (22.6%, n=40). (Table 11)

Vitamin D deficiency, hypercalcemia, hyperparathyroidism [21.5% (n=38), 11,9% (n=21), and 27.7% (n=49), respectively] were more common in patients with no fracture on treatment when compared to patients with a fracture on treatment [14.3% (n=3), 0.0% (n=0), and 14.3% (n=3), respectively] (Table 12). Hyperthyroidism was present in 4.8% (n=1) of patients with a fracture on treatment and in 4.0% (n=7) of patients with no fracture on treatment.

Multiple doses (3-6) of IV ZA were received by 71.4% (n=15)] of patients with a fracture on treatment compared with 46.3% (n=82) of patients with no fracture on treatment (Table 13).

Surprisingly, patients who had a fracture on treatment had a higher mean BMD at all sites at baseline and follow-up compared with those who had no fracture on treatment (Table 14).

2.5 Discussion

This is the first audit at Groote Schuur Hospital of patients with osteoporosis attending the Endocrine Clinic. This retrospective descriptive study was conducted to highlight the clinical presentation, risk factors and treatment outcomes for patients referred to the Endocrine Clinic for the management of osteoporosis. Although there is abundant descriptive data on osteoporosis worldwide, there remains sparse descriptive data on osteoporosis in sub-Saharan Africa and this study will add to the limited literature of osteoporosis in this region.

In our cohort, postmenopausal women aged above 65 years constituted the majority of the participants. This was expected as osteoporosis is most prevalent in post-menopausal women, as they lose the protective effects of estrogen on bone. This finding is similar to findings in other studies (1–3). Surprisingly, in this cohort, the males were younger than the females. This is in contrast to most studies that show men with osteoporosis to be older than women (4,5). This data may not be representative as osteoporosis remains under diagnosed in men, there were few men in this cohort and it is possibly biased as this cohort is in a tertiary centre where only the more severe forms of osteoporosis are referred.

Ethnicity is a well-defined risk factor for osteoporosis and fragility fractures with studies showing White and Asian ethnicities to be at higher risk (6–8). Since our study was a retrospective review it was not possible to accurately assess ethnicity. However, historically, the ethnicity of the majority of patients attending clinics at GSH would be from mixed-ancestry or black.

Most of the patients had a history of an acute fragility fracture at diagnosis and this is consistent with studies from developed countries where most cases of osteoporosis were diagnosed after a fragility fracture (9,10). In addition, since GSH is a tertiary medical facility, patients are mostly referred once they have sustained a fragility fracture. Vertebral fractures constituted the largest number of fragility fractures in this cohort. Studies from other countries suggest hip fractures are more common (11,12), (5). This is highlighted by a recent study on osteoporotic fractures, including 6

European countries, showing that hip, vertebral, forearm and proximal humerus fractures accounted for 49%, 19.6%, 15.5% and 17.9% of fractures, respectively (11). A study from the USA in patients admitted with a diagnosis of an osteoporotic fracture showed a higher prevalence of hip fractures (50%) compared to vertebral fractures (14%) (12). In addition, a study from Canada showed that the site of a fragility fracture depended on the sex of the patient with the forearm the dominant site in women and the ribs the dominant site in men (5). There were too few men in this cohort to make a meaningful comparison on sex differences in fracture site. The finding of a predominance of vertebral fractures in our cohort may be explained by the routine screening for vertebral fractures in our institution as part of a DEXA scan.

Current and previous smoking is a well described risk factor for osteoporosis and osteoporotic fractures and was found to be the most common risk factor among the study population (13–16). Excessive alcohol intake is also a well-recognised risk factor for osteoporosis, whereas light to moderate alcohol consumption is considered beneficial resulting in a higher BMD and reduced age-related bone loss (17–19). Alcohol consumption was not common in this cohort and, in the roughly 20% that did consume alcohol, there was no clear documentation of the amount of alcohol consumed.

Vitamin D deficiency is prevalent in South Africa. A recent study from KwaZulu-Natal revealed that vitamin D deficiency and insufficiency was present in 27% and 38%, respectively, in 327 study participants (20). In a study from Cape Town, Charlton *et al* (1996) showed a prevalence of vitamin D deficiency of 17% in 200 coloured participants (21). In this study, 29.2% of our participants were vitamin D deficient. Vitamin D has been shown to be more prevalent in patients with osteoporosis, although the prevalence does vary. In a study from Colombia, the prevalence of vitamin D deficiency was found to be 55.3% in 206 patients diagnosed with osteoporosis (22). A significantly higher prevalence of vitamin D deficiency (89%) was shown in a study from Germany in 246 patients with a vertebral fragility fracture (23).

HIV and antiretroviral treatment are associated with an increased risk of osteoporosis. In a study from Malawi, 20% of an HIV-infected population was found to have reduced BMD (24). In a study from Senegal, the prevalence of osteoporosis in 193 HIV-infected patients above 50 years of age was 26% in women and 6% in men (25). In a multi-national study, including South Africa, the prevalence of osteoporosis in ART-naïve

HIV-infected adults with normal and low CD4 cell counts was found to be low (1.9%), while 35.1% of the participants were found to have a low BMD (26). Similar findings of a low prevalence of low BMD was reported in ART- naïve HIV-infected black South African women with low and preserved CD4 counts (27). A meta-analysis by Brown *et al* (2007) reported a 67% prevalence of low BMD in 884 HIV-infected individuals, of whom 15 were osteoporotic (28).

Antiretroviral therapy, especially efavirenz or lopinavir/ritonavir, was found to be associated with a low BMD in a young cohort of HIV-infected South Africans (29).

Despite South Africa having the highest prevalence of HIV infection worldwide we only had one patient with HIV-infection referred to our clinic. This could be explained by HIV-infection being more prevalent in young black females who are considered a low risk population for osteoporosis. In addition, lack of routine osteoporosis screening may be another explanation.

Bisphosphosphonates (IV zoledronic acid or oral alendronate) were the main definitive therapy prescribed for patients in this cohort. About 25% of the cohort had not yet been started on treatment (bisphosphosphonates) at the time of enrolment as they were either at their initial visit after referral or their first follow-up appointment after completion of the osteoporosis workup.

The recommended dose of zoledronic acid in national and international guidelines is 5 mg annually (30,31), however, all patients who were treated with zoledronic acid in this study received an annual dose of 4 mg. This lower dose of zoledronic acid is a decision adopted by our institution on the basis of cost. Other therapeutic agents for osteoporosis like denosumab and anabolic agents (teriparatide and abaloparatide) were not prescribed to any patient in this cohort as they are not available in our institution.

After a mean duration of 5.2 years, treatment with bisphosphonates increased the BMD at the lumbar spine but had no effect at the hips. This is in contrast to other studies showing an increase in BMD at all sites after treatment with zoledronic acid. A meta-analysis comparing zoledronic acid with placebo showed a difference in BMD in favour of zoledronic acid at the lumbar spine of 6.10-6.71%, total hip of 2.10-6.40% and femoral neck of 3.30-5.06% after 24 months of treatment (32). Another meta-analysis revealed an improvement of femoral neck BMD for both zoledronic acid (3.20%) and alendronate (3.11%) compared to placebo for average duration of 1.8 years (33). In contrast to these studies and in agreement with our study, a study from

Southern India showed a higher increment in BMD at the lumbar spine (6.1%) while the BMD at the femoral neck and total hip remained stable with no statically significant increment in patients treated with zoledronic acid (34). A study from China reported a 5.39% improvement in BMD at the lumbar spine and a 1.9% improvement at the total hip in those patients treated with zoledronic acid for two years (35).

Our study showed an incidence of fracture while on bisphosphonate therapy of 10.6%. Of those who had a history of a previous fracture, 12.9% refractured whilst on treatment. This is marginally higher than what has been reported in the literature. There are no studies from Africa, but in a large study from the USA, the three-year subsequent fracture rate was 7.5% in patients receiving different types of anti-osteoporotic therapies including oral or injectable bisphosphonates, raloxifene, teriparatide, denosumab, and calcitonin (36). Another study from the USA demonstrated an 11.3% incidence of subsequent fragility fracture within three years (37). A 9.7% refracture rate was demonstrated in a study from 37 fracture clinics in Ontario, Canada (38).

It is surprising that the baseline and follow-up mean BMD at all sites was found to be higher in patients who had a fracture on treatment compared to those who had no fracture on treatment. Although BMD is known to be a predictor of osteoporotic fracture, the high prevalence (85.7%) of a previous fracture in this cohort may explain the increased prevalence of fractures whilst on treatment (39,40). This is supported by the recommendation for initiation of anti-osteoporotic treatment for postmenopausal women with a fragility fracture regardless of the BMD, reflecting the importance of a previous fracture as a strong predictor of a subsequent fracture (41). The small proportion (10.6%) of patients who had a fracture on treatment might hinder making strong comment on this observation.

The lower improvement of BMD and marginally higher rate of fracture in our study compared to previous studies might be explained by the lower dose of zoledronic acid we used. Furthermore, genetic factors and different types of bones could also contribute.

This study has several limitations. It is a cross-sectional study so only associations can be shown and causation cannot be implied. It contains a biased sample as only those with more severe disease or a fragility fracture are referred to a tertiary medical centre. Interim exposure to risk factors were not assessed. There was missing blood data for some patients. The low numbers of men in the cohort preclude any meaningful

sex comparisons.

The strengths of this study reside in it being the first description of patients with osteoporosis and fractures at Groote Schuur Hospital. It represents real-world local clinical data that can now be used to design long-term prospective studies to better guide investigation and management of osteoporosis in our local population. Furthermore, it provides some data showing the outcome of using a lower dose of zoledronic acid to reduce fractures in people diagnosed with osteoporosis.

Future studies could include:

1. Assessing whether men are actually at lower risk for osteoporosis and a fragility fracture or whether the low numbers are just a consequence of reduced screening for osteoporosis in males as they are deemed to be at lower risk for osteoporosis
2. Prospective study assessing whether the lower dose of ZA used in the public sector is effective at reducing recurrent fractures

2.6 Conclusion and Recommendations

This is the first descriptive study and clinical audit on patients with osteoporosis attending the Endocrine Clinic at Groote Schuur Hospital. Although our study describes some interesting differences when compared to other studies in the literature it does show that our current treatment prevents recurrent fractures in over 85% of high-risk patients with osteoporosis. The interesting differences highlighted in the study deserve further investigation in adequately powered and well-designed prospective studies.

Using the NOFSA guidelines for osteoporosis to screen for high risk groups will help in the early initiation of treatment and reducing the number of patients presenting with a fragility fracture. Our institution might need to revisit the policy of using the modified dose of zoledronic acid (4 mg), as this may be one of the reasons implicated in the lower improvement of BMD and marginally higher rate of fractures on treatment in our patients compared with studies using the recommended 5 mg dose. However, this would have to be balanced with cost and a prospective study would be needed to evaluate how many extra fractures would be prevented using the 5 mg dose of zoledronic acid.

2.7 References

1. Sitati FC, Gichangi P, Obimbo MM. Prevalence of osteoporosis and its associated factors among postmenopausal women in Kiambu County, Kenya: a household survey. Arch Osteoporos. 2020;15(1):31.
2. Kruger MC, Wolber FM. Osteoporosis: Modern paradigms for last century's bones. Nutrients. 2016;8(6):376.
3. Chen P, Li Z, Hu Y. Prevalence of osteoporosis in China: a meta-analysis and systematic review. BMC Public Health [Internet]. 2016;16(1):1–11. Available from: http://dx.doi.org/10.1186/s12889-016-3712-7
4. Alswat KA. Gender Disparities in Osteoporosis. J Clin Med Res [Internet]. 2017;9(5):382–7. Available from: http://www.jocmr.org/index.php/ JOCMR/article/view/2970
5. Prior JC, Langsetmo L, Lentle BC, Berger C, Goltzman D, Kovacs CS, et al. Ten-year incident osteoporosis-related fractures in the population-based Canadian Multicentre Osteoporosis Study - Comparing site and age-specific risks in women and men. Bone [Internet]. 2015;71:237–43. Available from: http://dx.doi.org/10.1016/j.bone.2014.10.026
6. Tsai AJ. Disparities in osteoporosis by race/ethnicity, education, work status, immigrant status, and economic status in the United States. Eur J Intern Med [Internet]. 2019;64(April 2019):85–9. Available from: https://doi.org/10.1016/j.ejim.2019.04.011
7. Munhoz L, Aoki EM, Cortes ARG, de Freitas CF, Arita ES. Osteoporotic alterations in a group of different ethnicity Brazilian postmenopausal women: An observational study. Gerodontology. 2018;35(2):101–9.
8. Curtis EM, van der Velde R, Moon RJ, van den Bergh JPW, Geusens P, de Vries F, et al. Epidemiology of fractures in the United Kingdom 1988-2012: Variation with age, sex, geography, ethnicity and socioeconomic status. Bone [Internet]. 2016;87(2016):19–26. Available from: http://dx.doi.org/10.1016/j.bone.2016.03.006
9. Weaver J, Sajjan S, Michael Lewiecki E, Harris ST. Diagnosis and treatment of osteoporosis before and after fracture: A side-by-side analysis of commercially insured and Medicare Advantage osteoporosis patients. J Manag Care Spec Pharm. 2017;23(7):735–44.
10. Gleason LJ, Menzies IB, Mendelson DA, Kates SL, Friedman SM. Diagnosis

and Treatment of Osteoporosis in High-Risk Patients Prior to Hip Fracture. Geriatr Orthop Surg Rehabil. 2012;3(2):79–83.

11. Borgström F, Karlsson L, Ortsäter G, Norton N, Halbout P, Cooper C, et al. Fragility fractures in Europe: burden, management and opportunities. Arch Osteoporos. 2020;15(1):59.
12. Weycker D, Li X, Barron R, Bornheimer R, Chandler D. Hospitalizations for osteoporosis-related fractures: Economic costs and clinical outcomes. Bone Reports [Internet]. 2016;5:186–91.
    Available from: http://dx.doi.org/10.1016/j.bonr.2016.07.005
13. Thorin MH, Wihlborg A, Åkesson K, Gerdhem P. Smoking, smoking cessation, and fracture risk in elderly women followed for 10 years. Osteoporos Int. 2016;27(1):249–55.
14. Ch. KFC. Smoking is Associated with Osteoporosis Development in Primary Care Population. Am J Nurs Sci. 2015;4(2):96.
15. Wu ZJ, Zhao P, Liu B, Yuan ZC. Effect of cigarette smoking on risk of hip fracture in men: A meta-analysis of 14 prospective cohort studies. PLoS One. 2016;11(12):1–11.
16. Bijelic R, Milicevic S, Balaban J. Risk Factors for Osteoporosis in Postmenopausal Women. Med Arch [Internet]. 2017;71(1):25.
    Available from: http://www.scopemed.org/fulltextpdf.php?mno=257800
17. Jang HD, Hong JY, Han K, Lee JC, Shin BJ, Choi SW, et al. Relationship between bone mineral density and alcohol intake: A nationwide health survey analysis of postmenopausal women. PLoS One. 2017;12(6):1–11.
18. Cheraghi Z, Doosti-Irani A, Almasi-Hashiani A, Baigi V, Mansournia N, Etminan M, et al. The effect of alcohol on osteoporosis: A systematic review and meta-analysis. Drug Alcohol Depend. 2019;197(January):197–202.
19. Gaddini GW, Turner RT, Grant KA, Iwaniec UT. Alcohol: A Simple Nutrient with Complex Actions on Bone in the Adult Skeleton. Alcohol Clin Exp Res. 2016;40(4):657–71.
20. Chutterpaul P, Paruk F, Cassim B. Prevalence of vitamin D deficiency in older South Africans with and without hip fractures and the effects of age, body weight, ethnicity and functional status. J Endocrinol Metab Diabetes South Africa. 2019;24(1):10–5.
21. Charlton KE, Labadarios D, Lombard CJ, Louw MEJ. Vitamin D status of older

South Africans. South African Med J. 1996;86(11):1406–10.

22. Mendoza E-PN, Marín J-WT, Carrillo DC, Guzmán GE, Arango LG. Prevalence of vitamin D deficiency in patients with osteoporosis. Rev Colomb Reumatol. 2016;23:17–23.
23. Maier GS, Seeger JB, Horas K, Roth KE, Kurth AA, Maus U. The prevalence of vitamin D deficiency in patients with vertebral fragility fractures. Bone Joint J. 2015;97-B(1):89–93.
24. Chisati EM, Constantinou D, Lampiao F. Reduced bone mineral density among HIV infected patients on anti-retroviral therapy in Blantyre, Malawi: Prevalence and associated factors. PLoS One. 2020;15(1):1–12.
25. Cournil A. Prevalence of Osteoporosis among HIV-1-Infected Men and Women Aged 50 years and Older in Dakar, Senegal: A Cross-Sectional Study. J AIDS Clin Res. 2015;06(04):443
26. Carr A, Grund B, Neuhaus J, Schwartz A, Bernardino J, White D, et al. Prevalence of and risk factors for low bone mineral density in untreated HIV infection: A substudy of the INSIGHT Strategic Timing of AntiRetroviral Treatment (START) trial. HIV Med. 2015;16(S1):137–46.
27. Hamill MM, Ward KA, Pettifor JM, Norris SA, Prentice A. Bone mass, body composition and vitamin D status of ARV-naïve, urban, black South African women with HIV infection, stratified by CD4 count. Osteoporos Int. 2013;24(11):2855–61.
28. Brown TT, Qaqish RB. Response to Berg et al. “Antiretroviral therapy and the prevalence of osteopenia and osteoporosis: A meta-analytic review” [2]. Aids. 2007;21(13):1830–1.
29. Dave JA, Cohen K, Micklesfield LK, Maartens G, Levitt NS. Antiretroviral Therapy, Especially Efavirenz, Is Associated with Low Bone Mineral Density in HIV-Infected South Africans. PLoS One. 2015;10(12):1–9.
30. Hough S, Ascott-Evans BH, Brown SL, Cassim B, De Villiers TJ, Lipschitz S, et al. NOFSA guideline for the diagnosis and management of osteoporosis. J Endocrinol Metab Diabetes South Africa [Internet]. 2010;15(3):107–8. Availablefrom: http://reference.sabinet.co.za/webx/access/electronic_journals/m_jemdsa/m_jemdsa_v15_n3_a2.pdf
31. Eastell R, Rosen CJ, Black DM, Cheung AM, Murad MH, Shoback D.

Pharmacological management of osteoporosis in postmenopausal women: An endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2019;104(5):1595–622.

32. Liu M, Guo L, Pei Y, Li N, Jin M, Ma L, et al. Efficacy of zoledronic acid in treatment of osteoporosis in men and women-a meta-analysis. Int J Clin Exp Med. 2015;8(3):3855–61.
33. Sanderson J, Martyn-St James M, Stevens J, Goka E, Wong R, Campbell F, et al. Clinical effectiveness of bisphosphonates for the prevention of fragility fractures: A systematic review and network meta-analysis. Bone [Internet]. 2016;89:52–8. Available from: http://dx.doi.org/10.1016/j.bone.2016.05.013
34. Sooragonda B, Cherian KE, Jebasingh FK, Dasgupta R, Asha HS, Kapoor N, et al. Longitudinal changes in bone mineral density and trabecular bone score following yearly zoledronic acid infusion in postmenopausal osteoporosis—a retrospective-prospective study from southern India. Arch Osteoporos. 2019;14(1):1–5.
35. Liang BC, Shi ZY, Wang B, Wu P, Kong LC, Yao JL, et al. Intravenous Zoledronic Acid 5 mg on Bone Turnover Markers and Bone Mineral Density in East China Subjects with Newly Diagnosed Osteoporosis: A 24-month Clinical Study. Orthop Surg. 2017;9(1):103–9.
36. Bawa HS, Weick J, Dirschl DR. Anti-osteoporotic therapy after fragility fracture lowers rate of subsequent fracture: Analysis of a large population sample: Analysis of a large population sample. J Bone Jt Surg - Am Vol. 2014;97(19):1555–62.
37. Dang DY, Zetumer S, Zhang AL. Recurrent Fragility Fractures: A Cross-sectional Analysis. J Am Acad Orthop Surg. 2019;27(2):E85–91.
38. Sujic R, Beaton DE, Mamdani M, Cadarette SM, Luo J, Jaglal S, et al. Five-year refracture rates of a province-wide fracture liaison service. Osteoporos Int. 2019;30(8):1671–7.
39. Crandall CJ, Hovey KM, Andrews CA, Cauley JA, Manson JAE, Wactawski-Wende J, et al. Bone mineral density as a predictor of subsequent wrist fractures: Findings from the women's health initiative study. J Clin Endocrinol Metab. 2015;100(11):4315–24.
40. Cummings SR, Cawthon PM, Ensrud KE, Cauley JA, Fink HA, Orwoll ES. BMD and risk of hip and nonvertebral fractures in older men: A prospective study

and comparison with older women. J Bone Miner Res. 2006;21(10):1550–6.

41. Cosman F, de Beur SJ, LeBoff MS, Lewiecki EM, Tanner B, Randall S, et al. Clinician's Guide to Prevention and Treatment of Osteoporosis. Osteoporos Int. 2014;25(10):2359–81.

TABLES

Table 1: Baseline Characteristics and pre-existing risk factors for the whole population, females and males

	Total	Female	Male
	N=264	N=245 (92.8%	N=19 (7.2%)
Age	65.7 (12.3)	66.2 (11.9)	60.1 (15.9)
BMI	26.7 (5.5)	26.6 (5.4)	27.1 (6.9)
Menarche	13.7 (1.9)	13.7 (1.9)	
Menopausal	237 (96.7%)		
Premature	26 (11.0%)	26 (11.0%)	
Early	31 (13.1%)	31 (13.1%)	
Normal	129 (54.4%)	137 (57.8%)	
Late	14 (5.9%)	6 (2.5%)	
Uncertain	37 (15.6%)	37 (15.6%)	
Smoking	134 (50.8%)	121 (49.4%)	13 (68.4%)
Alcohol	58 (22.0%)	54 (22.0%)	4 (21.1%)
HIV-infected	1 (0.4%)	1 (0.4%)	0 (0.0%)
Vitamin D deficiency	77 (29.2%)	68 (27.8%)	9 (47.4%)
Hyperparathyroidism	40 (15.2%)	38 (15.5%)	2 (10.5%)
Hyperthyroidism	5 (1.9%)	4 (1.6%)	1 (5.3%)
IBD	11 (4.2%)	8 (3.3%)	3 (15.8%)
Rheumatoid arthritis	14 (5.3%)	14 (5.7%)	0 (0.0%)
Hypogonadism	29 (11.0%)	26 (10.6%)	3 (15.8%)
Coeliac Disease	1 (0.4%)	1 (0.4%)	0 (0.0%)
Family hx Osteoporosis	73 (27.8%)	67 (27.5%)	6 (31.6%)
Family hx Fragility fracture	47 (17.8%)	44 (18.0%)	3 (15.8%)
Steroid Use	57 (21.6%)	53 (21.6%)	4 (21.1%)

Table 2: Baseline blood test results for the whole population, females and males

	Total	Female	Male
	n=264	n=245	n=19
Fracture at diagnosis/presentation	181 (68.6%)	166 (67.8%)	15 (78.9%)
Vitamin D deficiency	68 (25.8%)	59 (24.1%)	9 (47.4%)
Vitamin D insufficiency	71 (26.9%)	67 (27.3%)	4 (21.1%)
Hypercalcaemia	32 (12.1%)	30 (12.2%)	2 (10.5%)
Hypocalcaemia	8 (3.0%)	8 (3.3%)	0 (0.0%)
Hyperphosphataemia	5 (1.9%)	5 (2.0%)	0 (0.0%)
Hypophosphataemia	5 (1.9%)	4 (1.6%)	1 (5.3%)
Hyperparathyroidism[#]	76 (28.8%)	71 (29.0%)	5 (26.3%)
Paraproteinaemia[$]	4 (1.5%)	4 (1.6%)	0 (0.0%)
Hypothyroidism*	14 (5.3%)	12 (4.9%)	2 (10.5%)
Hyperthyroidism*	6 (2.3%)	5 (2.0%)	1 (5.3%)
Renal failure	28 (10.6%)	28 (11.4%)	0 (0.0%)

[#] n=205, 191 females, 14 males; [$]n=161, 151 females, 10 males;
*n=248, 231 females, 17 males

Table 3: Fracture History among the Study population

		Total	Female	Male
		N=264	N=245	N=19
Age		65.7 (12.3)	66.2 (11.9)	60.1 (15.9)
Menopause	Premature	26 (11.0%)	26 (11.0%)	
	Early	31 (13.1%)	31 (13.1%)	
	Normal	129 (54.4%)	137 (57.8%)	
	Late	14 (5.9%)	6 (2.5%)	
	Uncertain	37 (15.6%)	37 (15.6%)	
BMI		26.7 (5.5)	26.6 (5.4)	27.1 (6.9)
Height		155.4 (8.2)	154.7 (7.2)	165.1 (14.3)
Weight		64.3 (14.1)	63.7 (13.4)	73.7 (20.6)
Fracture at diagnosis/presentation		181 (68.6%)	166 (67.8%)	15 (78.9%)
Fracture Site Category	No Fracture	83 (31.4%)	79 (32.2%)	4 (21.1%)
	Non-Vertebral	63 (23.9%)	57 (23.3%)	6 (31.6%)
	Vertebral	118 (44.7%)	109 (44.5%)	9 (47.4%)

Table 4: Baseline characteristics and pre-existing risk factors of patients with a non-vertebral or vertebral fracture

	Non-Vertebral	Vertebral	p-value
	n=63	n=118	
Age	69.2 (12.0)	66.3 (11.3)	0.11
Female sex	57 (90.5%)	109 (92.4%)	0.66
Weight	65.3 (14.7)	66.0 (15.0)	0.79
Height	158.0 (6.6)	154.1 (9.3)	0.009
BMI	26.5 (5.7)	27.6 (5.7)	0.25
Vitamin D deficiency	24 (38.1%)	27 (22.9%)	0.030
Hyperparathyroidism	6 (9.5%)	13 (11.0%)	0.75
CKD	12 (19.0%)	18 (15.3%)	0.51
Diabetes	9 (14.3%)	19 (16.1%)	0.75
IBD	1 (1.6%)	1 (0.8%)	0.65
Rheumatoid arthritis	3 (4.8%)	9 (7.6%)	0.46
Hyperthyroidism	1 (1.6%)	3 (2.5%)	0.68
Hypogonadism	3 (4.8%)	8 (6.8%)	0.59
Steroid Use	14 (22.2%)	28 (23.7%)	0.82
Smoking	30 (47.6%)	64 (54.2%)	0.40
Alcohol ever	10 (15.9%)	33 (28.0%)	0.069
Menarche (years)	13.6 (2.1)	13.5 (1.8)	0.82
Menopause	57 (100%)	106 (97.2%)	0.37
Early	3 (5.3%)	11	
Late	11 (14.3%)	12	
Normal	30 (52.6%)	58	
Premature	5 (8.8%)	7	
Uncertain	8 (14.0%)	18	
Family Hx osteoporosis	20 (31.7%)	30 (25.4%)	0.36
Family Hx Fracture	15 (23.8%)	19 (16.1%)	0.21

Table 5: Baseline blood test results of patients with a non-vertebral or vertebral fracture

	Non-Vertebral	Vertebral	p-value
	N=63	N=118	
Vitamin D deficiency	20 (31.7%)	25 (21.2%)	0.28
Vitamin D insufficiency	17 (27.0%)	34 (28.8%)	
Hypercalcaemia	4 (6.3%)	10 (8.5%)	0.048
Hypocalcaemia	6 (9.5%)	2 (1.7%)	
Hyperphosphataemia	3 (4.8%)	2 (1.7%)	0.098
Hypophosphataemia	0 (0.0%)	2 (1.7%)	
Hyperparathyroidism [#]	16 (25.4%)	32 (27.1%)	0.97
Hypothyroidism[$]	4 (6.3%)	5 (4.2%)	0.89
Hyperthyroidism[$]	1 (1.6%)	3 (2.5%)	
Renal failure	9 (14.3%)	14 (11.9%)	0.69

[#] n=144, 50 non-vertebral fractures, 94 vertebral fractures; [$]n=168, 59 non-vertebral fractures, 109 vertebral fractures; *n=248, 231 females, 17 males

Table 6: Baseline BMD of patients with a non-vertebral or vertebral fracture

	Non-Vertebral	Vertebral	p-value
	N=63	N=118	
L1-L4_BMD	0.777 (0.149)	0.746 (0.150)	0.20
left femoral neck_BMD	0.591 (0.123)	0.575 (0.104)	0.41
left total hip_BMD	0.714 (0.130)	0.708 (0.133)	0.80
right total hip_BMD	0.713 (0.122)	0.698 (0.135)	0.53
right femoral neck_BMD	0.580 (0.099)	0.576 (0.115)	0.82

Table 7: Baseline characteristics and pre-existing risk factors of patients with no fracture or with a fracture

	No Fracture	Fracture
	N=83	N=181
Age	62.3 (13.0)	67.3 (11.6)
Female sex	79 (95.2%)	166 (91.7%)
BMI	25.5 (5.0)	27.3 (5.7)
Height	155.5 (7.2)	155.3 (8.7)
Weight	61.3 (12.2)	65.8 (14.9)
Menarche (years)	14.0 (1.7)	13.5 (1.9)
Menopause	74 (93.7%)	163 (98.2%)
Premature	12 (16.2%)	14 (8.6%)
Early	8 (10.8%)	23 (14.1%)
Normal	41 (55.4)	88 (54.0%)
Late	2 (2.7%)	12 (7.4%)
Uncertain	11 (14.9%)	26 (15.9%)
Smoking	40 (48.2%)	94 (51.9%)
Alcohol	15 (18.1%)	43 (23.8%)
Vitamin D deficiency	26 (31.3%)	51 (28.2%)
Hyperparathyroidism	21 (25.3%)	19 (10.5%)
Hyperthyroidism	1 (1.2%)	4 (2.2%)
Hypogonadism	18 (21.7%)	11 (6.1%)
IBD	9 (10.8%)	2 (1.1%)
Rheumatoid arthritis	2 (2.4%)	12 (6.6%)
Coeliac Disease	0 (0.0%)	1 (0.6%)
Family Hx Osteoporosis	23 (28.0%)	50 (27.6%)
Family Hx of fragility fracture	13 (15.7%)	34 (18.8%)
Previous Steroid Use	15 (18.1%)	42 (23.2%)

Table 8: Baseline blood test results of patients with no fracture or with a fracture

	No Fracture	Fracture
	N=83	N=181
Vitamin D deficiency	23 (27.7%)	45 (24.9%)
Vitamin D insufficiency	20 (24.1%)	51 (28.2%)
Hypercalcaemia	18 (21.7%)	14 (7.7%)
Hypocalcaemia	0 (0.0%)	8 (4.4%)
Hyperphosphataemia	0 (0.0%)	5 (2.8%)
Hypophosphataemia	3 (3.6%)	2 (1.1%)
Hyperparathyroidism[#]	28 (33.7%)	48 (26.5%)
Paraproteinemia*	1 (1.2%)	3 (1.7%)
Hypothyroidism[$]	5 (6.0%)	9 (5.0%)
Hyperthyroidism[$]	2 (2.4%)	4 (2.2%)
Renal failure	5 (6.0%)	23 (12.7%)

[#] n=205, 61 no fracture, 144 fracture; *n=161, 43 no fracture, 118 fracture; [$]n=248, 80 no fracture, 168 fracture

Table 9: Distribution of medication use among study population

Medications		Count (n)	Percentage
Calcium		227	86%
Vitamin D		246	93.2%
Bisphosphonates		198	75%
	Alendronate	12	6.1%
	Alendronate followed by IV ZA	26	13.1%
	IV ZA	160	80.8%
	IV ZA dose*		
	one	45	17%
	two	40	15.2%
	three	42	15.9%
	four	17	6.4%
	five	28	10.6%
	six	10	3.8%
	seven	4	1.5%

* Dose = 4 mg (corrected to eGFR)

Table 10: Bone mineral density (BMD) (g/cm^2) at diagnosis and at current DEXA scan

Site	BMD baseline	BMD current	BMD change	Gain BMD	Loss BMD	No change BMD
L1-L4	0,755	0,788	0,033 (4.4%)	111 (73.5%)	39 (25.8%)	1 (0.7%)
Left						
femoral neck	0,594	0,591	- 0,003 (-0.5%)	71 (47.7%)	75 (50.3%)	3 (2.0%)
total hip	0,720	0,723	0,003 (0.4%)	82 (54.7%)	66 (44.0%)	2 (1.3%)
Right						
femoral neck	0,591	0,592	0,001 (0.2%)	72 (48.6%)	76 (51.4%)	0 (0.0%)
total hip	0,720	0,721	0,001 (0.1%)	77 (51.7%)	69 (46.3%)	3 (2.0%)

Table 11: Baseline characteristics and pre-existing risk factors of patients with no fracture or with a fracture whilst on treatment

Previous Hyperparathyroidism	No Fracture	Fracture
	N=177 (89.4%)	N=21 (10.6%)
Age	65.4 (10.8)	65.7 (14.0)
Female sex	171 (96.6%)	20 (95.2%)
Vitamin D deficiency	43 (24.3%)	3 (14.3%)
CKD	22 (12.4%)	2 (9.5%)
Diabetes	23 (13.0%)	4 (19.0%)
Fracture at diagnosis	121 (68.4%)	[#]18 (85.7%)
Fracture Site		
Non-Vertebral	36 (20.3%)	3 (14.3%)
Vertebral	85 (48.0%)	15 (71.4%)
IBD	8 (4.5%)	1 (4.8%)
RA	13 (7.3%)	1 (4.8%)
Hyperthyroidism	2 (1.1%)	1 (4.8%)
Hypogonadism	16 (9.0%)	3 (14.3%)
Steroid Use	40 (22.6%)	7 (33.3%)
HIV-infection	0 (0.0%)	1 (4.8%)
Coeliac Disease	1 (0.6%)	0 (0.0%)
Smoking	90 (50.8%)	8 (38.1%)
Alcohol ever	35 (19.8%)	8 (38.1%)
Menarche (years)	13.6 (1.9)	14.2 (2.1)
Menopause	168 (98.2%)	19 (95.0%)
Premature	14 (8.3%)	8 (42.1%)
Early	25 (14.9%)	2 (10.5%)
Normal	92 (54.8%)	7 (36.9%)
Late	9 (5.3%)	0 (0.0%)
Uncertain	28 (16.7%)	2 (10.5%)
Family Hx Osteoporosis	54 (30.7%)	4 (19.0%)
Family History fracture	34 (19.3%)	3 (14.3%)

Refracture rate (18/139) = 12.9%

Table 12: Baseline blood test results of patients with no fracture or with a fracture whilst on treatment

	No Fracture	Fracture
	N=177	N=21
Vitamin D deficiency	38 (21.5%)	3 (14.3%)
Vitamin D insufficiency	41 (23.2%)	6 (28.6%)
Hypercalcaemia	21 (11.9%)	0 (0.0%)
Hypocalcaemia	2 (1.1%)	1 (4.8%)
Hyperphosphataemia	2 (1.1%)	0 (0.0%)
Hypophosphataemia	3 (1.7%)	0 (0.0%)
Hyperparathyroidism [#]	49 (27.7%)	3 (14.3%)
Paraproteinemia*	4 (2.3%)	0 (0.0%)
Hypothyroidism[$]	7 (4.0%)	3 (14.3%)
Hyperthyroidism[$]	3 (1.7%)	1 (4.8%)
Renal failure	17 (9.6%)	2 (9.5%)

[#] n=151, 137 no fracture, 14 fracture; *n=112, 103 no fracture, 9 fracture; [$]n=182, 161 no fracture, 21 fracture

Table 13: Treatment of patients with no fracture or with a fracture whilst on treatment

IV Zoledronic Acid	No Fracture	Fracture
	N=177	N=21
Number IV ZA Doses		
0	11 (6.2%)	1 (4.8%)
1	45 (25.4%)	0 (0.0%)
2	35 (19.8%)	5 (23.8%)
3	37 (20.9%)	5 (23.8%)
4	16 (9.0%)	1 (4.8%)
5	21 (11.9%)	7 (33.3%)
6	8 (4.5%)	2 (9.5%)
7	4 (2.3%)	0 (0.0%)
Oral Bisphosphonates	34 (19.2%)	4 (19.0%)
Calcium Supplementation	161 (91.0%)	19 (90.5%)
Vitamin D Supplementation	173 (97.7%)	20 (95.2%)

Table 14: Bone mineral density (BMD) (g/cm^2) at diagnosis and at current DEXA scan patients with no fracture or with a fracture whilst on treatment

BMD	No Fracture	Fracture
At Diagnosis		
L1-L4	0.747 (0.127)	0.770 (0.087)
left total hip	0.713 (0.119)	0.732 (0.125)
left femoral neck	0.587 (0.101)	0.602 (0.130)
right total hip	0.705 (0.129)	0.763 (0.110)
right femoral neck	0.579 (0.118)	0.621 (0.104)
Current		
L1-L4	0.783 (0.125)	0.872 (0.109)
left total hip	0.720 (0.115)	0.752 (0.105)
left femoral neck	0.588 (0.099)	0.613 (0.107)
right total hip	0.712 (0.123)	0.771 (0.117)
right femoral neck	0.587 (0.105)	0.620 (0.124)

FIGURES

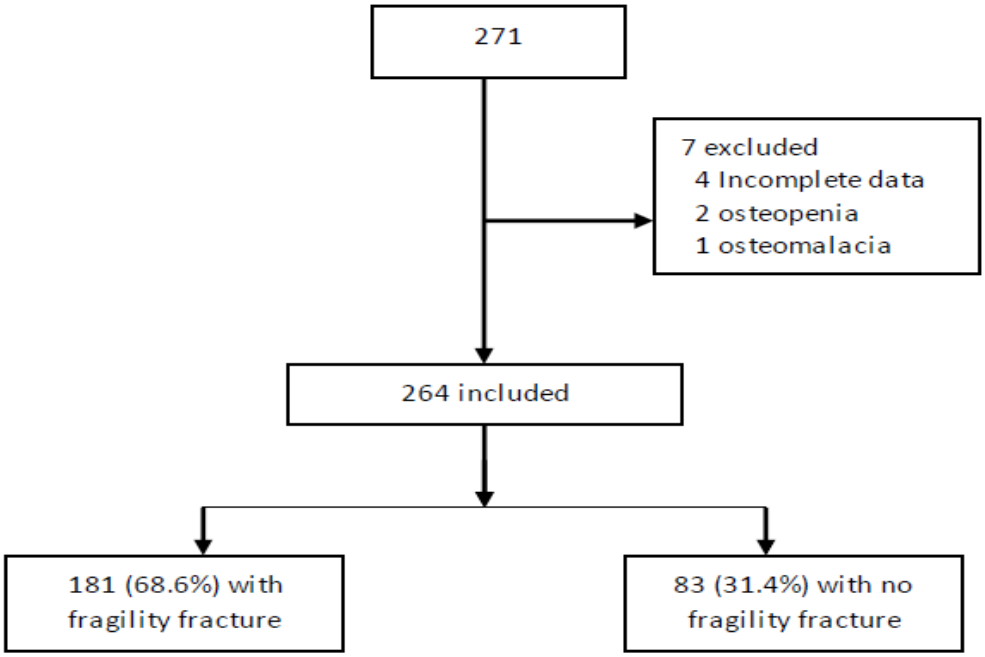

Figure 1: Study population selection and exclusion criteria

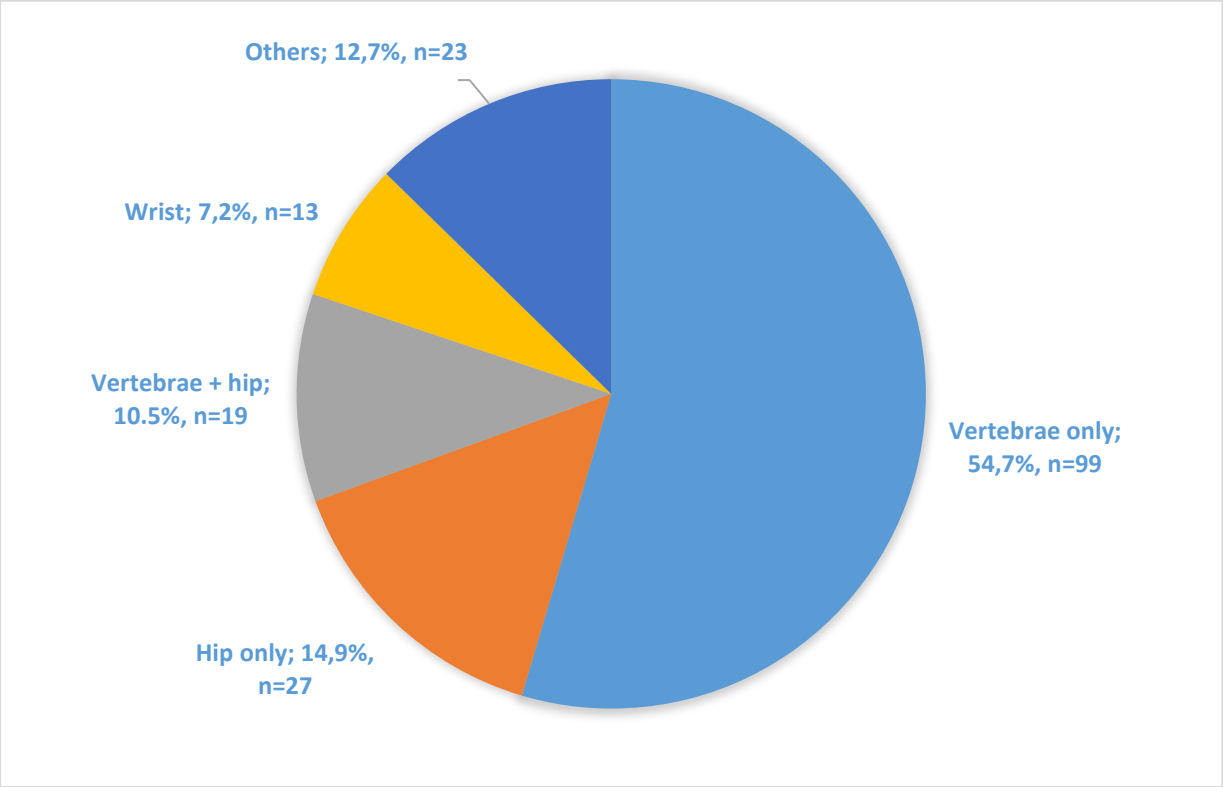

Figure 2: Distribution of fracture sites at diagnosis

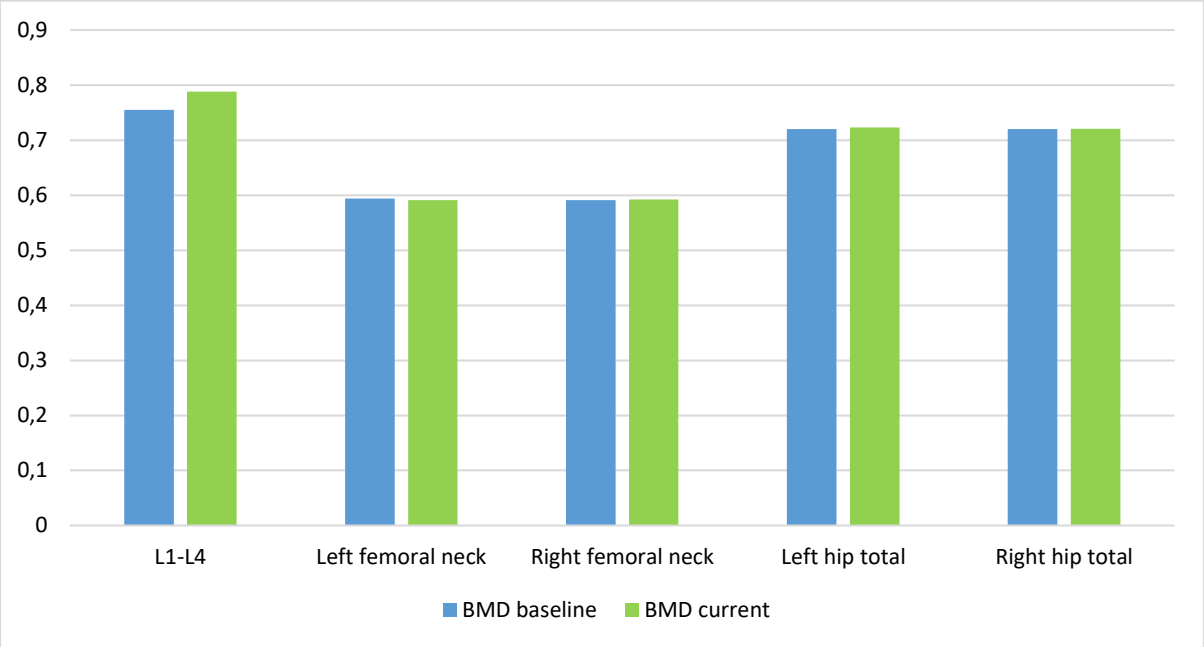

Figure 3: BMD change in follow-up DEXA scan (duration 5.4 (0.53) years)

APPENDICES

Data Capture Sheet

Patient's Sticker

Past history

Primary hyperparathyroidism	Yes / No	Rheumatoid arthritis	Yes / No
Vitamin D deficiency	Yes / No	Hypogonadism	Yes / No
CKD	Yes / No	Steroid use	Yes / No
Diabetes mellitus	Yes / No	HIV	Yes / No
Fracture	Yes / No	site: _____	
Inflammatory bowel disease	Yes / No	Celiac disease	Yes / No
Hyperthyroidism	Yes / No		

Habits

Current smoker Yes / No Previous smoker Yes / No Alcohol ever Yes / No

Menstrual

Menarche _____ Menopause _____ Oophorectomy Yes / No

Family history

Osteoporosis Yes / No Fragility fracture Yes / No

Treatment

Intravenous zoledronic acid Yes / No If yes, how many doses given? _____

Oral bisphosphonate Yes / No Calcium Yes / No Vitamin D Yes / No

Other: _____

Fragility fracture while on bisphosphonate? Yes / No region:_____

Weight _____ Height _____ BMI _____

DEXA scan results				
	Diagnosis		Current	
Date				
Site	BMD	T-score	BMD	T-score
L1-L4				
Total hip-Left				
Femoral neck-Left				
Total hip-Right				
Femoral neck-Right				

Blood results at diagnosis			
Vitamin D		GGT	
Calcium		ALT	
Phosphate		AST	
PTH		ALP	
SPEP		TSH	
LH		Creatinine	
FSH		Testosterone	
Estrogen			

Ethics Approval

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E53-46 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6626
Email: shuretta.thomas@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

15 March 2019

HREC REF: 169/2019

A/Prof J Dave
Endocrinology
J-floor, OMB

Dear A/Prof Dave

PROJECT TITLE: SPECTRUM, COMPLICATIONS AND TREATMENT OUTCOMES OF PATIENTS WITH DECREASED BONE MINERAL DENSITY ATTENDING THE ENDOCRINE CLINIC AT GROOTE SCHUUR HOSPITAL (MASTERS CANDIDATE: DR O ADBELFADIEL)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30 March 2020.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

The HREC acknowledge that the student, Dr Omer Abdelfadiel will also be involved in this study.

Yours sincerely

Signature Removed

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

HREC 169/2019