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AUDIT OF DXA SCANS DURING BISPHOSPHONATE THERAPY IN PATIENTS WITH OSTEOGENESIS IMPERFECTA AT CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

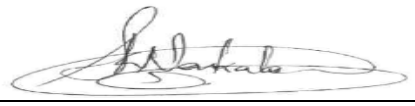
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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, in partial fulfilment for the degree of Master of Medicine in Paediatrics

Johannesburg 2020

DECLARATION

I, Akhona Siralarala, declare that this research report is my own work. It is being submitted for the degree of Master of Medicine in the branch of Paediatrics in the University of the Witwatersrand. It has never been submitted before for any degree or examination at this or any other university.



Signature

16th day of March 2020 in Johannesburg

DEDICATION

To my late parents who made me the person I am today and to my husband and my four beautiful children, for supporting me.

ABSTRACT

Introduction: DXA scan measurements and changes, pre and post bisphosphonate (BP) therapy have not been conducted at Chris Hani Baragwanath Academic hospital (CHBAH) or other centres in South Africa that are treating Osteogenesis Imperfecta (OI) patients. There are a few studies that have confirmed an increase in bone mineral content (BMC) in OI children treated with BPs. However, none of these studies have a predominantly black population which was novel to this study.

Objectives: The aim of this study was to evaluate and assess the change in bone mineral density in OI children treated with BPs at CHBAH, South Africa.

Methods: Medical files of 104 OI patients who were seen at the Metabolic Bone clinic from 01 January 2006 till 31 December 2015 were reviewed. DXA measurements were available on 33 patients that received BPs from baseline and during therapy at three time points (9-18 months, 18-30 months and >30 months). Three methods using white male and female reference values for calculating bone mineral content (BMC) and bone mineral density (BMD) Z- scores on whole body less head (WBLH) and lumbar spine (LS) were applied and analysed as follows: 1. Calculated Z-scores using the Zemel equation and 2. Height adjusted Z-scores for >5 year old children only and 3. DXA machine calculated Z-scores.

Results: WBLH BMC and BMD Z-scores and LS BMC and BMD Z-scores showed significant increases over 30 months of treatment ($p<0.01$). The mean BMC and BMD Z-scores (WBLH and LS) at baseline were < -2 confirming low bone mass. Mean calculated Z-scores after 30 months had reached a Z-score > -2; mean height adjusted Z-scores reached a Z-score > -2 from 9-18 months onwards and mean DXA machine calculated Z-scores reached a mean Z-score > -2 after 18 months. At baseline, 83% of patients had a LS BMD height adjusted Z-score < -2 and after 30 months of BPs treatment, none of the patients had a LS BMD height adjusted Z-score < -2 ($p<0.001$). The mean fracture rate at baseline prior to BP therapy was 16.44 per patient year (95% CI: -1.98-34.85) and significantly decreased to 0.62 (0.27-0.97) at 9-18 months and to 1.1 (0.49-1.65) at >30 months ($p<0.001$) during BP therapy.

Conclusion: Bisphosphonate therapy significantly increased height adjusted LS BMD Z-scores to >-2 and decreased the number of fractures after 9-18 months of BP treatment in South African OI patients thus supporting the use of BPs in OI patients to minimise hospitalisation and treatment costs related to fractures.

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LIST OF ABBREVIATIONS

aBMD	areal bone mineral density
AD	autosomal dominant
AR	autosomal recessive
BA	bone area
BMC	bone mineral content
BMD	bone mineral density
BPs	bisphosphonates
CHBAH	Chris Hani Baragwanath Academic Hospital
DI	dentinogenesis imperfecta
DXA	Dual Energy Xray Absorptiometry
GH	growth hormone
HAZ	height adjusted Z-score
LS	lumbar spine
OI	Osteogenesis imperfecta
PTH	parathyroid hormone
WBLH	whole body less head
WAZ	weight adjusted Z-score

CHAPTER 1: INTRODUCTION AND LITERATURE REVIEW

1.1 Introduction

Osteogenesis imperfecta (OI) is one of the most common skeletal dysplasias (1). It is an inherited disorder of connective tissue characterized by bone fragility and fracture (1, 2). The bone fragility has led to the adoption of the trivial name "brittle bone disease." This fragility is caused by mutations in one of the two genes, COL1A1 and COL1A2 that encode the chains of type 1 collagen, the major protein of bone, encoding pro alpha 1 and pro alpha 2 chains respectively (1, 3, 4). It occurs mainly due to an autosomal dominant mutation. These mutations are either genetically inherited or are new mutations and a recessive inheritance pattern can also occur (1).

The severity of OI ranges from lethal in the perinatal period, due to multiple severe fractures in utero; to occasional fractures (1, 3).

OI can manifest itself with one or more of the following features: blue sclerae, triangular facies, macrocephaly, adult onset hearing loss, joint laxity, fractures and growth retardation (4, 5). In addition, OI patients may present with skeletal deformities, short stature and wormian bones in the occipital region of the skull that is seen on lateral radiograph of the skull. (4, 5).

A multidisciplinary team approach is essential for the diagnosis, counselling of parents and patients and to tailor treatment needs for individual patients depending on the type or severity of OI and the age of the patient.

1.2 Incidence and classification of OI

Incidence of OI in South Africa is not well documented however it is estimated to be 1 per 20000 live births worldwide. However, the mild form is under-diagnosed and the prevalence may be higher (6).

There are no racial, ethnic or sex differences and age of onset varies with the type of OI. About 80-90% of people with OI have mutations in one of the two genes- COL1A1 or COL1A2 genes (4).

The classification of OI includes the different genetic causes, descriptive grouping of the syndrome, clinical characteristics and inheritance patterns as shown in Table 1 below (7).

Table 1.1 Expanded classification of OI

Type of OI	Inheritance	Phenotype	Genetic defect
Classical Sillence Types			
I	AD	Mild	COL1A1
	X-linked	Mild	PLS3
II	AD	Lethal	COL1A1 or COL1A2
III	AD	Progressive deformity	COL1A1 or COL1A2
IV	AD	Moderate	COL1A1 or COL1A2
Expanded classification			
V	AD	Moderate, hypertrophic callus and ossification of the interosseous membrane	IFITM5
VI	AR	Moderate to severe	SERPINF1
VII	AR	Severe to lethal	CRTAP
VIII	AR	Severe to lethal	LEPRE1
IX	AR	Severe to lethal	PPIB
X	AR	Severe	SERPINH1
XI	AR	Progressive deformity, contractures	FKBP10
XII	AR	Moderate	SP7
XIII	AR	Severe	BMP1
XIV	AR	Variable severity	TMEM38B
XV	AR or AD	Variable severity. Early-onset osteoporosis	WNT1

1.3 Clinical presentation of the different types

The clinical presentation depends on the type of OI. The most common form of the condition is OI Type I which is autosomal dominant disorder that varies in severity but is a milder form compared to other types of OI (16). OI Type II is the lethal form that causes still birth or death in the neonatal period (16).

OI Type III now became the focus of medical and scientific interest. Type III OI is a progressive deforming OI, inherited as autosomal dominant or autosomal recessive trait but in the South African population, it is most frequently autosomal recessive (16).

OI Type IV is typically of moderate severity whereas OI type V is characterised by the radiological appearance of calcification of the interosseous membranes (16).

1.4 Diagnosis

The diagnosis is based on clinical and radiological findings in South Africa. The first line of evaluation is a detailed medical history including a family history, physical examination, appropriate radiographs and routine laboratory testing to exclude other metabolic bone disorders (1, 4). The main radiological clinical features of OI include: osteopenia and cortical bone thinning and excessive trabecular bone transparency together with bone fractures and bone deformities. Patients commonly present with low bone mineral density as measured with Dual Energy Xray Absorptiometry (DXA).

There are no definitive tests but genetic testing maybe helpful in confirming the diagnosis in difficult cases or to help distinguish OI cases from cases of child abuse or idiopathic juvenile osteoporosis. Genetic testing is not routinely performed in South Africa for OI except mainly for research purposes. Collagen screening and DNA based testing are available at the University of Washington, Shriners Hospital for Children in Canada and the DNA-based testing is also available at the Tulane University Matrix DNA Diagnostic laboratory (1).The genetic mutations are listed in Table 1 above for the different types of OI (7). The Swedish study performed on 79 children with OI type I, III, and IV; analysed DNA samples for collagen Type I mutations (8). Mutations were found in collagen I genes in 81% of children (COL1A1 = 47, COL1A2 = 17, no collagen mutation in 15 children) (8). Mutations in COL1A1 and COL1A2 do not cause OI type V, VI or VII; which account for about 8% of all children with OI (1).

In addition, a negative genetic test or DNA analysis does not necessarily prove the absence of OI and thus the diagnosis is more dependent on clinical and radiological findings in most centres.

1.5 DXA scans

DXA is currently the gold standard to measure bone mineral density. In children, accurate interpretation of the results requires a good knowledge of the potential pitfalls or influential factors related to age, sex, pubertal age, and skeletal deformities (9).

Decreased bone mineral density is not specific for OI and it may be encountered in other metabolic disorders such as hypogonadism, GH deficiency, hyperthyroidism and vitamin D deficiency (10). However, when such causes are excluded a DXA scan may help to establish the diagnosis of OI and to monitor the response to bisphosphonates (10).

DXA scan is most often performed on the lumbar spine and whole body in children and the hip is scanned in older children (>10 years of age).

The fundamental principle behind the DXA scan is the measurement of the transmission of Xray beams of two different photon energies through the body (10). In DXA scanning, the two tissue types measured are bone mineral and soft tissue of which the bone mineral measurements are obtained by subtracting the soft tissue measurements from the combined measurements. An areal bone mineral density (aBMD) as opposed to a true volumetric density is calculated and it is called aBMD. DXA reports include the body composition measurements such as fat and lean mass, bone mineral content (BMC) and bone area (BA) measurements. The Z scores are calculated based on the age and gender of the child and are used in children to interpret the results (10) however, these Z scores are not adjusted for height. DXA is a simple, quick and non-invasive procedure (10). No anaesthesia is required. The amount of radiation used is extremely low (1 to 5μSv) (9, 10).

1.6 Treatment

There is no cure for OI. Treatment is aimed at increasing overall bone strength to prevent fractures and maintain mobility (2, 3).

Three modalities of treatment are available:

a) Nonsurgical management (physiotherapy, rehabilitation, bracing, splinting) (11).

b) Surgical (intramedullary rod positioning, spinal and basilar impression or invagination surgery) (11, 12).

c) Drugs such as bisphosphonates to increase the strength of bone and decrease the number of fractures (12).

Treatment with bisphosphonates has brought significant clinical improvement for children and adolescents suffering from moderate to severe forms of OI (2).The poor quality of the bone in OI patients is the major impediment to improving their quality of life (4).

Bisphosphonates binds to the hydroxyapatite crystals of bone and act as anti-resorptive agents by disrupting osteoclast action (4). Among the various bisphosphonates, intravenous pamidronate has been studied in most detail (11). Cyclic intravenous pamidronate increase bone mineral density by increasing cortical bone width and trabeculae bone and therefore decreases fracture incidence (4, 12). As the effect of bisphosphonates on the skeleton is largest during growth, it appears logical to start medical therapy of OI patients as early as possible (4, 11).

1.7 Justification for this study

The true incidence of OI in our South African population is not known. A detailed analysis of patients in terms of DXA scan measurements, prior to bisphosphonate therapy and changes after therapy has not been conducted at CHBAH or other centres in South Africa that are treating these patients. There are a few studies that have confirmed an increase in BMC in OI children treated with bisphosphonates (2, 13) however, none of these studies have a predominantly black population which will be novel to this study. This study is also aimed to help strengthen the evidence for the use of BP therapy, as it is the only medical therapy effective in alleviating or improving the pain symptoms and decreasing the number of fractures in patients living with OI as recently shown by Lindahl et al in 79 Swedish children with OI (8).

CHAPTER 2: METHODOLOGY

2.1 Aim of the study

To evaluate and assess the improvement of bone mineral density using DXA in OI children treated with bisphosphonates.

2.2 Objectives

1. To determine the demographic characteristics, number of children with OI and different types of OI that are treated at the Metabolic Bone clinic at CHBAH.
2. To assess the number of fractures before and after BPs.
3. To assess the improvement in bone mass measurements from baseline and thereafter at three time points (9-18 months, 18-30 months and >30 months) after BPs have been initiated in the different types of OIs.
4. To assess gross motor milestones from baseline and after BPs therapy at these three time points.

2.3 Study design

This was a retrospective, descriptive study of OI patients treated with BPs and this study was performed to assess DXA measurements from baseline and during BP therapy at three time points (9-18 months, 18-30 months and >30 months).

2.4 Sample population

The study included all patients seen at Metabolic Bone clinic for the first time with OI from 01 January 2006 till 31 December 2015. The medical files were reviewed and the total number of patients for the study was 104 patients.

2.5 Inclusion criteria

All patients diagnosed with OI from birth until 18 years of age.

2.6 Exclusion criteria

None

2.7 Data collection

Medical records or files of OI patients diagnosed from 1st January 2006 to 31st December 2015 were reviewed to select those that have the information that met the above criteria. The data collection sheet (Appendix A) captured demographic information, clinical presentation (including fractures or deformities noted), motor milestones, details of BPs administered and DXA measurements pre- and post-BPs. All variables measured were collected from the Metabolic Bone clinic medical files or records.

The DXA measurements included the whole body less head and lumbar spine BA, BMC and bone mineral density (BMD) Z-scores. DXA scans are routinely performed on a yearly basis as part of the Metabolic Bone clinic's management protocol for the patients with OI. The exact DXA data collection time points and administration of BPs vary due to factors such as unscheduled appointments or missed appointments but the actual dates were used for all calculations. Furthermore, the following cut-offs were used for the time period of follow-up visits: 9-18 months (Follow-up 1), 18-30 months (Follow-up 2), >30 months (Follow-up 3), to accommodate for the unscheduled and missed appointments.

The improvement in DXA measurements were assessed to evaluate the change in whole body less head and lumbar spine BMC or BMD Z-scores for each individual patient from baseline till each follow-up time point thereafter.

Three methods using white male and female reference values for calculating bone mineral content (BMC) and bone mineral density (BMD) Z-scores on whole body less head (WBLH) and lumbar spine (LS) were applied and analysed as follows: 1. Calculated Z-scores using the Zemel equation (14, 15) and 2. Height adjusted Z-scores for >5 year old children only (15) and 3. DXA machine calculated Z-scores.

The number of patients that obtained a BMC or BMD Z score (adjusted for age, sex and body size) of > -2 were classified as obtaining a normal bone mass after BPs whilst those that remained <-2 were classified as "low bone mass" according to ISCD guidelines (16).

2.8 Data analysis

Data collected from the medical files or records were entered into the data collection sheet and thereafter captured into a new Microsoft excel spreadsheet and basic statistical analyses were performed using Statistica (Stat soft USA version 13.2). Appropriate descriptive statistical analyses using percentages, means and standard deviation or medians and interquartile ranges were applied.

When comparing the effects of BPs on the numbers or rates of fractures, the Paired t-test was used. When comparing all fractures prior versus on BPs therapy, the Wilcoxon matched pair test was used. One-way ANOVA or Student's t-test for comparing variables between the different types of OI was applied for averages. When comparing more than two types of OI patients and more than two points in time, the repeated measurements of ANOVA and 2 by 2 post hoc analyses was applied.

Fracture rates were calculated for those patients receiving BPs, as fracture rates per year for each patient and a mean fracture rate for all patients at presentation and at each follow-up time point thereafter.

The Kaplan-Meier survival analysis was applied to investigate the effect of BPs on the increase in whole body less head and lumbar spine BMC or BMD Z scores from baseline and over the specified time periods to reach a mean Z score of ≥ 0 and > -2.

2.9 Ethical consideration

Human Research Ethics Committee of the University of the Witwatersrand provided ethical clearance (Approval no: M160325) and the certificate is attached as Appendix B. The CEO of CHBAH and the CHBAH protocol review committee had approved the study (Appendix C). Consent from the patients will not be required as this was a retrospective study.

CHAPTER 3: RESULTS

A hundred and four files of patients diagnosed with Osteogenesis Imperfecta (OI) based on their presenting clinical features and radiological findings were reviewed from CHBAH Metabolic Bone clinic.

Most of the patients were referred from the orthopaedic department either at CHBAH or from Charlotte Maxeke Johannesburg hospital (48%), followed by peripheral hospital and clinic referrals (26%), paediatricians (13%) and self-referrals (4%).

3.1 Area of residence

The area of residence of patients was classified according to townships, provinces and other African countries such as Zimbabwe and Mozambique.

For the township residents, it was further classified as Soweto and non-Soweto, and provinces were classified into Gauteng, Limpopo, North West, Kwa Zulu Natal, Free State, Eastern Cape and Western Cape. Represented in Figure 3.1 below are regions or areas of residence according to provinces or countries of origin for the sample of 104 patients. Gauteng had the majority of patients (64%), followed by North West (11%), Limpopo (8%), Zimbabwe and Mozambique (7%), Free State (5%), Eastern and Western Cape (3%). The least number of patients are from Kwa Zulu Natal (2%).

Out of the 104 patients, 12 patients were from Soweto and 92 patients were non-Sowetan residents. The aforementioned figures are inclusive of Non-South Africans (Zimbabweans and Mozambicans).

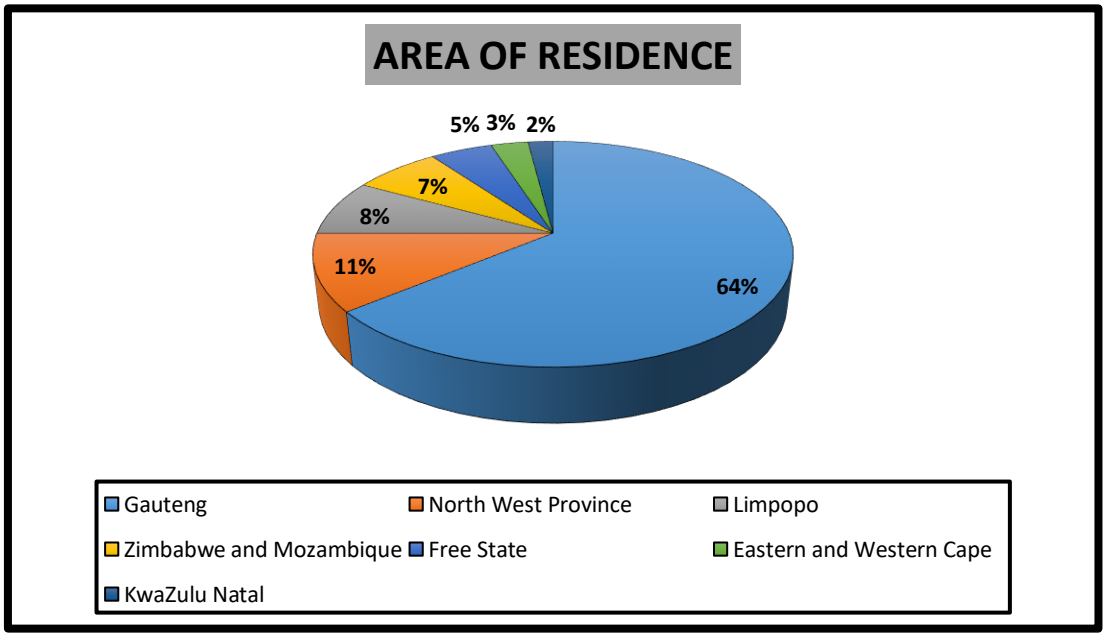


Figure 3.1 Area of Residence

3.2 Demographic data

Table 3.1 gives a representation and the demographics of the types of OI patients that were identified.

Type III OI (36%) patients were the most common type of OI patients presenting to the clinic followed by type I (27%) and IV (23%) OI patients; and the least common being Bruck syndrome (14%) (p=0.005).

There were more females 58 (56%) than males 46 (44 %) with OI in the entire group but this was not a significant difference. However, in type III OI patients, there was a greater number of female patients compared to male patients and similarly in type IV OI patients (p=0.04 and p=0.02 respectively).

As shown in the Table 3.1 below, the majority of the patients were black (82.5%), followed by white (11.5%), Indians (4%) and mixed ancestry (2%) in the entire group (p<0.001) and a similar pattern is shown in the sub-types of OI patients (p<0.001).

Table 3.1 Demographics of the different types of OI patients

Type of OI	**All types N (%)**	**Type I N (%)**	**Type III N (%)**	**Type IV N (%)**	**Bruck syndrome N (%)**
Total number	104 (100)	28 (27)	**37 (36)#**	24 (23)	15 (14)
Gender					
Male	46 (44)	17 (61)	14 (38)	8 (33)	7 (47)
Female	58 (56)	11 (39)	**23 (62)a**	**16 (67)b**	8 (53)
Ethnicity					
Black	**86 (82.5)***	**21 (75)***	**33 (89)***	**19 (79)***	**13 (87)***
White	12 (11.5)	6 (21)	2 (5)	4 (17)	0
Mixed ancestry	2 (2)	0	1 (3)	1 (4)	0
Indian	4 (4)	1 (4)	1 (3)	0	2 (13)

#p=0.005; ap=0.04; bp=0.02; *p<0.001

3.3 Chronological age and anthropometric measurements at first presentation

Table 3.2 below; shows ages and anthropometric measurements of patients at first presentation.

The median age at first presentation for the entire group of patients was 25 (4-58.5) months with the minimum to maximum age range of 0.06 months to 202 months. The median weight for the entire group of patients was 9.3 (4.5-12.4) kilograms (kgs) with the minimum to maximum weight of 2.3 - 36 kgs. Type III OI patients presented at the youngest age of 5 months which was significantly lower compared to Type I and IV OI patients. Bruck syndrome was the second youngest age group of patients and lower than Type IV patients. Type I patients presented with normal weight for age Z-score (WAZ) and height for age Z-score (HAZ) but Type III OI patients were severely wasted and stunted with significantly lower WAZ compared to the all other types of OI patients. Similarly, in Type III OI patients the HAZ was lower compared to Types I and IV OI patients. Head circumference was lower in Type III compared to Type IV patients.

Table 3.2 Chronological age and anthropometric measurements at first presentation

Age and anthropometric measurements at first presentation	**All types OI N=104 Median (IQR)**	**Type I OI n=28 Median (IQR)**	**Type III OI n=37 Median (IQR)**	**Type IV OI n=24 Median (IQR)**	**Bruck Syndrome n=15 Median (IQR)**
Age at first presentation (months)	25 (4-58.5)	32.5 (10-61)	5.0[a] (1.7-41)	42.5[c] (18.5-91.5)	15[b] (4-35)
Weight (kgs)	9.3 (4.5-12.4)	10.6 (7.4-18)	4.9 (3.1-10.3)	11.4 (8.4-18)	9.3 (3.3-10.7)
WAZ score	-2.5 (-3.8- -1.8)	-1.3* (-2.8- -0.2)	-3.7** (-4.3- -2.4)	-2.1 (-2.6- -1.3)	-2.8*** (-5- -1.9)
Height (cm)	75 (53-93) n=101	83.1 (70-104) n=28	56 (44-80) n=37	85 (73-105) n=23	74 (47-82) n=13
HAZ score	-3.4 (-5.1- -1.8)	-1.9[#] (-3.2- -0.4)	-5.1[#] (-6.12- -4.5)	-2.4 (-3.4- -1.4)	-3.9[##] (-5.9- -0.3
Head circumference (cm)	47 (39-50) n=81	49 (42-51) n=21	40[d] (36-50) n=29	49 (47-51) n=19	46.8 (38-49) n=12

[a] p<0.05 between type I and III
[b] p<0.01 between Bruck syndrome and Type IV
[c] p<0.001 between type III and IV
*p<0.001 WAZ between type I and III and between type I and Bruck syndrome
** p = 0.001 WAZ between type III and IV
*** p<0.03 WAZ between type III and Bruck syndrome
[#] p<0.001 HAZ between type I and III and between type III and IV
[##] p<0.01 HAZ between type I and Bruck syndrome
[d] p<0.01 between type III and IV

3.4 The clinical presentation, presence of wormian bones and family history in OI patients at initial presentation

As shown in Table 3.3 below, in all types of OI, blue sclera (86.5%) is the most frequently occurring clinical feature followed by ligament laxity (63%), dentinogenesis imperfecta (DI) (46%), and wormian bones (43%). A significantly lower number of patients presented with DI in Bruck syndrome compared to the other types of OI ($p<0.05$).

The prevalence of a positive family history was similar in all types of OI patients except in Bruck syndrome where there was no family history of OI ($p<0.05$).

Table 3.3 Clinical features, presence of wormian bones and family history in OI patients at initial presentation

Clinical features	**All Types OI N=104 n (%)**	**Type I OI n=28 n (%)**	**Type III OI n=37 n (%)**	**Type IV OI n=24 n (%)**	**Bruck Syndrome n=15 n (%)**
Blue sclera	90 (86.5)	24 (94.5)	35 (94.5)	20 (83)	11 (73)
Ligament laxity	66 (63)	20 (71)	23 (62)	17 (71)	6 (40)
DI	48 (46)	13 (46)	21 (57)	12 (50)	**2 (13)***
Wormian bones (n=101)	45 (43)	11 (39)	17 (46)	9 (38)	8 (53)
Family history	31 (30)	11 (39)	10 (27)	10 (42)	**0***

**p<0.05*

3.5 Fractures at presentation

Majority of the patients presented with a history of fractures (97%). Three patients had sustained no fractures but were assessed because of their positive family history of OI (3%). Table 3.4 shows the number of fractures sustained in each subtype of OI and the age at which the first fracture was sustained. In each subtype of OI, the majority of patients presented with multiple fractures. There was no fracture history in one patient with type I OI (4%) and two Bruck syndrome (13%) patients. The median number of fractures at baseline or presentation was 3 (2-5). Type I OI patients had a significantly lower number of fractures at baseline compared to type III and Bruck syndrome patients.

The median age at first fracture was at birth for Bruck syndrome patients and was significantly lower to type IV OI patients and at 0.27 months or 8 days of age in type III OI patients which were significantly lower compared to type I and IV OI patients.

Table 3.4 Fracture history at baseline presentation and age of first fracture

Fracture history	All types n=104 n (%)	Type I n=28 n (%)	Type III n=37 n (%)	Type IV n=24 n (%)	Bruck syndrome n=15 n (%)
Single fractures	9 (9)	3 (11)	3 (8)	3 (12.5)	0 (0)
Multiple fractures >3	72 (69)	16 (61)	29 (78)	15 (62.5)	9 (60)
No fracture history	3 (3)	1 (4)	0	0	2 (13)
Number of fractures at baseline (Median (IQR))	3 (2-5)	3 (2-4)*	4 (3-5)	4 (2-5)	4 (3-5)*
Age of first fracture in months (Median (IQR))	5 (0-24)	10 (0.46-36)	0.27[a] (0-5)	14.5[c] (6.5-43.5)	0[b] (0-18)

*p<0.05 between Type I and III, and between Bruck syndrome and Type I

[a] [b]p<0.01 between type I and III and Bruck syndrome and Type IV

[c]p<0.001 between type IV and III

3.6 Fracture rates from baseline until follow-up 3

Ninety seven percent of patients presented with a fracture history or fractures at baseline presentation and subsequently the prevalence of fractures decreased by nearly two-thirds at follow-ups 1, 2 and 3. The mean fracture rate at baseline prior to BP therapy was 16.44 (95% CI: -1.98-34.85) and significantly decreased to 0.62 (0.27-0.97) at 9-18 months and to 1.1 (0.49-1.65) at >30 months (p<0.001) during BP therapy.

Compared to baseline, the median number of fractures also decreased significantly at each follow-up time period and this was also evident on BP therapy with more than half of the patients remaining fracture free at follow-up three after receiving BPs.

Table 3.5 Fracture history, number of fractures and fracture rates from baseline until follow-up 3

	Baseline **n (%)**	**Follow up 1 (9-18 months)** **n (%)**	**Follow up 2 (18-30 months)** **n (%)**	**Follow up 3 (>30 months)** **n (%)**
Patients with fractures	101 (97)	25 (32.5)	19 (30)	19 (34)
Patients with no fractures	3 (0)	45 (58)	32 (50)	17 (30)
Patients with missing fracture history	0 (0)	7 (7)	13 (12.5)	20 (19)
Patients lost to follow-up	0 (0)	27 (26)	40 (38.5)	48 (46)
Total number of fractures	360	38	25	37
Number of fractures (Median (IQR))	3 (2-5)	0 (0-1)*	0 (0-1)*	0 (0-1)*
Total number of fractures before and on BPs n = 33	119	19	20	36
Patients with no fractures (before and on BPs)	1 (3)	20 (61)	15 (45)	14 (44)
Fracture rates before and on BPs (Mean (95% CI))	16.44 (-1.98-34.85)	0.62* (0.27-0.97)	0.60* (0.32-0.89)	1.1* (0.49-1.65)
Number of fractures before and on BPs (Median (IQR))	4 (2-5)	0 (0-1)*	0 (0-1)*	1 (0 -1.5)*

*P<0.001 between baseline and each of the follow-up visits 1, 2 and 3 using Wilcoxon matched paired tests.

3.7 Bisphosphonate (BP) therapy

Table 3.6 demonstrates the type of bisphosphonate therapy that patients received from baseline visit until follow-up 3.

Table 3.6 Type of bisphosphonate (BP) therapy received from baseline to follow-up 3

BP therapy	**Baseline** **n (%)**	**Follow up 1 (9-18 months)** **n (%)**	**Follow up 2 (18-30 months)** **n (%)**	**Follow up 3 (>30 months)** **n (%)**
Patients receiving BP therapy	79 (76)	63 (61)	46 (44)	33 (32) ***(58% lost to follow-up)***
Type of BP therapy				
Zoledronic acid	61 (77)	58 (92)	44 (96)	33 (100)
Pamidronate	18 (24)	5 (8)	2 (4)	0

A total of 79 (76%) patients received bisphosphonate (BP) therapy at baseline of which 18 (24%) patients received pamidronate and 61 (77%) patients received zoledronic acid.
The twenty five patients that did not receive BP therapy at baseline visit had several different reasons for not receiving therapy. One patient demised secondary to a bronchopneumonia or a lower respiratory infection at one month of age and thus did not reach 3 months of age when BP therapy is commenced. Some patients presented at baseline and did not return for the follow-up visit to receive BP therapy after receiving a month's treatment of calcium and vitamin D supplementation. Other patients presented at an older age with a history of fracture in early infancy or as a toddler but had already attained good milestones for their age and were observed for recurrent fractures thus BP therapy was not commenced.
During follow-up 1 and 2, the majority of patients were changed from pamidronate therapy to zoledronic acid. Finally, on follow-up 3; all 33 patients that were seen had received zoledronic acid (of which only one had commenced BP from follow-up 1 onwards and the rest received BPs from baseline visit); thus 58 % of the patients that received BPs at baseline were lost to follow up.

3.8 Assessment of milestones on BP therapy

Of the 79 patients that received BPs at baseline nearly more than half of the patients or 51% (n = 40) had delayed milestones. Of the 24 patients that did not receive BPs, 17% (n = 4) had delayed milestones at baseline. Only 16 patients with delayed milestones were consecutively assessed for improvement or regression in milestones from baseline until follow-up 3; the remainder of the patients were lost to follow-up or did not have a complete assessment of their milestones at every follow-up visit.

Table 3.7 illustrates that there was significant improvement in milestones at each of the follow-up visits. More than half of the patients at follow-up 1 had improvement in milestones and more than two-thirds of the patients at follow-up 2 and 3. Of the 7 patients that had no improvement in milestones or remained the same at follow-up 1, two had delayed milestones at follow-up 2 and two improved but of the two that had delayed milestones at follow-up 2, milestones regressed at follow-up 3 as they were now wheelchair-bound.

Table 3.7 Assessment of patients with delayed milestones from baseline and on BP therapy (n=16)

Milestones during BP therapy	**Follow up 1 (9-18 months) n (%)**	**Follow up 2 (18-30 months) n (%)**	**Follow up 3 (>30 months) n (%)**
Improved	**9 (56)***	**11 (69)***	**11 (69)***
No improvement or remained the same	7(44)	3 (18)	3(18)
Delayed	0	2 (13)	0
Regressed	0	0	2 (13)

*p<0.001 compared to baseline

3.9 DXA measurements on patients that received BP therapy

WBLH and LS BMC and BMD Z-scores showed significant increases after follow-up 3 or over 30 months of treatment ($p<0.01$) as shown in Table 3.8 below. The mean BMC and BMD Z-scores (WBLH and LS) at baseline were < -2 confirming low bone mass. Mean calculated Z-scores at follow-up 3 had reached a Z-score above -2; and mean height adjusted

Z-scores reached a Z-score above -2 from follow-up 1 onwards and mean DXA machine calculated Z-scores reached a mean Z-score above -2 at follow-up 2 onwards.

There was a positive correlation at follow-up 3 or after 30 months of treatment in both LS BMD calculated Z-scores and height adjusted Z-scores compared to machine calculated Z-scores ($r = 0.9484$, $p < 0.001$; $r = 0.8697$, $p < 0.001$).

Using the paired student-t test to compare the baseline calculated LS BMD Z-scores to each follow-up visit showed significant increases in LS Z-scores with the greatest increase at -4.78 (±2.42)

Table 3.10 provides the percentage of patients with a Z-score less than -2 from baseline visit till follow-up 3. At baseline, 83% of patients had a LS BMD height adjusted Z-score < -2 and at follow-up 3 or after 30 months of BPs treatment, none of the patients had a LS BMD height adjusted Z-score < -2 ($p < 0.001$).

Figures 3.2 and 3.3 show the cumulative number of patients reaching a mean LS height adjusted Z-score of ≥ 0 and ≥ -2 at follow-up 3 or greater than 30 months on BPs. The median time to reach a Z-score ≥ 0 was 54 months (4.5 years) and ≥ -2 was 50 months (4.2 years) during BP therapy.

Table 3.8 Dual energy Xray absorptiometry (DXA) measurements from baseline till follow-up 3 on BP therapy

Calculated Z-scores								
	Baseline		**Follow-up 1**		**Follow-up 2**		**Follow-up 3**	
	n	**Mean (±SD)**	**n**	**Mean (±SD)**	**n**	**Mean (±SD)**	**n**	**Mean (±SD)**
WBLH BMC Z-score	5	-5.59 (±2.99)	6	-3.19 (±1.04)	9	-3.11 (±2.21)	10	-1.48** (±1.56)
WBLH BMD Z-score	6	-4.5 (±1.79)	6	-2.50* (±1.09)	9	-2.34* (±1.78)	10	-0.70*** (±1.15)
LS BMC Z-score	6	-5.34 (±2.27)	7	-2.20** (±0.60)	12	-2.78* (±1.88)	18	-1.80*** (±1.86)
LS BMD Z-score	16	-5.24 (±2.22)	20	-2.24*** (±2.01)	24	-1.77*** (±2.80)	24	-0.37*** (±1.70)
Height adjusted Z-scores								
	Baseline		**Follow-up 1**		**Follow-up 2**		**Follow-up 3**	
	n	**Mean (±SD)**	**n**	**Mean (±SD)**	**n**	**Mean (±SD)**	**n**	**Mean (±SD)**
WBLH BMC Z-score	5	-2.98 (±1.98)	6	-1.41 (±1.05)	9	-0.34** (±1.25)	10	0.75*** (±1.11)
WBLH BMD Z-score	6	-2.57 (±1.16)	6	-1.13 (±1.11)	9	-0.17** (±1.43)	10	1.03*** (±1.03)
LS BMC Z-score	6	-3.12 (±1.32)	7	-0.31*** (±0.53)	12	-0.23*** (±1.44)	18	0.54*** (±1.34)
LS BMD Z-score	6	-3.25 (±1.17)	7	-0.42*** (±0.60)	12	0.19*** (±1.31)	19	1.04*** (±1.41)

Machine calculated Z-scores								
	Baseline		**Follow-up 1**		**Follow-up 2**		**Follow-up 3**	
	n	**Mean (±SD)**	**n**	**Mean (±SD)**	**n**	**Mean (±SD)**	**n**	**Mean (±SD)**
WBLH BMD Z-score	6	-2.71 (±1.17)	8	-1.97 (±1.65)	11	-0.92 (±2.30)	9	0.57** (±1.70)
LS BMD Z-score	11	-4.78 (±1.30)	14	-2.54** (±1.69)	15	-1.55*** (±2.03)	22	-0.33*** (±1.63)

* P<0.05, **P<0.01, ***P<0.001 comparisons between baseline and follow-up visits

Table 3.9 Calculated LS BMD Z-scores comparing baseline and each follow-up visit using paired student-t tests

	n	Mean (±SD)	Diff	Std. Dv. Diff	p value
Baseline calculated LS BMD Z-score	10	-4.64 (±1.63)	-2.27	1.84	p<0.01
Follow-up 1 calculated LS BMD Z-score		-2.38 (±2.47)			
Baseline calculated LS BMD Z-score	14	-5.38 (±2.22)	-3.46	2.29	p<0.001
Follow-up 2 calculated LS BMD Z-score		-1.92 (±2.21)			
Baseline calculated LS BMD Z-score	13	-4.89 (±2.30)	-4.78	2.42	p<0.001
Follow-up 3 calculated LS BMD Z-score		-0.11 (±1.90)			

Table 3.10 Dual energy Xray absorptiometry (DXA) Z-scores ≤ -2 from baseline till follow-up 3 on BP therapy

Z-scores ≤ -2				
	Baseline	**Follow-up 1**	**Follow-up 2**	**Follow-up 3**
	n (%)	n **(%)**	**n (%)**	**n (%)**
Calculated LS BMD Z-score	16 (100)	8 (40)	9 (37.5)	5 (21)
Height Adjusted LS BMD Z-score	5 (83)	0 (0)	0 (0)	*0 (0)
DXA machine calculated LS BMD Z-score	11 (100)	7 (50)	4 (27)	3 (14)

*p<0.001 from baseline till follow-up 3

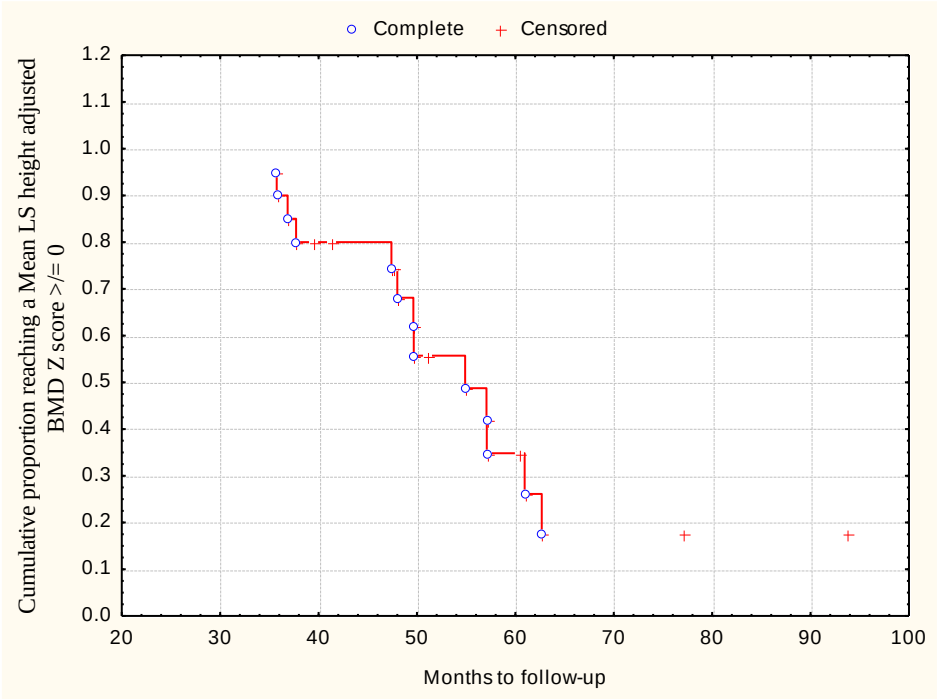


Figure 3.2 Cumulative proportion of patients reaching a mean LS height adjusted BMD Z-score >/= 0

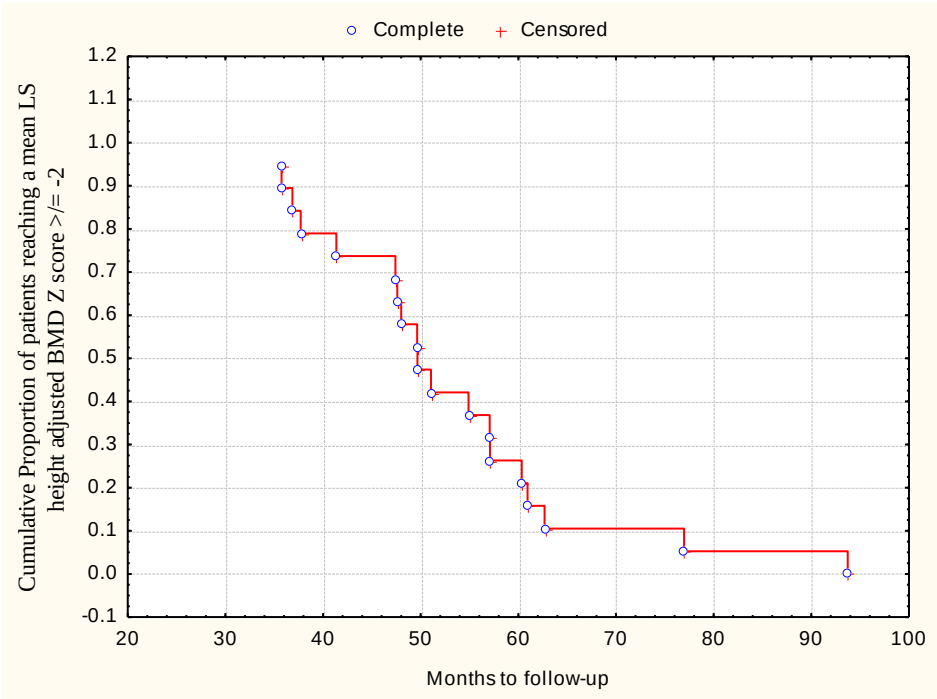


Figure 3.3 Cumulative proportion of patients reaching a mean LS height adjusted BMD Z-score >/= -2

CHAPTER 4: DISCUSSION

4.1 Demographic data

Osteogenesis imperfecta is not an uncommon metabolic bone condition seen at the Metabolic Bone clinic in CHBAH in Gauteng. A hundred and four patients diagnosed with OI over a 10 year period were seen at the Metabolic Bone clinic at CHBAH of which the majority of patients (64%) were from Gauteng, followed by North West (11%), and Limpopo (8%) provinces. A small percentage (3-5%) was from Eastern Cape and Free State and due to the emigrational factors or poor health services in other countries; there was also a number of patients from the neighbouring countries such as Zimbabwe and Mozambique (7%). Patients were referred from orthopaedic departments either at CHBAH or from Charlotte Maxeke Johannesburg hospital (48%). Peripheral hospital and clinic referrals were less common (26%) and a smaller percent of patients were referred by paediatricians (13%).

Type III OI (36%) was the most common type of OI patients presenting to the clinic, followed by type I OI (27%) and type IV OI (23%) patients. Black patients in this cohort presented with type III OI being the most common type followed by Bruck syndrome then types IV and I OI. In a survey of black patients with OI in the 1970s attending the CHBAH, the severe autosomal recessive OI type III was recognized in 21 patients of whom 18 did reside in the Johannesburg area (17). Only 5 of these patients had the common mild autosomal dominant OI type I (17, 18). This correlated with the recent study done in South Africa that enrolled 91 affected patients (none from CHBAH or Johannesburg but from Cape Town, Bloemfontein, Pretoria, Pietermaritzburg and Kwa Zulu Natal) and investigated the molecular genetics of OI type III in the indigenous black South African population. FKBP10 mutations were identified in 45.1% (41/91) of the OI type III affected persons. The frameshift mutation c.831dupCp.(Gly278Argfs95*) was identified as the homozygous mutation in 38.5% (35/91) of individuals in the study cohort (18). The Shona and Ndebele people, who comprise the major tribal groups in Zimbabwe, both had a similar and relatively high gene frequency for type III OI (19). The Kamba tribe in Kenya was also noted to have a greater number of patients to be affected by type III OI (20). The clinical and radiological phenotype was similar in the Zimbabwean and South African populations and it was proposed that the determinant mutation or mutations may be common in both these indigenous black communities which need to be further investigated and tested (17).

The estimated minimum population frequency is 0.6 per hundred thousand for OI type III in this group and 0.1 per hundred thousand for OI type I (18). This presentation in South Africa is the reverse of the population in White or Caucasian Australians, where the ratio between OI type I and III is of the order of 7 to 1 (17). This difference in presentation of predominantly Type III OI patients in the African countries as compared to Australia, may be due to the more severe types of OI seeking medical treatment and not the mild OIs in the African countries but there is no literature to support this or a OI registry to confirm the prevalence of OI and the different types of OI.

The majority of the patients in this study were black (82.5%), followed by white (11.5%), Indians (4%) and mixed ancestry (2%) ($p=0.001$) and a similar pattern is shown in the sub-types of OI ($p<0.001$). This however, maybe bias results as the majority of patients serviced at CHBAH are of Black ethnic backgrounds.

4.2 Chronological age and anthropometric measurements at first presentation

Type III OI patients were severely wasted and stunted as compared to all other types of OI patients in our study. Osteogenesis imperfecta is characterised by numerous fractures, gross deformity of tubular bones, spinal malalignment and marked impairment of growth (18). All patients whom height or length was measured; their HAZ fell below the 5^{th} centile (18). Physical handicap is severe and affected children often become wheelchair bound (18).

4.3 Clinical presentation

In terms of clinical presentation, the most common presenting feature was blue sclera (n=90 (86.5%)), ligament laxity (n=66 (63%)), DI (n=48 (46%)), and wormian bones (n=45 (43%)) in this study. This presentation was similar to the study done in Brazil (21) where blue sclera (93.4%) was the most common presenting feature followed by wormian bones (29.4%) and DI (27.6%) (17). A study performed on 554 subjects in North America from different centres found a similar pattern of clinical features on presentation where blue sclera was the leading feature followed by hypermobility and DI as shown in this study (3).

A positive family history in both studies was also a common finding (30% at CHBAH versus 44.6% in Brazil) but the prevalence varied between the different types of OI (21). In the retrospective study done in Shriners Hospital for children in Houston Texas in January 2011; sixty eight patients were enrolled under the age of 18 years and the most common type of OI was type IV OI (22). This finding differs to our study, where most of our patients were type

III OI. A positive family history of OI was reported in 46% of children with OI and OI type III patients had the least number of patients with a family history (only 1 of 17 (6%) patients). In comparison to our study, Bruck syndrome patients had no family history and Type III OI also had a lower number of patients with a positive family history of 27% compared to Types I and IV OI patients.

Another study had similar pattern of presentation like the South African population; with OI type III encountered in most patients but the study numbers were small. This study was done in Timisoara, Romania; where 9 children were enrolled of which there were three patients with type III OI, two patients with type II OI, while the other patients were diagnosed with other forms of OI such as types IV, V, VI, and VIII (23). This study also reported multiple fractures at baseline presentation with a maximum number of 39 fractures in a 5 month old infant with type III OI (18). This provides evidence that the most severe types of OI were diagnosed at an earlier age compared with the milder forms. The study done in Timisoara also showed that initial fractures tend to occur in utero or during the perinatal period and a high incidence of fractures during growth often causes progressive deformities (23). In the same study, patients with OI type I had fewer fractures, compared with patients with type III, IV, or V which is similar to our study where Type I OI patients at baseline had a lower number of fractures compared to type III and Bruck syndrome patients and is due to the milder forms of OI having a lower fracture prevalence during childhood (21). Initial fractures tend to occur during the period in which children begin to walk, because their upright posture promotes increased weight load on the lower limbs resulting in fractures (21).

4.4 DXA scans

Mean BMC and BMD Z scores (WBLH and LS) at baseline in this study confirmed low bone mass. In the study done in Ninewells Hospital and the Medical School in Scotland (University of Dundee), a total of 61 patients were recruited and mainly type I and type IV OI patients were studied(24). All 3 patients with type III OI had bone mass values below -2 SD for age and sex compared to normal subjects ($p<0.001$) (24). For the 47 patients with type I and type II OI, the bone mass was significantly lower than normal subjects ($p<0.001$) (24). This study was similar to our findings were LS BMD Z scores were <-2 in 83% of patients at baseline. Another study done in California-Los Angeles, combining BMD of nine children aged from 2-13 years who had mild OI were studied (25) and these patients had mild clinical symptoms but DXA detected highly significant differences in BMD between patients and the controls

(25). The mean BMD in the OI children was 76.7% lower at the LS ($p<0.001$) and 71.2% lower in the femoral neck ($p<0.001$) compared to normal controls. The study had shown that DXA can detect abnormal bone density in children with even mild forms of OI (25).

4.5 Treatment of OI

There was significant improvement in motor milestones after receiving BP therapy although the number of patients followed up was only 16 from baseline till follow-up 3. More than half of these patients at follow-up 1 and more than two-thirds at follow-up 2 and 3 showed improvement in motor milestones. Older pre-bisphosphonate reports indicated a higher number of wheelchair bound non-treated patients compared to the childhood treated cohort whom had higher levels of moderate activity (26). In this study, wheelchair bound patients were those that presented late and defaulted follow up which in addition, supports the benefits of early childhood BP treatment.

WBLH and LS BMC and BMD Z-scores improved significantly after 30 months of BP treatment and the median time to reach a Z-score ≥ 0 was 4.5 years and ≥ -2 was 4.2 years after BP therapy. The results of our study were similar to international studies. Multiple studies concur on the effect of BPs in increasing aBMD at the spine and several other skeletal sites (2, 12, 23, 26, 27). A study done in Canada enrolled nine patients with severe OI aged less than 3 years old, of which eight patients were diagnosed as having type III OI and one patient had type IV OI (12). The clinical course in these children during the first 12 months of treatment was compared to a group of historical controls with severe OI seen before the age of 2 years (12). Cyclical pamidronate infusion was used and patients received 4 to 8 cycles during the treatment period (12). In all the treated patients, BMD had increased by the time of the second infusion cycle and this trend continued thereafter, resulting in a rise between 86-227% during the study period ($p<0.001$) (12). There was a significant decrease in mean –Z-scores of both weight (-1.2 +-1.6 and -3.9 +-1.1) and height (-2.4 +-1.7 to -7.7+-2.6) by the time treatment started, confirming the delay in physical development typically associated with severe OI (12).This study proved that pamidronate infusion not only increases lumbar spine BMD, but also protects bone integrity. Another randomized controlled study concurs with the above findings where sixty-four children were enrolled with no signs of puberty and who were never treated with bisphosphonate previously. Study patients were commenced on BP therapy when enrolled and control patients were given the same BP therapy at the end of the first year of the study (2). BP therapy significantly increases the growth in height and in the

projected area of lumbar spine in those patients that were initially treated with BPs at enrolment (2).

Treatment with pamidronate proved to be beneficial for the patients with OI, their family and society and increases their quality of life (23). It improves bone density and the clinical symptoms, improves mobility and reduces fracture frequency and prevents severe deformity (23).

A prospective, observational study performed on 20 adult patients with OI proved that there were beneficial effects of bisphosphonates in improving bone mineral density. These patients were given zoledronic acid infusions every 6 months for 3 years and annually thereafter; and treatment induced significant increases in LS BMD (6.7%) after 12 months of follow up ($p=0.003$) and at three and five years of follow up (27).

Another study done in Royal Children's Hospital (RCH) in Melbourne, showed the effect of bisphosphonates in 52 adult OI patients that received at least one infusion of BP treatment at RCH Melbourne prior to age 18 years and comparing to those with OI that never received bisphosphonate under the age of 18 years (26). LS Z-scores were significantly higher in the childhood treated cohort compared to the adult treated cohort (-0.4 at mean age 21.3 years versus -1.9 at mean age 40.9 years $p=0.005$) (26).

In another study done in China, a total of 136 patients with OI completed a 2 year clinical study of which 90 patients were assigned to receive alendronate, while 46 received zoledronic acid treatment. The percentage change in LS BMD was $60.01 \pm 7.08\%$ in the alendronate group and $62.04 \pm 5.9\%$ in the zoledronic acid group ($p=0.721$) (28).

The corresponding BMD Z-score increased by 0.50 ± 0.05 in the alendronate group and 0.71 ± 0.06 in the zoledronic acid group ($p=0.013$). Zoledronic acid was superior to alendronate in reducing the clinical fracture rate (28). There are no other studies that report on reduction of fracture rates with BPs except for one study that showed no effect on the number of new fractures (29). In this study, the mean fracture rate at baseline prior to BP therapy was 16.44 (95% CI: -1.98-34.85) and significantly decreased to 0.62 (0.27-0.97) at 9-18 months and to 1.1 (0.49-1.65) at >30 months ($p<0.001$) during BP therapy and thus supporting the use of BP to reduce hospitalisations and surgical costs related to fractures.

4.6 Limitations

This was a retrospective study and therefore data was collected from the existing records which were incomplete and there were missing data or records. In addition, the weight and

height measurements of the patients were not performed by a dedicated researcher or assistant and could affect the reliability of the study findings.

DXA technicians and machines have changed during the specified time period for the study and may affect the DXA results in terms of variance between systems and technicians. There are missing measurements for LS and WBLH BMD Z-scores as these values could not be calculated for the following reasons:

1. DXA calculated BMD Z-scores could only be done in children greater than 5 years of age.
2. Height adjusted BMD Z-scores could also only be done in children greater than 5 years of age.
3. Calculated BMD Z-scores using the Zemel's calculation also only allowed for greater than 5 years of age calculations and Kalkwarf's calculations allowed for 1 month to 3 years of age calculations so calculated BMD Z scores between 4-5 years were not done.

Another limitation was intramedullary rodding of the long bones and thus WBLH DXA measurements had to be omitted from the analyses in those patients that had rodding and thus there were a smaller number of results for WBLH compared to LS measurements.

CHAPTER 5: CONCLUSION

This study tries to answer the fundamental question which is to compare the clinical and bone density features pre and post bisphosphonate therapy in OI children that presented to the Metabolic Bone Disease clinic at CHBAH.

In spite of the challenges faced, CHBAH serves a large number of patients with Osteogenesis Imperfecta from Gauteng (64%) and different provinces in South Africa (31%) as well as patients from outside of South Africa mainly Mozambique and Zimbabwe. Osteogenesis Imperfecta is a common metabolic bone disorder following rickets and the more severe types of OI are prevalent at CHBAH.

Bisphosphonate therapy significantly increased height adjusted LS BMD Z-scores to >-2 and decreased the number of fractures after 9-18 months of treatment in South African OI patients thus supporting the use of BPs in OI patients to minimise hospitalisation and treatment costs related to fractures.

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7. APPENDICES

APPENDIX A: DATA COLLECTION SHEET

Study number:_____ Initials:_____

Date:_____

Section A: Demographic data

Date of Birth…….. Age (Yrs)…….. (Months)…….

Sex…….

Birth Place…….Race……..

Residential Area……..Province: ……

Section B: Clinical Presentation

Age at presentation (Yrs) ……. (Months)……

Date of first Presentation: ……..

Referred Yes/No… if (YES), Referred by

Orthopaedic surgeon…..GP…..Clinic…….Peripheral Clinic……Paediatrician…….Self……

Presenting Symptoms:

Blue Sclera: YES/NO

Dentinogenesis Imperfecta: YES/NO

Type of OI: ……

Ligament/hypermobility: …….

Family History of OI: YES/NO, if YES,

First degree relative: …….Second degree relative: …… Not recorded:……

Weight: …… Height: …… BMI: …….

Head Circumference: ……

Section C: The numbers, pattern and distribution of fractures

Fractures? YES….NO……Age of First Fracture: ……. Number of Fractures: ……..

Fractures: <3….. or >3… at presentation

Extremity Bones involved: Humerus: ….(R) (L); Radius:….. (R) (L); Femur: ….(R) (L); Tibia:…..(R) (L); Axial Skeleton involved: Ribs……Spine:…….

Number of Fractures at Follow- up 1 (9-18 months): …….

Number of Fractures at Follow- up 2 (18-30 months): ..…….

Number of Fractures at Follow- up 3 (>30 months): …….

Section D: Medical Management using bisphosphonates and DXA measurements

Received Bisphosphonates? YES:……. NO: ……

Type of Bisphosphonates Given: ……

1(a) Date of commencement: ……. 1(b) Period of Treatment: ……

2(a) Date of commencement: …….. 2(b) Period of Treatment: ……...

Serial BMD Z-score (with dates of recorded Z-scores):

Whole Body less head

	Baseline	Follow Up 1	Follow up 2	Follow up 3
BA				
BMC				
BMD				
Z-score				

Lumbar Spine

	Baseline	Follow Up 1	Follow up 2	Follow up 3
BA				
BMC				
BMD				
Z-score				

Number of Cycles of bisphosphonates: …….

Total Duration of follow up: ……

Section E: Milestones after bisphosphonate therapy

Ambulation prior to Bisphosphonates OR at presentation:

(a) Crawling/Bum shuffling: …….

(b) Cruising: ……

(c) Walking: …….

(d) Crutch dependent: …….

(e) Wheelchair dependent: ……

Ambulation at follow-up 1:

(a) Crawling/Bum shuffling: …….

(b) Cruising: ……

(c) Walking: …….

(d) Crutch dependent: …….

(e) Wheelchair dependent: ……

Ambulation at follow-up 2:

(a) Crawling/Bum shuffling: …….

(b) Cruising: ……

(c) Walking: …….

(d) Crutch dependent: …….

(e) Wheelchair dependent: ……

Ambulation at follow-up 3:

(a) Crawling/Bum shuffling: …….

(b) Cruising: ……

(c) Walking: …….

(d) Crutch dependent: …….

(e) Wheelchair dependent: ……

APPENDIX B: HOSPITAL PERMISSION LETTER TO CONDUCT RESEARCH

GAUTENG PROVINCE
REPUBLIC OF SOUTH AFRICA

MEDICAL ADVISORY COMMITTEE
CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

PERMISSION TO CONDUCT RESEARCH

Date: 1 March 2016

TITLE OF PROJECT: Audit of DXA scans during bisphosphonate therapy in patients with osteogenesis imperfecta at Chris Hani Baragwanath Academic Hospital

UNIVERSITY: Witwatersrand

Principal Investigator: A Siralarala

Department: Paediatrics

Supervisor (If relevant): K Thandrayen

Permission Head Department (where research conducted): Yes

Date of start of proposed study: March 2016
Date of completion of data collection: Dec 2018

The Medical Advisory Committee recommends that the said research be conducted at Chris Hani Baragwanath Hospital. The CEO /management of Chris Hani Baragwanath Hospital is accordingly informed and the study is subject to:-

- Permission having been granted by the Human Research Ethics Committee of the University of the Witwatersrand.
- the Hospital will not incur extra costs as a result of the research being conducted on its patients within the hospital
- the MAC will be informed of any serious adverse events as soon as they occur
- permission is granted for the duration of the Ethics Committee approval.

.....
Recommended
(On behalf of the MAC)
Date: 01 March 2016

.....
Approved/Not Approved
Hospital Management
Date: 02/03/16

APPENDIX C: ETHICS APPROVAL LETTER

R14/49 Dr Akhona Siralarala

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M160325

NAME: (Principal Investigator)	Dr Akhona Siralarala
DEPARTMENT:	Paediatrics Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	Audit of DXA Scans during Bisphosphonate Therapy in Patients with Osteogenesis Imperfecta at Chris Hani Baragwanath Academic Hospital
DATE CONSIDERED:	01/04/2016
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr Kebashni Thandrayen

APPROVED BY: Professor P Cleaton-Jones, Chairperson, HREC (Medical)

DATE OF APPROVAL: 08/04/2016

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

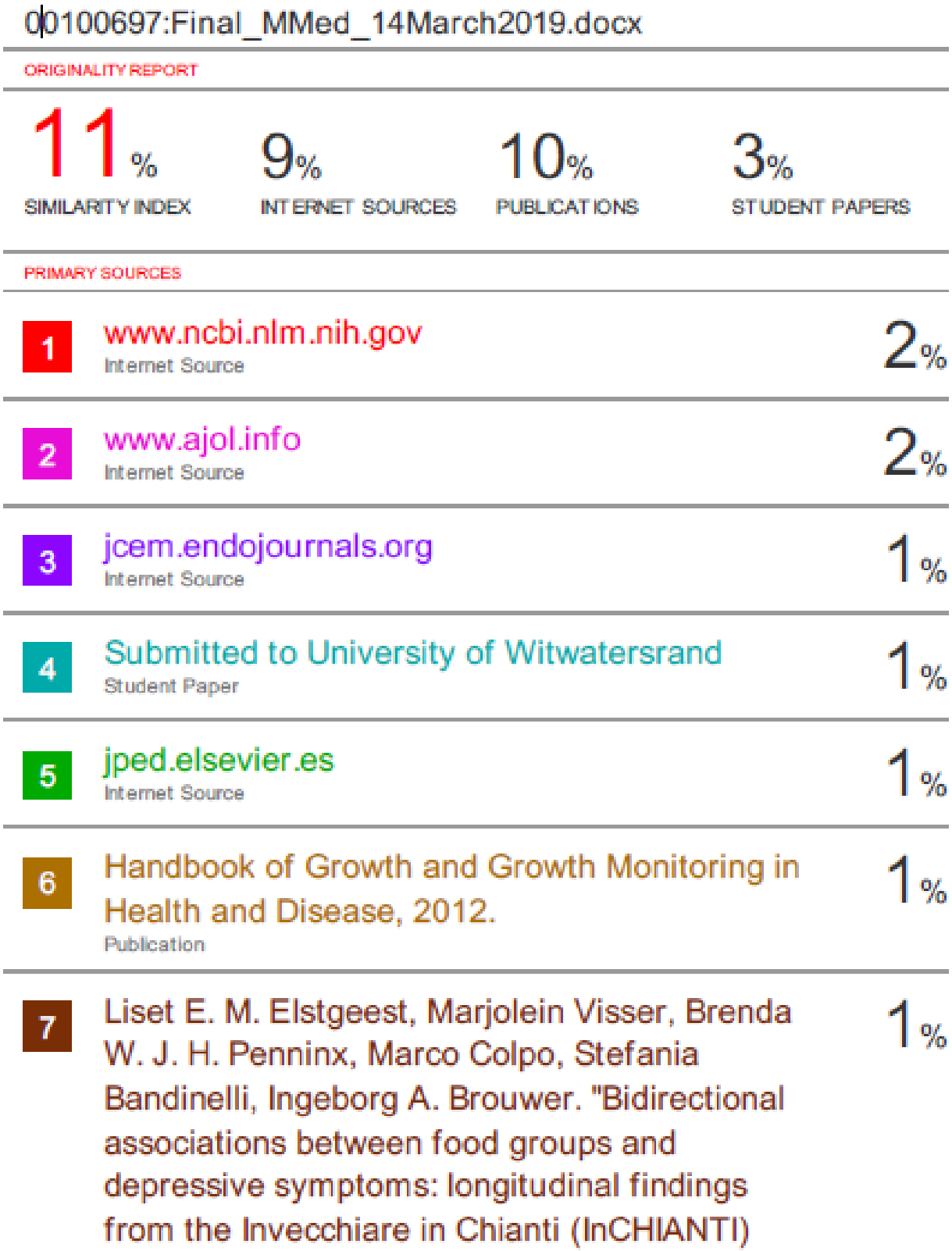
DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 10004, 10th floor, Senate House/2nd Floor, Phillip Tobias Building, Parktown, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized 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 the application 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 March and will therefore be due in the month of March each year.

Principal Investigator Signature

Date 01/05/2016

Appendix D: Turnitin report



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ORIGINALITY REPORT

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study", British Journal of Nutrition, 2018
Publication

8	Andrew G. Feehan, Margaret R. Zacharin, Angelina S. Lim, Peter J. Simm. "A comparative study of quality of life, functional and bone outcomes in osteogenesis imperfecta with bisphosphonate therapy initiated in childhood or adulthood", Bone, 2018 Publication	1%
9	PJ Roughley, F Rauch, FH Glorieux. "Osteogenesis imperfecta - Clinical and molecular diversity", European Cells and Materials, 2003 Publication	1%

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