IMPACT OF A BISPHOSPHONATE DRUG HOLIDAY ON THE BONE MINERAL DENSITY IN PATIENTS WITH OSTEOPOROSIS AT CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

FROM 2000-2016

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A research report submitted to the Faculty of Health Sciences, University of Witwatersrand, Johannesburg, in partial fulfillment of the requirements for the degree of Master of Medicine in the branch of Internal Medicine

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i. Declaration

I, Rutendo Yvonne Rukarwa, do hereby declare that this research report is my unaided work. It is being submitted for the degree of Master of Medicine in the branch of Internal Medicine. This research report is submitted in the submissible format (with my protocol and an extended literature review) as recognized by the Faculty of Health Sciences. I further declare that this work has not been submitted for any other examination or degree at this or any other University.

……..

The 13th day of March 2019.

ii. Dedication

To my amazing husband, Hans, for his love, motivation, unwavering support and sacrifice, and making it all possible.

To my mother, Lilian for the many years of guidance, support, encouragement and prayers.

For my beloved daughters, Zoe and Shamiso.

iii. Presentations originating from this research

Selected for poster presentation at the School of Clinical Medicine Research Day, University of Witwatersrand, Johannesburg, 6 September 2018

iv. Ethical considerations

Permission for this retrospective study was obtained from Prof F.J Raal (Head of Division, Endocrinology, Faculty of Health Sciences, University of the Witwatersrand), Dr M.I Mofokeng (Clinical Director, Charlotte Maxeke Academic Hospital) and the Human Research Ethics Committee of the University of Witwatersrand (clearance number – M170710).

v. Abstract

Background: Bisphosphonate therapy has efficacy in the management of osteoporosis. Rare adverse effects related to its prolonged use has resulted in the concept of a "drug holiday" (DH).

Objective*:* To evaluate the effect of a bisphosphonate DH on bone mineral density (BMD).

Methods: A retrospective cohort study of 97 patients with osteoporosis who had undertaken a DH was conducted.

Results: The median age at the initiation of bisphosphonate therapy was 63 years. The median duration of the DH was 2 years. The overall effect of the DH on BMD as a percentage change from the beginning to the end of the DH showed a decrease in BMD at the lumbar spine [-3.3%, p=0.398]; radius and ulnar [-16.7%, p=0.03] and total hip [-8.9%, p=0.001]. 4 patients sustained fractures during the DH.

Conclusion: An individualised approach is key in assessing the duration of the DH and only low risk patients should be considered.

vi. Acknowledgements

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xi. Nomenclature

AACE	American Association of Clinical Endocrinology
AFF	Atypical femoral fractures
ANOVA	Analysis of variance
BMD	Bone mineral density
BMI	Body mass index
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
CRFs	Clinical risk factors
CTD	Connective tissue diseases
DEXA	Dual energy X-ray absorptiometry
DH	Drug holiday
FDA	Food and Drug Administration
FIT	Fracture Intervention Trial
FLEX	Fracture Intervention Long Term Extension
FN	Femur neck
FRAX®	Fracture Risk Assessment Tool
HORIZON-PFT	Health Outcomes and Reduction Incidence with Zoledronic Acid Once Yearly- Pivotal Fracture Trial
IQR	Interquartile range
IV	Intravenous

LS	Lumber spine
NOFSA	National Osteoporosis Foundation of South Africa
NOGG	National Osteoporosis Guideline Group
ONJ	Osteonecrosis of the jaw
RA	Rheumatoid arthritis
RANKL	Receptor activator of NFκB ligand
Ref	Reference
RU	Radius and ulnar
SD	Standard deviation
TH	Total hip
USA	United States of America
VERT- MN	Vertebral Efficacy with Risedronate Therapy- Multinational

Chapter 1: PROTOCOL WITH EXTENDED LITERATURE REVIEW

1.1 Introduction

Every 3 seconds, worldwide, a fracture occurs as a result of osteoporosis, mainly hip and spine fractures resulting in great morbidity and mortality and at considerable cost to society (1). However, despite being such a common metabolic bone disease, osteoporosis has attracted little attention in many developing nations. This is probably because it is viewed as a disease of developed nations, due to health care planners' preoccupation with infectious diseases and other non-communicable diseases; its acceptance as a consequence of aging and the fact that patients with fractures are rarely investigated for osteoporosis. There is also shortage of diagnostic equipment as well as epidemiological data (2, 3). Osteoporosis has no warning signs, and usually, the first indication of the disease is a fracture. Non-vertebral fractures are generally as a result of a fall, and vertebral fractures often occur spontaneously without a history of a fall.

Globally there has been a shift towards the distribution of deaths from the younger to the older population and also from communicable to non-communicable diseases (2). As a result of the increase of age in our population, the correct management of patients with osteoporosis becomes crucial in reducing the mortality and morbidity that results from fragility fractures that can affect persons with the disease.

1.1.1 Justification for the study

Patients attending Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) osteoporosis clinic receive 5 doses of zoledronic acid annually for 5 years after which they have a "drug holiday" (DH). The protocol at the clinic is based on the recommendations made in the 2010 National Osteoporosis Foundation of South Africa (NOFSA) guidelines. However, there has been no clear answer as to which patients should have a DH, when the DH should begin as well as the duration of the DH. The question also remains as to what happens to the bone mineral density (BMD) of these patients during the DH.

1.2 Osteoporosis

1.2.1 Definition of Osteoporosis

Osteoporosis is a progressive systemic disease of the skeletal system characterised by micro-architectural deterioration of the bone tissue as well as low bone mass, increasing bone fragility and susceptibility to fractures (3). Osteoporosis is diagnosed mainly by measurement of BMD using dual energy X-ray absorptiometry (DEXA) of the lumbar spine, femur neck and total upper femur (3).

The World Health Organisation (WHO) definition of osteoporosis is a BMD 2.5 standard deviations (SD) or more below the young adult mean value for a woman (thus a T score $\leq$-2.5 SD in postmenopausal women) (4). The BMD at the femoral neck has a high predictive value for future fractures, and is thus frequently used. Other sites, especially the spine, are not used commonly as they may be affected by osteoarthritis and other spinal conditions, more so in the elderly, resulting in this changing the BMD measured. There are however many limitations to the use of this definition (4).

Although a diagnosis of osteoporosis uses BMD, the drawback is that it has high specificity and low sensitivity. It does not take into account the bone quality and although osteoporosis increases the risk of a fracture, it does not mean the risk is negligible with a normal BMD. Another limitation of the use of DEXA in the diagnosis of osteoporosis is that of cost, availability and more importantly the lack of ethnic specific reference ranges (2).

1.2.1.1 Fracture Risk Assessment Tool (FRAX®)

As a result of these limitations the WHO has developed an algorithm for a 10-year absolute fracture risk called FRAX® (2). FRAX® uses a combination of BMD, clinical risk factors (CRFs) and country-specific fracture and mortality data to quantify a person's 10-year probability of a hip fracture. The risk factors included are age, body mass index (BMI), parental fracture history, ethnicity, smoking, alcohol use (more than two units a day), glucocorticoid use ($\geq$ 5mg per day of prednisone or equivalent steroid for >3 months), secondary osteoporosis

and rheumatoid arthritis (5). Risk factor assessment is used with or without BMD to guide treatment decisions.

The advantage of the use of FRAX® in managing osteoporosis is that it incorporates the relative importance of the different CRFs, and also these CRFs are additive and interactive in their predisposition to fracture. The limitations are that although it provides an estimate of the 10-year fracture risk, it cannot be used to suggest intervention thresholds. Also, before application of the model, data with regards to mortality and incidence of hip fractures specific to a population need to be known, which are not readily available in many countries. Lastly, it leaves out other important predisposing risk factors, uses only femoral neck BMD and cannot be used in persons under the age of 40 years (4).

1.3 Clinical risk factors.

There are many CRFs for osteoporosis that have been identified.

1.3.1 Age

The more advanced the age of a person, the higher is the risk of developing osteoporosis as well as fractures (6). It is a universal phenomenon that with an increase in age there is progressive loss in bone mass, affecting all races and sexes from about age 40 years onwards (7).

1.3.2 Gender

The risk of osteoporosis is much greater in female than in males. Males have greater bone mass and therefore higher average BMD than females. Another factor is that males undergo a less abrupt decline in gonadal function with ageing compared to females. Also men have a shorter life expectancy then females and a larger muscle mass with reduced risk of them developing osteoporosis (4).

1.3.3 Ethnicity

Different races and populations have significantly different incidences of both osteoporosis and fractures. The prevalence of osteoporosis in the White, Asian and Mixed race populations of South Africa seem to be similar to that of the developed countries (4). In the United States of America (USA), there is a significantly lower incidence of osteoporosis in Blacks compared to Whites and this is attributed mainly to the higher average BMD in the former. A slower decline in BMD in both the spine and femur with aging was observed in a cross sectional study comparing Black South African woman to their White counterparts (8). Osteoporosis of the hip, is less prevalent in Black South Africans than in Whites, although the vertebral bone mass and likely also vertebral fracture prevalence appears to be similar, as is the case in the USA (7-9).

1.3.4 Low Body Mass Index (BMI)

BMI is a value derived from the mass (weight) and height of a person. It is defined by the body mass divided by the square of the body height. The 2011 South African hypertension guidelines classify BMI into six categories as tabulated below *(Table 1.1)*

BMI= Weight /Height^2

Table 1.1: The six categories of Body Mass Index

Classification	**BMI** (Kg/m^2) *
Under weight	<18.5
Normal weight	18.5-24.9
Pre-obese (overweight)	25.0-29.9
Obese (class I)	30.0-34.9
Obese (class II)	35.0-39.9
Obese (class III)	≥ 40

Source: South African Hypertension Guideline 2011(10).

*Values independent of sex and age

BMI which is a measure of body composition, when low, is associated with a risk of osteoporosis (11). BMI is more predictive of osteoporosis than using weight alone as it adjusts for the differences in height and is therefore more reflective of body composition (12). Low BMI typically results in low body fat, which reduces the circulating oestrogen levels, and oestrogen is vital to prevent bone loss. As a result, there is a significant association between thinness and low bone mass, as well as an increase in post-menopausal bone turnover, which in turn increase the risk of development of osteoporosis (12, 13).

Despite having a normal bone mass at menopause, thinner women are still at an increased risk of developing menopause with 2 proposed mechanisms:

1. Body fat provides an indirect protection from bone loss as it serves as a source for the peripheral conversion of androstenedione to oestrogen. A deficiency of this depot increases bone turnover and bone loss.
2. Heavier individuals in early adulthood exert a greater load on their weight bearing joints and reach a higher peak BMD than thinner individuals. This results in higher BMD (12).

As a result of the strong relationship between low BMI and low bone density, there should be emphasis to encourage elderly patients not to become underweight.

1.3.5 Alcohol

Excessive alcohol use of more than 2 standard drinks per day has been associated with an increased risk of developing osteoporosis. The chronic use of alcohol results in a decrease in bone mass and strength (14). Alcohol is also directly toxic to bone cells. It also indirectly affects bone mass in that its chronic use results in hypogonadism, liver disease, malnutrition and metabolic acidosis with hypovitaminosis D, pseudo Cushing's syndrome and hypercortisolaemia (15, 16). All of which can result in the development of osteoporosis.

1.3.6 Smoking

Smoking is associated with a reduction in BMD in postmenopausal men and women through various mechanisms. Firstly, smoking results in the increased metabolism of both endogenous and exogenous oestrogen. Although it results in higher androgen levels, there is however a

decrease in the rate of conversion of these androgens into oestrogen. Smoking is also associated with the development of early menopause as well as a low BMI, both of which are risk factors of developing osteoporosis. There is also a reduction in the absorption of calcium associated with smoking (17, 18). It also impairs the response of bone as well as other target organs to oestrogen as well as other actions independent of oestrogen (19).

1.3.7 Early Menopause

Throughout life, sex steroids play an essential role in skeletal homeostasis (20). Oestrogen deficiency in women, at any age, results in an associated decrease in bone mass. With menopause, there is an increased rate of bone remodelling of which the rate of bone resorption is more rapid than that of bone formation. Conditions which result in oestrogen deficiency such as early menopause, late menarche, anorexia, hyperprolactinemia, ovarian failure and athletic-induced amenorrhea, all predispose women to the development of osteoporosis (21). Different mechanisms have been proposed to explain this such as, increased osteoclast recruitment as well as their prolonged survival in states of oestrogen deficiency. There is also an increase in the rate of activation of new remodelling cycles on bone surfaces which in turn increases trabecular penetration and this eliminates templates for new bone formation. Also recognised is the role of Receptor Activator of NFκB Ligand (RANKL), a cytokine secreted by osteoblasts and other marrow cells as well as the modulation of interleukins (21).

1.3.8 Hypogonadism

Osteoporosis in men remains a condition that is underdiagnosed and undertreated. It is mostly due to secondary causes such a hypogonadism, excessive alcohol intake and corticosteroid use (22). In men, androgens are needed to attain a peak bone mass as well as to maintain it. Hypogonadism results in rapid bone loss and an increase in biochemical markers of bone turnover resulting in the development of osteoporosis. The rate of bone formation is also reduced by hypogonadism (23). There is increasing evidence that oestrogen also has an important role in skeletal maintenance in men. The main source of the oestrogen is from peripheral aromatization of androgens to oestrogen. Therefore a deficiency in testosterone can result in an increase of bone loss as with oestrogen deficiency in women (24). The role of testosterone in skeletal homeostasis is illustrated below in figure 1.1. The oestrogen formed by

the aromatization of testosterone plays a greater role in the maintenance of skeletal health than testosterone. However, androgens also directly have a beneficial effect on bone via the androgen receptors (24).

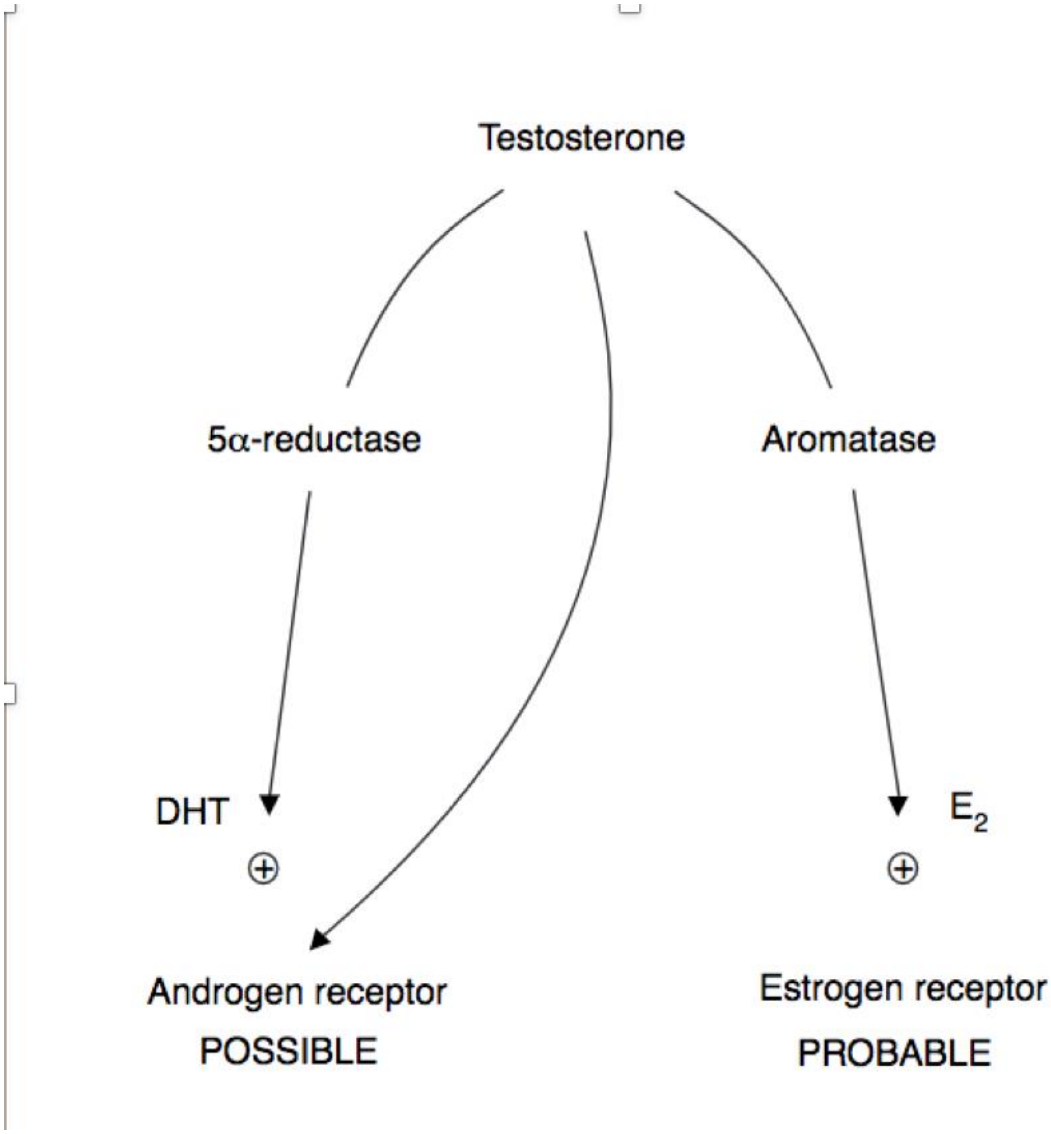

Fig 1.1 Direct and indirect effects of androgens on skeletal maintenance

DHT=dihydrotestosterone; E_2 = estradiol.

Adapted from Ebeling (24).

1.3.9 Corticosteroids

The main feature of glucocorticoid-induced osteoporosis is a decline in the number of functional osteoblasts resulting in a decrease in bone formation. Glucocorticoids also cause a reduction in calcium absorption form the intestines, with an increase in calcium renal excretion. About 50 % of patients on long term glucocorticoid therapy develop osteoporosis (25-27). Bone loss occurs at a dose of prednisone of ≥7.5 mg per day, but it can occur in patients despite lower doses taken. With glucocorticoid therapy, there is rapid development of osteoporosis within the first 6 to 12 months of therapy. The effect is not only that of a reduction in BMD, but corticosteroids also have an adverse effect on bone quality. As a result of this, fractures tend to occur at a higher BMD with glucocorticoid use compared to those with primary osteoporosis (4). Histologically there is a depletion in osteoblast numbers, a decreased trabecular wall thickness compared to cortical bone, and a decrease in bone formation rates, all indicating a deficient osteoblast state. This reduction in functional osteoblasts is as a result of a combination of factors including corticosteroid-induced impairment in mitogenic response of preosteoblasts to growth factors, corticosteroid-induced apoptosis of osteoblasts and a trans-differentiation of osteoblasts into adipocytes (28).

1.3.10 Family history

Genetics influence the determination of peak BMD from components that contribute to bone resorption and formation. About 60% to 80% of the variances in BMD estimated by the twin studies are due to a genetic component (29). A family history of osteoporosis is cited widely as a risk factor for developing osteoporosis. Daughters of women with osteoporosis have reduced bone mass, and are at an increased risk of fractures (30). One of the mechanisms by which genetics affects BMD has been attributed to allelic variation in the receptor for 1,25 dihydroxyvitamin D, one of the controllers of calcium metabolism. This polymorphism of the vitamin D receptor gene locus accounts for as much as a 75% variance in BMD (31).

1.3.11 Rheumatoid arthritis and other connective tissue diseases

Osteoporosis is a complication of rheumatoid arthritis (RA) and other connective tissue diseases (CTD) (32). With RA, there is both local or periarticular as well as systemic

osteoporosis. The periarticular diseases result from osteoclast activation and differentiation due to the presence of inflammatory cytokines resulting in absorption of bone matrix. Systemic osteoporosis is mainly due to a combination of factors such as the reduction of physical activity, as a result of the disease, and therapy used such as glucocorticoids. Other factors contributing to the development of osteoporosis in patients with CTD include advanced age, low BMI and female gender (33). An additional risk for osteoporosis with RA is in patients who are seropositive for rheumatoid factor and anti-cyclic citrullinated peptide antibody as well as those with longer disease duration (34).

1.4 Treatment of Osteoporosis

The treatment of osteoporosis comprises of both pharmacological and non-pharmacological interventions (35). Although non-pharmacological interventions are important they are often overlooked (36). These non-pharmacological approaches include vitamin D and calcium supplementation, muscle strengthening, weight-baring exercises and prevention of falls (35-37).

The primary goal of pharmacological therapy in osteoporosis is to prevent fractures by improving bone strength, relieve symptoms of fractures and skeletal deformities as well as maintain normal physical function (38).

1.4.1 Bisphosphonates

The gold standard and most widely used first-line pharmacological treatment for osteoporosis are bisphosphonates (39). For more than two decades they have been the leading agent used for osteoporosis treatment (40). They have efficacy in preventing fractures as well as bone loss due to aging, oestrogen deficiency as well as glucocorticoid use (1, 41, 42). Their mechanism of action is a complex combination of the inhibition of osteoclast function, increased osteoclast apoptosis and a decrease in osteoclast production. Unlike other therapies whose effects resolve after discontinuation, bisphosphonates are unique in that they bind to hydroxyapatite. This high affinity of bisphosphonates to hydroxyapatite results in a long skeletal half-life of the treatment and the bones become a reservoir for the drugs resulting in their effect remaining for years after discontinuation of treatment (42, 43). As a result of these properties bisphosphonates are able

to continue inhibiting bone resorption even though treatment has been discontinued, but to a lesser extent than with continued therapy (44). The binding affinity increases in rank order from risedronate, ibandronate, alendronate to zoledronic acid respectively (45).

Stemming from this prolonged effect on bones is a concern with regards to the continued use of these drugs. Reports related to severe complications, potentially associated with the continued use of these drugs, have now appeared in the literature. Of these, the most worrying being osteonecrosis of the jaw (ONJ) and atypical femoral fractures (AFF) (46, 47).

1.5 Osteonecrosis of the jaw

ONJ is defined as the development of necrotic bone in the oral cavity as a result of bisphosphonate therapy in patients who have not received radiation to the head and neck (48). Oral surgeons first reported this complication in 2003 (1). Most of the cases of ONJ have been as a result of zoledronic acid given intravenously (IV) for metabolic bone disease. Zoledronic acid is also used for the management of non-metabolic bone disease such multiple myeloma, and metastatic cancers, commonly breast and lung cancer which may be complicated by hypercalcaemia (49, 50). The dose of bisphosphonate therapy in cancer patients is usually a higher accumulative dose compared to patients treated for osteoporosis. However, in osteoporosis, the incidence of ONJ is estimated to only be between 1/10 000 and 1/100 000, which is just slightly higher than its incidence in the general population (1).

1.6 Atypical Femoral Fractures

The other concern is that of atypical femoral fractures (AFF), first reported in 2005 (47, 51). AFF are thought mainly to be a result of accumulation of fatigue damage due to the over suppression of bone turnover by bisphosphonate therapy. This accumulation of fatigue damage causes a delay in the healing of stress fractures which may result in AFF (40). The risk of development of AFF increases with the long-term cumulative use of bisphosphonate therapy, resulting in an increased risk of subtrochanteric or femoral shaft fractures with 5 or more years of treatment (52). Despite the risk associated with prolonged use of bisphosphonates, the risk of these AFF is 100 times less common than that of proximal femoral fractures. As a result the

risk/benefit ratio of bisphosphonate therapy far exceeds the number of fractures likely related to their use as more fractures are prevented by it (53).

1.7 Food and Drug Administration

Bisphosphonate therapy is generally safe and well tolerated. However, as a consequence of concern of the likely development of ONJ and AFF with prolonged bisphosphonate therapy, the Food and Drug Administration (FDA), in September 2011, reviewed the long-term safety and efficacy of bisphosphonate use, and recommended that use of bisphosphonates be reassessed after 3-5 years (54, 55). This led to the concept of a DH with bisphosphonate therapy.

1.8 Drug Holiday

Bisphosphonates are incorporated into the bone and continue to exert their effect for a period of time despite discontinuing treatment. As a result of this characteristic, as well as the concerns regarding their perceived harm, the concept of a DH was developed (56). The DH is an attempt to maximise benefit while minimising risk as has been seen with other chronic diseases such as parkinsonism (57). For the treatment of most chronic diseases it is unusual to think of the concept of DH as the beneficial effects of the drug rapidly deteriorate after stopping treatment. However, this is not the case with bisphosphonates as their anti-resorptive effect continues for many years after their discontinuation (56).

Currently, there is little evidence to support the need for the DH or to establish the effectiveness of treatment after restarting it. Furthermore, there is no evidence to guide how long to treat osteoporosis, the duration of the DH and when bisphosphate therapy should be re-introduced (58, 59). There is still more research needed to establish the length of time bisphosphonates continue to work after stopping them and whether stopping them actually reduced the risk of adverse effects (56).

1.8.1 Clinical Trials

Three large clinical trials for the long-term use of alendronate, risedronate and zoledronic acid and their discontinuation were used as a guide on the duration of continuous therapy and the DH (60). The primary goal for the treatment of osteoporosis is that of prevention of fractures. The three prospective trials were designed to assess the continued protection against osteoporotic fractures after discontinuing treatment versus those on treatment. The Fracture Intervention Trial (FIT) Long Term Extension (FLEX) trial looked at postmenopausal women treated for an average of 5 years with alendronate and then randomised for another 5 years of treatment or placebo. In the placebo group, there was an increased risk of clinical vertebral fractures compared to the treatment group (5.3% vs 2.4% respectively) and the hip BMD also declined, however levels remained above pre-treatment values. There were no differences for non-vertebral and morphometric fractures between the two groups (61). The 3-year extension of Health Outcomes and Reduction Incidence with Zoledronic Acid Once Yearly (HORIZON)-Pivotal Fracture Trial (PFT; HORIZON-PFT) enrolled patients who following 3 years of zoledronic acid, were randomised to either an additional 3 years of IV zoledronic acid or to placebo. The placebo arm resulted in a small decrease in BMD of 1.04% at the femoral neck. This shows evidence of the residual benefits of bisphosphonates even after discontinuation of use. The group with continued use of zoledronic acid had a 52% lower risk of morphometric vertebral fractures compared to the placebo (fracture rates 3.0% vs 6.2%, respectively). The risk of the clinical fractures did not vary between the two groups (62). The third trial is the Vertebral Efficacy with Risedronate Therapy (VERT) Multinational (VERT-MN). This had a group of patients given risedronate or placebo for 3 years, who were then followed up for a year after discontinuing treatment. Morphometric vertebral fractures were 46% lower in the treatment group vs the placebo (6.5%vs. 11.6% respectively). As there was no group continuing treatment, it was not possible to compare the fracture risk of stopping versus continued therapy in this study (63). The recommendations by clinical guidelines regarding the duration of therapy, and initiation on the DH are based on the evidence obtained from these 3 trials.

The American Association of Clinical Endocrinology (AACE) 2016 guidelines suggest a DH for high risk patients after 10 years on oral bisphosphonates and 6 years of IV zoledronic acid, as the risk benefit ratio of treatment beyond 10 years have yet to be established (64). High risk patients are those with a low hip T score $\leq$ -2.5, high fracture risk score according to FRAX®,

previous major osteoporotic fractures, older women or those who develop a fracture while on therapy, as defined by the American Society of Bone Mineral Research algorithm for the management of patients on long term bisphosphonate treatment (1). A DH is recommended for low risk patients after 5 years on oral bisphosphonates and after 3 years of IV zoledronic acid (64). The recently updated 2017 National Osteoporosis Guideline Group (NOGG) suggest a DH for patients with no fracture history where FRAX® risk falls below the NOGG threshold for intervention and the hip BMD T-score is ≥-2.5 (65). Locally the 2010 NOFSA guidelines recommend the implementation of a DH after 5 years of bisphosphonate use for low risk patients, but advocate individualization of therapy. With high fracture risk patients, a choice can be made to continue bisphosphonate therapy or switch to other non-bisphosphonate agents (4).

Non- bisphosphonate agents for the treatment of osteoporosis include other anti-resorptives anabolic agents as well as a combination of both. (66, 67). Denosumab is the first biological agent for osteoporosis treatment. It is a human monoclonal antibody that inhibits RANKL and decreases bone resorption (68). There is also use of selective oestrogen receptor modulators such as raloxifen (66). Calcitonin a synthetic peptide is reserved for when no other therapy is feasible (66). Teriparatide is an anabolic agent which is a parathyroid hormone analogue, and is mainly indicated for those with a history of prior fragility fractures (69). The recently approved sclerostin inhibitors such as romosozumab have dual action as they increase bone resorption markers and reduce bone resorption ones (67).

Despite these guidelines, the challenge remains in selecting the right patients who qualify for a DH. The current guidelines are based on the above-mentioned trials and do not offer guidance in many areas with regards to the management of patients in a real life clinical setting. There are no clear recommendations as to when to resume treatment after the DH and with what therapy. The exact frequency of BMD measurements, bone turnover measurements and assessment of CRFs during the DH, in guiding clinical decisions on restarting bisphosphonate treatment after the DH is lacking. However, the use of FRAX® may aid in decision making (60).

The question still remains, what happens to patients BMD density while on a DH? A recent retrospective study was carried out to look at the effect of a DH at various intervals on BMD

after stopping bisphosphonate therapy (60). BMD was measured at 12-18 months as well as 24-30 months after the discontinuation of therapy. Results at 12-18 months after discontinuation show that BMD decreased significantly at the lumbar spine (LS) [% change mean SD: -0.94(3.6), p=0.008], total hip (TH) [-1.4(2.4), p<0.001] and femur neck (FN) [-1,8(4.4), p<0.001]. After 24-30 months, a progressive decline in BMD was seen at the TH and FN with a percentage decrease of -2.52 (3.5) and -2.7 (4.76), [p<0.001] respectively. This study concluded that both bone loss and bone turnover increased within 12-18 months of stopping both oral and parental bisphosphonates suggesting that the persistence of effects of bisphosphonates may be shorter lived in real life compared to the clinical trial settings (60).

It is in light of this that it is important to determine data on what effect a DH has on the BMD on patients attending the CMJAH Osteoporosis clinic. The current protocol on the initiation of a DH at the clinic is based on the 2010 NOFSA guidelines, which in turn were written based on evidence from the above mentioned clinical trials.

Aim

To evaluate the effect of a bisphosphonate DH on BMD in the treatment of osteoporosis with IV zoledronic acid and/or oral alendronate.

Study Objectives

Primary Objective

1. To determine the effects of a DH on BMD.

Secondary Objectives

2. To describe the study population.
3. To analyse the effect of bisphosphonate on BMD during therapy.
4. To compare the group of patients with improved or maintained BMD versus those with a decrease in BMD, specifically within the following parameters:
    - Demographics

- Risk factor profile
- Co-morbidities

5. To determine the presence of any co-existing diseases and risk factors in the study population, within the following parameters:
    - BMI
    - Smoking
    - Glucocorticoid therapy
    - Excessive alcohol intake
    - Family history of osteoporosis
    - Co-existing medical conditions
    - Hypogonadism or premature menopause
6. To assess the relevant biochemistry results in the study population
7. To assess the compliance to the 2010 NOFSA guidelines by doctors treating patients at the Osteoporosis clinic.

Methodology

Study Design

This was a retrospective review of clinical data with an analytical and descriptive element. The data was collected from records of patients attending the Osteoporosis clinic at CMJAH between 2000 and 2016.

Setting

Osteoporosis clinic, which is a specialised endocrine clinic at a tertiary institution (CMJAH), located in area 356.

Study Population and Samples

This study was conducted at the Osteoporosis clinic at CMJAH. The population under study were all adults (above the age of 18 years), attending the clinic, being treated for osteoporosis, who have received zoledronic acid from inception of its use up to 31 December 2016. The

sample size was dependent on the total number of patients who have received at least 5 yearly doses of zoledronic acid or the equivalent of 5 years of alendronate therapy.

Eligibility Criteria

Inclusion Criteria

1. Age above 18 years.
2. All patients who have received at least 5 yearly doses of zoledronic acid.
3. All patients who have received a total equivalent of 5 years of treatment with oral alendronate switched to zoledronic acid.
4. All patients with at least one DEXA scan before and at least one follow-up DEXA scan after a DH.

Exclusion Criteria

1. Patients who have received less than 5 yearly doses of zoledronic acid.
2. Patients with no follow-up DEXA scan after a DH.

Study Tools

All records of patients who had received at least 5 doses of zoledronic acid or equivalent oral alendronate as well as their BMD at the Osteoporosis clinic were identified. A data sheet (Appendix A) was used to collect and record the number of doses of zoledronic acid or equivalent oral alendronate given to the patients. It also recorded their initial BMD at diagnosis, the last BMD before stopping treatment, and their subsequent BMD done during a DH. These values were obtained from the patients' files during the years 2000-2016.

Statistical analysis

For the descriptive statistics, continuous variables were reported using mean and SD from the mean if the data was normally distributed. In the case where the data was not normally

distributed median and interquartile range (IQR) were applied. The categorical variables were reported using frequencies and percentages. One-way repeated measured analysis of variance (ANOVA) was used to compare BMD measured at different time points. Multiple liner regression was used to explore the relationship between the risk factor variables listed above and the change in BMD. The effect of the DH on the BMD was assessed using ANOVA. Adherence to protocol by the doctors treating patients was based on descriptive data, with frequencies and percentages.

Ethics

This study was carried out at CMJAH, Osteoporosis clinic, in partial fulfilment of the requirements of the Masters in Medicine degree. Ethics approval was sought from the University of Witwatersrand Human Research Ethics Committee and permission was also obtained from the hospital authorities.

Written permission to access patient files from the Bone clinic was obtained from Professor Raal (Head of Endocrinology Department at CMJAH). Unique patient identifications numbers were used on the data collection sheet to protect the identity of the study participants. The patients file number and the information from the file was kept on a separate sheet for further reference use if needed. No remuneration was given for the medical records reviewed. Findings will be published in academic journals and will be used to help improve the care and management of patients with osteoporosis at CMJAH as well as other units in the country.

Limitations of the study

1. The study population was small as per inclusion criteria, and only patients who had completed at least 5 doses of zoledronic acid or switched from alendronate to zoledronic and have a subsequent DEXA scan after a DH were used.
2. The data obtained was also dependent on the quality of the recording of information done by the doctors attending to the patients during this period under study and at times may not have been complete or accurate.
3. The study was retrospective and therefore there was no control group of those who did not go on a DH.

4. There were variable time periods between the initial and subsequent BMD done during therapy as well as the duration of the DH and this varies from the standardized clinical trial scenario. This was due to the fact that the study was a retrospective observational one.

Timing

Gant Chart showing the timeline of the study:

2017	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
Literature Review								
Preparing Protocol								
Protocol Assessment								
Ethics Application								
Data Collection								
Data Analysis								

2018	Jan	Feb	Mar	Apr	May
Data Analysis					
Write Up					

Funding

Study expenses were self-funded, and these costs included stationary, printing and transport. Courses offered by the University to assist with knowledge on data analysis and writing up of the thesis were attended

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Chapter 2: Submissible Article

TITLE: IMPACT OF A BISPHOSPHONATE DRUG HOLIDAY ON THE BONE MINERAL DENSITY IN PATIENTS WITH OSTEOPOROSIS AT CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL (2000-2016)

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Short title: Impact of a Drug Holiday on Bone Mineral Density at Charlotte Maxeke Johannesburg Academic Hospital

Conflict of Interest: Nil

Keywords: Drug holiday, bone mineral density, bisphosphonate

Word count: 3051

Abstract word count:151

Abstract

Background: Bisphosphonate therapy has efficacy in the management of osteoporosis. Rare adverse effects related to its prolonged use has resulted in the concept of a "drug holiday" (DH).

Objective*:* To evaluate the effect of a bisphosphonate DH on bone mineral density (BMD).

Methods: A retrospective cohort study of 97 patients with osteoporosis who had undertaken a DH was conducted.

Results: The median age at the initiation of bisphosphonate therapy was 63 years. The median duration of the DH was 2 years. The overall effect of the DH on BMD as a percentage change from the beginning to the end of the DH showed a decrease in BMD at the lumbar spine [-3.3%, p=0.398]; radius and ulnar [-16.7%, p=0.03] and total hip [-8.9%, p=0.001]. 4 patients sustained fractures during the DH.

Conclusion: An individualised approach is key in assessing the duration of the DH and only low risk patients should be considered.

Introduction

Every 3 seconds, worldwide, a fracture occurs as a result of osteoporosis, mainly hip and spine fractures resulting in significant morbidity and mortality and a massive cost to society (1). However, despite being such a common metabolic bone disease, osteoporosis has attracted little attention in many developing nations. Globally there has been a shift towards the distribution of deaths from the younger to the older population and also from communicable to non-communicable diseases (2).

Osteoporosis is a progressive systemic disease of the skeletal system characterised by micro-architectural deterioration of the bone tissue as well as low bone mass, increasing bone fragility and susceptibility to fracture (3). The diagnosis of osteoporosis is made by measurement of bone mineral density (BMD) using dual energy X-ray absorptiometry (DEXA) of the lumbar

spine, neck of femur and total upper femur (3). The World Health Organisation (WHO) definition of osteoporosis is a BMD 2.5 standard deviations (SD) or more below the young adult mean value for a woman (thus a T score ≤-2.5 SD in postmenopausal women) (4). A rapid bone loss defined as an annualised bone loss rate of at least 1 SD of the sex- specific loss rate at each skeletal site is also used to determine a high risk of fractures (5). Due to the low sensitivity and high specificity associated with use of BMD the World Health Organisation (WHO) has developed an algorithm for a 10-year absolute fracture risk called the Fracture Risk Assessment tool (FRAX®) (2).

The primary goal of pharmacological therapy in osteoporosis is to prevent fractures by improving bone strength, relieve symptoms of fractures and skeletal deformities as well as maintain normal physical function (6). The gold standard and most widely used first line treatment for osteoporosis are bisphosphonates (7). Unlike other therapies whose effects resolve after discontinuation, bisphosphonates are unique in that they bind to hydroxyapatite, and therefore their effects remain for years after discontinuing this therapy (8). As a result of a prolonged effect on bones there is a concern with regards to the continued use of these drugs, mainly the possible development of osteonecrosis of the jaw (ONJ) and atypical fragility fracture (AFF) (9, 10).

As a consequence of these concerns the Food and Drug Administration (FDA), in September 2011, reviewed the long-term safety and efficacy of bisphosphonate use, and recommended that use of bisphosphonates be reassessed after 3-5 years (11, 12). Thus, the concept of a drug holiday (DH) was developed. Currently, there is little evidence to support the need for a DH or to establish the effectiveness of treatment after restarting it. Furthermore, there is no evidence to guide how long to treat osteoporosis, the duration of the DH and when bisphosphate therapy should be re-introduced (13, 14).

Three large clinical trials for the long-term use of alendronate, risedronate and zoledronic acid and their discontinuation were used as a guide on the duration of continuous therapy and the DH (15-18). The recommendations by clinical guidelines regarding the length of treatment and initiation of a DH are based on these 3 trials.

The American Association of Clinical Endocrinology (AACE) 2016 guidelines suggest a DH for high risk patients after 10 years of oral bisphosphonates and 6 years of IV zoledronic acid (19). In South Africa the 2010 NOFSA guidelines recommend a DH after 5 years of bisphosphonate use for low risk patients (4). However, the real impact of a DH in a real-life setting versus the clinical trial setting is poorly established. Our study goal was to describe the effect of a DH on BMD at our facility.

Methods

This study was a retrospective review of clinical records looking at the changes in BMD during a bisphosphonate DH in patients with osteoporosis attending a clinic in area 356 at Charlotte Maxeke Johannesburg Academic Hospital. The data was collected during the period from January 2000 till December 2016. The population under study was all adults (above the age of 18 years) attending the clinic and had received zoledronic acid and or the equivalent of oral alendronate for at least 5 years and subsequently gone on a DH with a DEXA scan done during the DH. The quantity of alcohol consumed by the patients was defined in the clinical notes by the attending physician as either nil, moderate or high. Premature menopause was defined as any woman who attained menopause before the age of 45 and male hypogonadism was defined by a recorded low testosterone level. Exclusion criteria were those who had received less than 5 yearly does of intravenous and or oral therapy as well as those who did not have a follow up DEXA scan after the DH. This study was approved by the University of Witwatersrand Medical Human Research Ethics Committee (Ethics clearance number – M170710).

Measurements

Demographics and clinical information, as well biochemical laboratory parameters such as serum creatinine and calcium, were collected from each of the patient's file. The presence and absence of fractures as well as site and timing together with the BMD by DEXA were also extracted from the records. The presence or absence of co-morbidities as well as other medication was noted. The effect of bisphosphonates on BMD during treatment was demonstrated by categorising BMD into yearly time points based on the duration of treatment with a bisphosphonate. The BMD values at different time points during the drug holiday were obtained and also categorised into yearly time points at 1,2,3,4,5 and beyond. All scans were

performed on a HOLOGIC® DEXA machine. Additional information was gathered on the indication for initiation of bisphosphonate therapy, type and duration of therapy, correct termination of therapy and adherence to the yearly blood tests, in order to assess the adherence to protocol by the attending doctors at the clinic.

Statistical analysis

Demographics, risk factors and clinical features of patients included in the study were described using proportions for categorical variables, mean and SD for normally distributed continuous variables and median and inter-quartile range (IQR) for non-normal continuous variables. Characteristics of patients who had fractures during treatment and during the DH were compared to those of patients who did not get fractures using Fisher's exact tests for categorical variables and paired T-tests for comparison of means. To investigate the effect of bisphosphonates on BMD of the radius and ulnar (RU), lumbar spine (LS) and total hip (TH), linear prediction graphs with confidence intervals of the respective BMD by time on treatment and duration of DH were plotted. Linear regression models were fitted to investigate whether the trends in BMD over time were statistically significant. Binary logistic regression models were fitted to compare patients with improved or maintained BMD versus those with a decrease in BMD during the DH.

Results

A total of 97 patients (96.9% female; with 47.4% White, 30.9% Indian, 15.5% African and 6.2% Coloured) were included in this study (*Table 2.1*). The median age at the time initiation of therapy was 63 (IQR 56-68) years, with a median BMI of 26.9 (IQR 23.5-30.6) kg/m^2. The median duration of treatment between the first and last BMD scan done before initiation of the DH was 5 (IQR 4-5) years with the median duration of the DH being 2 (IQR 2-3) years. Regarding the type of therapy used, 79 % used zoledronic acid, 15% alendronate and 5% used a combination of both treatments at different time points. The reasons for initiating therapy included, BMD (T score $\leq$-2.5) in 58%; osteopenia and a fracture history in 22%; increased bone turnover in 16% and rapid bone loss in 4% of the subjects. The majority of the patients had other co-morbidities (88.7%). Of these, 16% had rheumatoid arthritis, 16% had hypothyroidism, 6% had other connective tissue or autoimmune diseases, 6% had with

inflammatory bowel disease and the remaining 69% had other co-morbid conditions such as hypertension, diabetes mellitus, dyslipidaemia and asthma.

Effect of bisphosphonate on BMD

The mean ± SD BMD (T score) before treatment with bisphosphonates was -2.34±1.01 at the LS, -1.56±0.99 at TH, and -2.29±1.13 at the RU. The overall percentage change BMD (median and IQR) at the various sites on bisphosphonate therapy showed an increase at LS 12.90 (-2.38-25.93) p<0.001, RU 8.00 (-50.00-14.89) p=0.601 and TH 5.72 (-12.13-26.97) p=0.297.

Figure 2.1 shows the relationship of the effect of time on treatment on BMD at the various sites. In relation to change in BMD and duration of treatment, there was an increase in BMD at TH (p=0.193) and LS (p=0.413), however none of these where statistically significant. There was no significant change in BMD at RU (p=0.967).

Effect of drug holiday on BMD

The overall effect of the DH on BMD (% change expressed as median (IQR) was assessed at the various sites. All three sites showed a decrease in BMD with only the RU and TH being statistically significant [LS -3.13(-25.00-12.50) p=0.398; RU -16.67(-26.67--2.13) p=0.031 and TH -8.89(-27.78-10.71) p=0.001]. Figure 2.2 shows the relationship of the duration of the DH and its effect on the BMD at the different site. There were no statistically significant changes in BMD with time on a DH at all sites [RU (p=0.993), LS (p=0.971)] except for a trend towards significance for TH (p=0,058).

Predictors of change in BMD during drug holiday

The association of demographic, clinical variables and risk factors on BMD at the various site during the DH was also assessed (*Table 2.2).* There was no statistically significant risk factor associated a decrease in BMD during the DH versus an increased or maintained BMD during this period.

Fractures during treatment and drug holiday

Nearly half of the patients, 46% (n=45 of 97) had a history of a fracture at various sites, vertebral 13% (n=13), non-vertebral 23% (n=22) and at both sites 10 % (n=10). It was however not specified if they were fragility fractures and the exact sites of some of the none vertebral fractures was not specified. Of these, 87% of the patients (n=39) had fractures sustained before initiation of therapy. 18% of the fractures (n=8) were sustained during therapy. There was no significant risk factor associated with the fractures that occurred during bisphosphonate therapy. The remaining 9% (n=4) of the fractures occurred during the DH, and age (p=0.030) was the only significant risk factor in these patients. Only one patient who sustained a fracture during the DH had had a previous history of a fracture prior to initiation of treatment.

Biochemical data analysis

Of the 97 patients in the study population only 19 had chronic kidney disease with (n=18) 94.7% stage 3A and (n=1) 5.3% stage 3B. Prior to initiation of therapy (n=3) 3.1% of the patients had hypocalcaemia, (n=81) 83.5% had normal serum calcium levels, (n=7) 7.2% had hypercalcaemia and a total of (n=6) 6.2% were unknown. Of the 7 with hypercalcemia only one patient had associated hyperparathyroidism, and thus primary hyperparathyroidism. There were however 25 patients with high parathyroid hormone levels. The 25-OH-Vitamin D levels for the patients prior to therapy were as follows, deficient (n=22) 22.7%, insufficient (n=19) 19.6%, sufficient (n=38) 39.2% and unknown (n=18)18.6%. Of the 22 with 25-OH-Vitamin D deficiency(n=8) 36.4% also had hyperparathyroidism and (n=14) 63.6% had normal parathyroid hormone (PTH) levels. There were no patients with thyrotoxicosis prior to the initiation of therapy or secondary to thyroxine over replacement for hypothyroidism.

Adherence of clinicians to protocol

During the management of the patients at the clinic by the various clinicians, (n=89) 92% received yearly dosing of their bisphosphonate therapy. There was however poor adherence to the yearly blood investigations required as per protocol with only ((n=1) 1% of the patients having had all their yearly tests done. This however could have been compounded by the non-compliance of patients to getting their bloods done once ordered by the treating doctors. The

correct termination of therapy with the initiation of the DH was also checked with only (n=6) 6% of the patients having been inappropriately terminated.

Discussion

Outside the setting of clinical trials, there is limited information available in a real life setting on the evolution of BMD and the prediction of fracture risk during bisphosphonate DH (20, 21). This retrospective study was conducted in order to determine the effect of a bisphosphonate DH in a cohort of 97 patients with osteoporosis being followed up at a single speciality clinic at CMJAH.

There is limited if any data in South Africa on the effect of bisphosphonate therapy on BMD in patients with osteoporosis as well as the effect of a DH on BMD. This study was the first that we are aware of that looked at the effect of a DH on the BMD of patients with osteoporosis in South Africa as well as in Africa

In our study, there was an overall decrease in BMD during the DH at all sites measured. The BMD at the RU ($p=0.031$) and TH ($p<0.001$) were the two sites that had a statistically significant decline in BMD during the DH. This is in keeping with the main clinical trials carried out to assess the effect of a DH on BMD(16-18). This was also the case in a study that looked at the effect of a DH on BMD in a non-trial setting (22). There were no significant risk factors associated with the decrease in BMD during DH at all sites.

There is a substantial mortality associated with both hip and vertebral fractures (23). Four patients sustained fractures during the DH, two of which were non-vertebral, one had both a vertebral and non-vertebral site and one sustained a vertebral fracture. Age was the only significant risk factor for fractures during the DH ($p=0.030$). There is therefore need for caution in elderly patients with low BMD as they can fracture during the DH despite years on treatment (24).

The efficacy of the use of bisphosphonate therapy in osteoporosis resulting in an increase in BMD and a reduced risk of fractures is well proven (25). The greatest and only statistically significant increase in BMD on treatment, of 12.9%, was observed at LS ($p<0.001$) compared

to all the other sites. This is mainly because the LS is made up primarily of trabecular bone which exhibits greater uptake of bisphosphonate during treatment than predominantly cortical bone, of which the TH and RU is made up of a greater proportion (26).

In our study population, there was as greater number of White (47.4%) and Asian (30.9%) compared to the African (15.5%) and Coloured (6.2%) patient population. This confirms the findings of studies carried out in South Africa as well as in the USA, that showed a significant difference in the incidence of both osteoporosis and fractures among different races and ethnic groups (4, 27-29).

The main reason for initiation of bisphosphonate therapy for the cohort, 58%, was a low BMD (T score ≤-2.5). However, 46 % of the cohort sustained fracture and of these 87 % occurred before the initiation of bisphosphonate therapy. 22% were initiated based on a diagnosis of a history a fracture with osteopenia. Despite the proven efficacy of bisphosphonate therapy in osteoporosis patients and fracture prevention, treatment of only patients with osteoporosis has a limited capacity in total fracture prevention (30). This is because fractures tend to occur in a larger group of women with BMD in the osteopenic range (31). A recent study showed a significant risk reduction of vertebral fragility fractures in osteopenic woman who received zoledronic acid than women who received placebo (30). There is therefore a need to consider early treatment of patients with osteopenia with bisphosphonate therapy as a means of a greater fracture risk reduction.

The main reason for the need of a DH with bisphosphonate therapy is the fear of the severe adverse events, namely ONJ and AFF (9, 10). The concept of a DH seems logical based on the pharmacokinetics of bisphosphonates and the concern for these long term adverse events (23). As a result, many physicians have been noted to stop bisphosphonate therapy automatically without putting into consideration a patient's individual risk of a fracture (23). In our study, there was no record of any of these severe adverse events in the cohort. The incidence of these rare side effects is low (1). As a result, high risk patients with moderate to high risk of fractures, in whom the benefit of bisphosphonate therapy outweighs the risk of the rare adverse events, may be considered for on-going therapy (23). The decision of who goes on a DH must be individualized based on multiple risk factors such as a low BMD, clinical risk factors and a history of incident fractures (32, 33). Low risk patients may however benefit from a DH (19).

However, there is still no consensus on the duration of a DH and how to best monitor patients once they are on a DH (23). There is therefore need for further research in this area.

A limitation of the study was that it was retrospective in nature. There was no control group as all patients do go on a DH. Data was collected from clinical notes which at times have missing data and the information was in relation to patient visits which were inconsistent throughout the cohort. Despite this challenge, the information that was available was extensive and enabled the data collection process to take place. There were variable durations of bisphosphonate therapy, different bisphosphonates used, varied intervals between DEXA scans as well as the length of the DH between patients, compared to a clinical trial scenario. However, this allows us to appreciate what really takes place in a real life clinical situation. Lastly a single clinical practice was used and additional replication with a larger sample size from multiple centres is needed. Despite these limitations this is the first and largest study of its kind reported in South Africa, and therefore its findings open the doorway for further, larger and possible prospective studies in this area.

Conclusion

The study showed a significant decrease in BMD at the total hip and the distal forearm after a mean DH of 2 years. A DH should be cautiously considered with the long-term use of bisphosphonates, especially in the elderly, those with very low BMDs and with on-going steroid use. An individualised approach based on risk factor assessment, fracture risk, and BMD is key in assessing the duration of the DH. Therefore, only low risk patients should be considered for a DH.

Table 2.1: Patients characteristics

Demographic Characteristics	**N (%)**
Gender	
Male	3 (3.09)
Female	4 (96.91)
Age (median, IQR) years	63 (56-68)
Race	
African	15 (15.46)
Indian	30 (30.93)
White	46 (47.42)
Coloured	6 (6.19)
Risk Factors	
BMI (kg/m²)	26.89 (23.52-30.61)
Smoking	
Yes	14 (14.43)
No	70 (72.16)
Ex-smoker	12 (12.37)
Unknown	1 (1.03)
Alcohol	
Nil	36 (37.11)
Moderate	4 (4.12)
Unknown	57 (58.76)
Glucocorticoid use	
Yes	28 28.87)
No	69 (71.13)
Family history	
Yes	20 (21.05)
No	75 (78.95)
Premature menopause	
Yes	9 (9.28)
No	85 (87.63)
Unknown	3 (3.09)
Male hypogonadism	
Yes	1 (33.3)
No	2 (66.7)
Co-medical conditions	
Yes	86 (88.66)
No	11 (11.34)
Clinical Features	
Duration of treatment (Median, IQR) years	5 (4-5)
Duration of drug holiday (Median, IQR) years	2 (2-3)

Table 2.2: Factors associated with decreased BMD during the drug holiday

Demographic Characteristics	Lumbar spine Odds ratio (95% CI)	P value	Total Hip Odds ratio (95%)	P value
Age (at initiation of therapy) years	0.94 (0.89-1.01)	0.094	1.03 (0.98-1.10)	0.233
Race				
African / Coloured	1 (Ref)		1 (Ref)	
Indian	0.50 (0.12-2.03)	0.336	0.90 (0.22-3.61)	0.878
White	0.58 (0.13-2.57)	0.482	0.70 (0.15-3.15)	0.640
Risk Factors				
BMI (kg/m²)	0.97 (0.91-1.05)	0.494	1.0 (0.97-1.02)	0.935
Smoking				
No	1 (Ref)		1 (Ref)	
Yes / Ex-Smoker	1.43 (0.48-4.25)	0.525	3.10 (0.91-10.60)	0.071
Glucocorticoid use				
No	1 (Ref)			
Yes	0.82 (0.24-2.79)	0.773	1 (Ref)	0.836
Family History			0.88 (0.25-3.04)	
Yes	1 (Ref)			
No	1.24 (0.39-3.98)	0.706	1 (Ref)	0.537
Premature menopause / Male hypogonadism			1.49 (0.42-5.55)	
No	1 (Ref)			
Yes	0.67 (0.13-3.25)	0.620	1 (Ref)	0.207
Co-medical conditions			0.37 (0.08-1.74)	
No	1 (Ref)			
Yes	2.07 (0.47-9.13)	0.337	1 (Ref)	0.370
			2.03 (0.43-9.54)	

Ref= Reference.

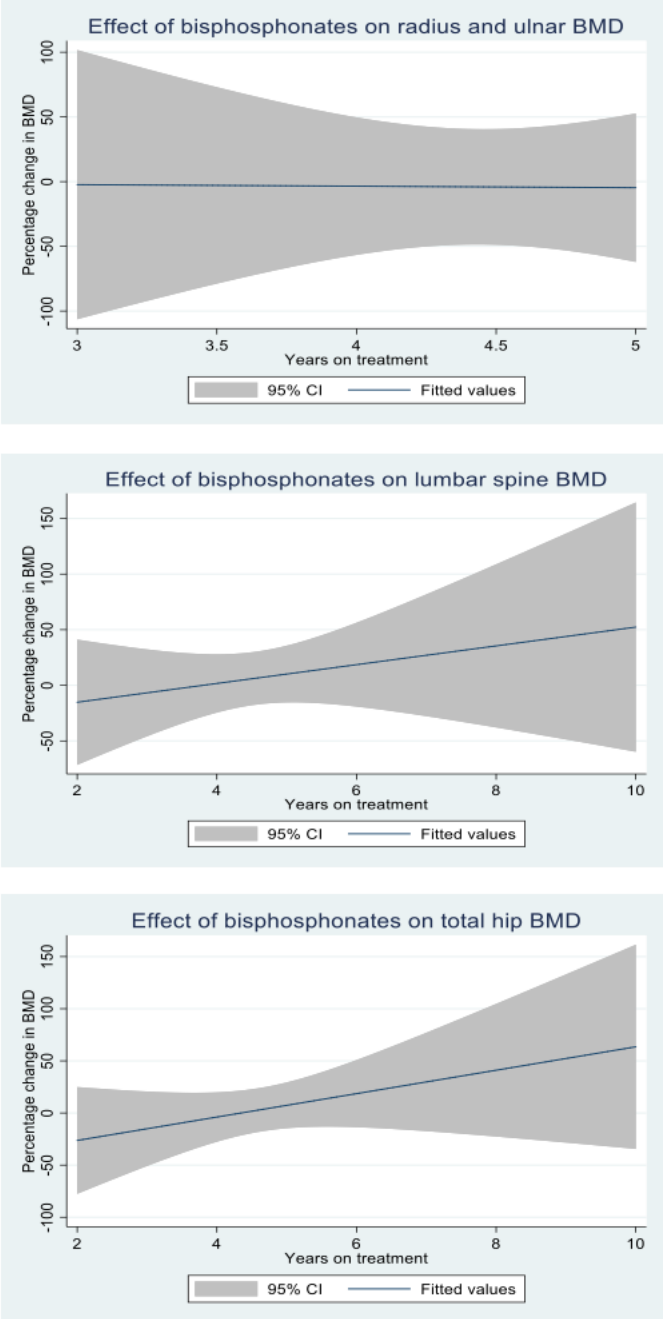
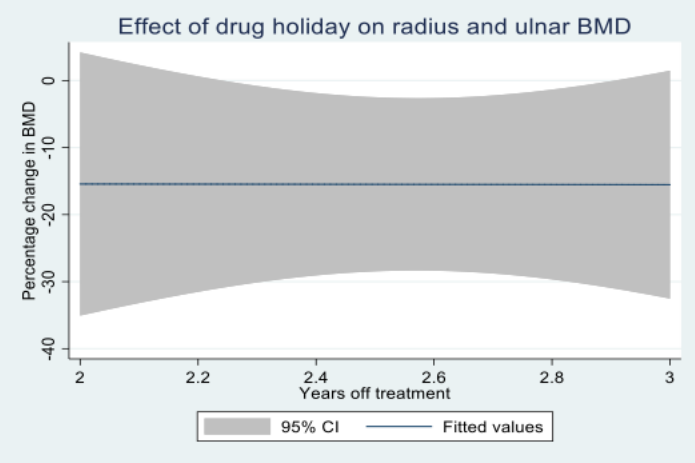
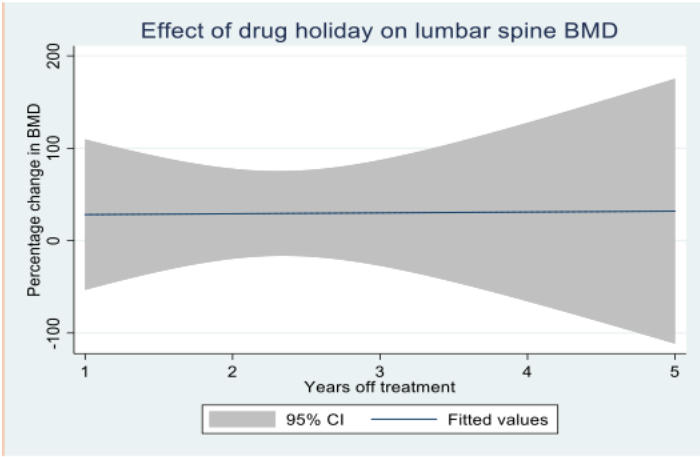


Fig 2.1 Effect of bisphosphonate therapy on BMD at radius and ulnar, lumber spine and total hip





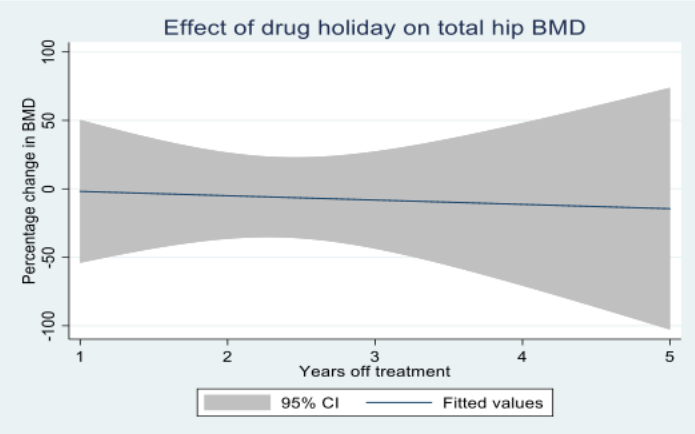


Fig 2.2 Effect of drug holiday on BMD at radius and ulnar, lumber spine and total hip

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Chapter 3: Appendix

A: Data collection sheet

Study number | | | | | | |

Date of data collection | | | | | | |

DEMOGRAPHIC DATA

Age at enrolment | |

Gender (male =1; female=2) |

Self-identified ethnic group |

(African=1; Indian=2; White=3; Coloured=4; Missing=5)

RISK FACTORS

Weight at enrolment ☐

Height at enrolment ☐

BMI ☐

Smoking (yes=1; no=2; ex=3) ☐

Alcohol intake ☐
(nil=1; moderate=2; high=3;unknown=4)

Glucocorticoid therapy (yes=1; no=2) ☐

If yes, please specify reason and type and dose of steroid therapy/day:

_____

Duration of glucocorticoid use Months ☐

Years ☐

Family history of osteoporosis (yes=1; no=2) ☐

Co-medication

.

.

.

.

.

Co-existing medical condition(s) (yes=1; no=2) ☐

Rheumatoid arthritis

Connective tissue disease (SLE, scleroderma)

Inflammatory bowel disease

Celiac disease

Hyperthyroidism

Renal disease

Other

Male Hypogonadism (yes=1; no=2) ☐

Premature menopause (age<40 yrs.) ☐

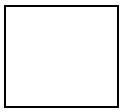
(yes=1; no=2)

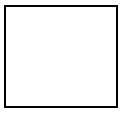
CLINICAL DATA

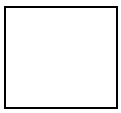
Table 3.1 Bone mineral densities and sites

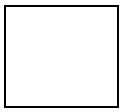
Date of visit	BMD1	BMD2	BMD3	Site 1	Site 2	Site 3	Treatment	Treatment type

Initiation of treatment done correctly (yes =1; no=2) ☐

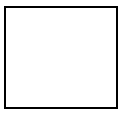
Yearly dosing given (yes=1; no=2) 

Compliance to routine investigations (yes=1; no=2) 

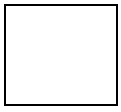
Appropriate termination of therapy based on risk profile (yes=1; no=2) 

Duration of drug holiday (years) 

History of fracture/s (yes=1, no=2) 

Site/s of fractures (vertebral=1; non-vertebral=2; both=3) 

Timing of fracture:

(pre-treatment=1; during treatment=2; during drug holiday=3) 

BIOCHEMICAL DATA

Table 3.2 Biochemical Data

	Initial; date	Latest; date
Creatinine(eGFR)		
Parathyroid Hormone		
Corrected Calcium		
Gamma-glutamyltransferase		
Thyroid Stimulating hormone		
25-OH-Vitamin D		
Alkaline Phosphatase		

APPENDIX B – Ethics certificate

R14/49 Dr R Rukarwa

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M170710

NAME: (Principal Investigator)	Dr R Rukarwa
DEPARTMENT:	School of Clinical Medicine Department of Internal Medicine CH Baragwanath Hospital
PROJECT TITLE:	Impact of biophosphate drug holiday on the bone mineral density, on patients with osteoporisis at Charlotte Maxege Johannesurg Academic Hospital from 2000 to 2016
DATE CONSIDERED:	28/07/2017
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Professor FJ Raal
APPROVED BY:	Professor C Feldman, Co-Chairperson, HREC (Medical)
DATE OF APPROVAL:	30/08/2017

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on 3rd floor, Phillip V Tobias Building, Parktown, University of the Witwatersrand.
I/We fully understand the conditions under which I am/we are authorised to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to resubmit to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. in this case, the study was initially reviewed in July and will therefore be due in the month of July each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

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ORIGINALITY REPORT

6%	1%	6%	0%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	Xu, L. H. R., B. Adams-Huet, J. R. Poindexter, and N. M. Maalouf. "Determinants of change in bone mineral density and fracture risk during bisphosphonate holiday", Osteoporosis International, 2015. Publication	3%
2	"IOF World Congress on Osteoporosis & 10th European Congress on Clinical and Economic Aspects of Osteoporosis and Osteoarthritis : Poster Presentation Abstracts", Osteoporosis International, 05/2010 Publication	1%
3	Handa, R.. "Osteoporosis in developing countries", Best Practice & Research Clinical Rheumatology, 200808 Publication	1%
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